COMMENTARY

FOCUS ON SPATIAL COGNITION

Spatial representation in the hippocampal formation: a history

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Since the first place cell was recorded and the cognitive-map theory was subsequently formulated, investigation of spatial representation in the hippocampal formation has evolved in stages. Early studies sought to verify the spatial nature of place cell activity and determine its sensory origin. A new epoch started with the discovery of head direction cells and the realization of the importance of angular and linear movement-integration in generating spatial maps. A third epoch began when investigators turned their attention to the entorhinal cortex, which led to the discovery of grid cells and border cells. This review will show how ideas about integration of self-motion cues have shaped our understanding of spatial representation in hippocampal–entorhinal systems from the 1970s until today. It is now possible to investigate how specialized cell types of these systems work together, and spatial mapping may become one of the first cognitive functions to be understood in mechanistic detail.

Although the study of the cellular and circuit mechanisms of spatial representation in the brain today is centered on the hippocampal and parahippocampal formation, the study of spatial coding did not begin there, but rather began with the parietal cortex, in the form of early observations on patients with parietal damage[1,2]; in many respects, one takes a risk in attempting to limit the discussion to the hippocampal formation[3]. Nevertheless, in studies of spatial coding, some of the most 'paradigm-shifting' discoveries and ideas have come from recordings within the greater network of the hippocampal formation, particularly the dorsal parts of hippocampus, entorhinal cortex, presubiculum, and parasubiculum, where cells exhibit place-dependent activity independently of the animal's behavior or the task that it is performing (**Fig. 1**). Key among these insights were the discoveries of place cells (**Fig. 2**)[4], head direction cells (**Fig. 3**)[5–7], and grid cells[8,9], each of which represent quantum jumps in our understanding that there is a system in the brain that has evolved to produce a representation manifold that can be linked to position (grid cells), an inertial compass (head direction cells), and a system for mapping external features and events onto internal and, at least locally, metric coordinates (place cells). In broad terms, these components and their interactions were predicted by O'Keefe in 1976 (ref. 10).

Also key to the emergence of a model for spatial representation was a gradual understanding of the role played by different spatial reference frames and their interactions. Space can be represented in three reference frames: egocentric (defined in relation to a body part axis), allocentric (based on spatial relationships to or among external features), and inertial or idiothetic (relative location and orientation based on direction and distance moved from an arbitrary reference point). Navigation in an idiothetic reference frame is often referred to as 'path integration', a process by which animals use self-motion cues (such as motor efference, optical flow, and vestibular information) to keep track of their own location relative to a starting point[11–14]. Decades of investigation have shown that egocentric space is not represented primarily in the hippocampal formation but rather in parietal cortex and associated regions[15–17]. O'Keefe's studies showed from the outset that, instead, place cells encode an animal's location in an orientation-independent reference frame[10]. Although the term allocentric was applied to place cell representations, O'Keefe recognized early on that these representations may rely "on the fact that information about changes in position and direction in space could be calculated from the animal's movements."[10] Yet it was not until the discovery of head direction cells in the 1980s[5–7] and the realization that these cells were indeed performing integration of head angular velocity[18] that the concept emerged, in the 1990s, that the entire hippocampal formation might be using an idiothetic reference frame—or path integration—as a basis for its coordinate system[19]. The possibility of a path-integration mechanism outside the hippocampus proper[3,20,21] was reinforced at this time by studies showing that, unlike place cells, spatially modulated cells in the entorhinal cortex and subiculum had environment-independent spatial firing patterns[22,23]. Today it is generally recognized that path integration plays a fundamental role in spatial coding in the hippocampal formation, although there continues to be controversy as to whether path integration is the primary determinant of place cell and grid cell firing or whether it plays an equal or subordinate role to the integration of information from external stimuli[24–26].

Finally, a discussion of model shifts would not be complete without some realization of the role that technology has played (**Fig. 4**).

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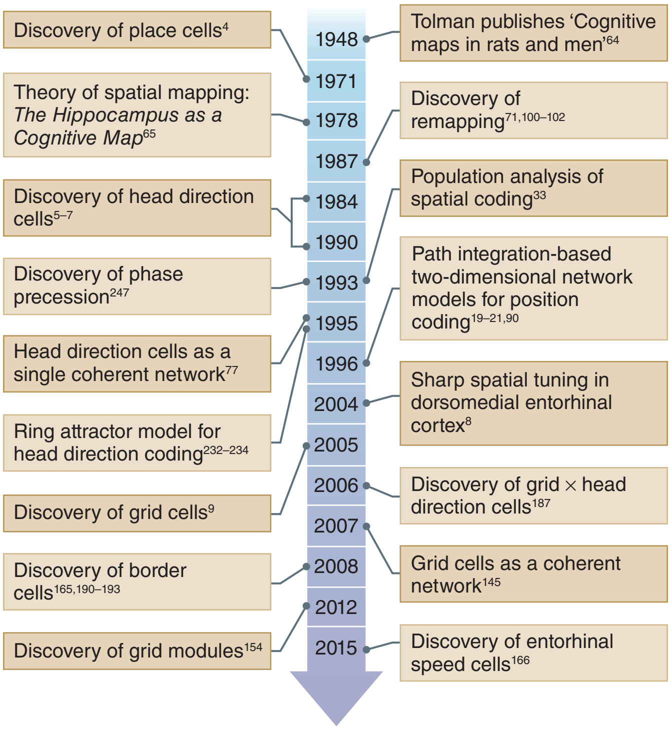


Figure 1 Selection of historical milestones in the study of spatial coding in the hippocampal formation.

Key technical advances have been the shift from recording single cells in restrained, usually anesthetized, animals to recording in freely behaving ones[4,27–29]; the development of quantitative video-tracking methods for rodents during hippocampal recording experiments[30,31]; the invention of stereo (tetrode) recording[32] (**Fig. 4a**) and its extension to large neuronal ensembles[33] (**Fig. 4b–d**); the development of micromachined silicon electrode arrays[34]; new cell-type-specific optical and chemical methods for stimulation[35–37]; and, most recently, the development of large-scale Ca^{2+} cellular imaging in both freely moving animals[38] and in restrained animals locomoting in virtual reality environments[39,40]. The importance of recording from substantial numbers of cells in interpreting coding dynamics for the hippocampus or any other neural system cannot be overemphasized. Apart from the obvious computational and statistical analysis power enabled by collecting data from large numbers of simultaneously active neurons, it is clear that many results that we now understand as across-trial variations in population dynamics may have been attributed to differences in single neuron classes in early single-neuron recording studies.

We have taken on the task of trying to present, in a relatively small space, an historical overview of some of the paradigm-shifting developments that led to our current understanding of spatial coding in the hippocampal formation. This task is daunting for several reasons, not the least of which is that the number of important experimental and theoretical contributions has risen (and continues to rise) almost exponentially since 1971, when O'Keefe and Dostrovsky, after recording in freely behaving rats from what today would be considered a very small sample of CA1 units, made the bold claim that the hippocampus might construct a spatial map[4] (**Fig. 2**). Length restrictions have forced us to focus the review on one particular set of ideas that has inspired the investigation of hippocampal representations of space almost since the beginning of studies of place cells, namely that spatially localized firing to a large extent reflects the dynamic integration of self-motion—or path integration—as animals move around in the environment. We shall demonstrate how the idea of a path-integration input explains many fundamental properties of place cells and how this, in turn, led investigators in the single-cell recording field to identify a path-integration-dependent neural system consisting of multiple functionally specialized cell types in the parahippocampal cortices.

We shall demonstrate that path integration appears as a leitmotif that follows the history of spatial representation in the hippocampal formation across generations of investigators. Yet by directing our spotlight to path integration, we are forced to leave out contributions and research directions that have contributed critically to the broader understanding of place cells and hippocampal systems function, beyond the representation of self-location. First of all, the more than four decades of hippocampal spatial mapping studies have developed alongside an equally productive line of investigations, using a variety of methodological approaches, into the basis of memory in the same brain system[3,41–47]. The focus of this review is on the coding of space, but, as we will acknowledge, this does not rule out a broader participation of hippocampal neurons and place cells in representation of experience[48–50]. In shying away from the memory functions of the hippocampus, we shall also pass over the vast and growing literature on how replay and preplay of firing sequences may enable consolidation and storage of hippocampal memory through interactions with neocortical neural networks[51–54], and we shall not discuss the important but separate question of whether or how place cells are used for goal-directed navigation and route planning[55–59]. We have also left out dozens of pioneering studies of temporal coding and network oscillations, including theta rhythms, that have shaped our current understanding of hippocampal function beyond the representation of space[49,60–62]. Finally, this review is dominated by work in rats and mice, reflecting the use of freely moving rodents as subjects in nearly all studies of spatially modulated cells in the hippocampal formation (see **Box 1** for extensions to the primate brain).

The origin of the spatial signal

In 1971, O'Keefe and Dostrovsky observed that neurons in the rat hippocampus had what appeared to be spatial receptive fields[4] (**Fig. 2a**,**b**). In their 1971 paper, the number of place cells and evidence for localized firing was limited, but much more substantial data were presented by O'Keefe in 1976 (ref. 10). By this time, after thorough study of hippocampal activity in unrestrained rats[29], Ranck had also seen place cells[63]. The O'Keefe paper showed that place cells fired whenever the rat was in a certain location in the local environment. Different cells had different place fields, such that at all locations investigated in the hippocampus, the animal's location could, in principle, be inferred from the joint activity of a fairly small sample of neurons[10] (for direct demonstration, see ref. 33 and **Fig. 4c**,**d**). Based on this observation and inspired by Tolman's proposal that navigation is guided by internal cognitive maps[64], O'Keefe and Nadel[65] suggested that place cells are the basic element of a distributed allocentric cognitive map of the animal's environment (**Fig. 2c**). The spatial relations between landmarks provided by this map were thought to enable animals to find their way independently of local view or movement trajectories, using what O'Keefe and Nadel called a locale strategy. This contrasted with route strategies, which do not take into account the relationship between landmarks. The latter strategies included a spectrum of routines from simple beacon navigation to more complex action sequences. O'Keefe and Nadel's proposal represented a major landmark in the conceptualization of hippocampal function. Their book, *The Hippocampus as a Cognitive Map*, synthesized and reinterpreted decades of discordant experimental studies using a range of experimental approaches, particularly lesions, and put these studies into a coherent theoretical framework organized around the concept of place cells as the cellular basis for representation of space as well as events and experiences associated with space. The book proposed a neural implementation of Tolman's concept of the cognitive map, with visionary perspectives on how such a map might enable a breadth of cognitive functions in higher species, including humans. Today, 40 years after its publication, *The Hippocampus as a Cognitive Map* remains the theoretical pillar on which nearly all subsequent study of spatial coding in the hippocampal formation rests.

The early years of research on place cells, in the late 1970s and 1980s, were dominated by attempts to prove that the place signal was indeed spatial and, given this, to understand what caused place cells to fire where they did, based on the idea that it was some constellation of external sensory cues, rather than a single cue or some other cause (for example, ref. 66). Two salient observations in this period that both advanced knowledge and increased perplexity were the findings that place cells appeared to be completely direction-dependent when animals ran repeatedly on restricted paths[30] but were unaffected by head direction during free foraging in a large cylinder[67]. Perplexity about the mechanism of place cells was further increased by the fact that place cells had a sort of 'memory': they rotated their fields when external cues were rotated but continued to fire in relation to the last-seen cue location when the cues were removed[68,69]. Indeed, early studies indicated not only that place cells continued to fire in the 'correct' location in total darkness but also that fields could be formed when animals were introduced to an environment in darkness and were minimally affected when the lights were subsequently turned on[70]. Nevertheless, place fields became linked to external cues and rotated to maintain registration with them when the cues were rotated between sessions[68,71].

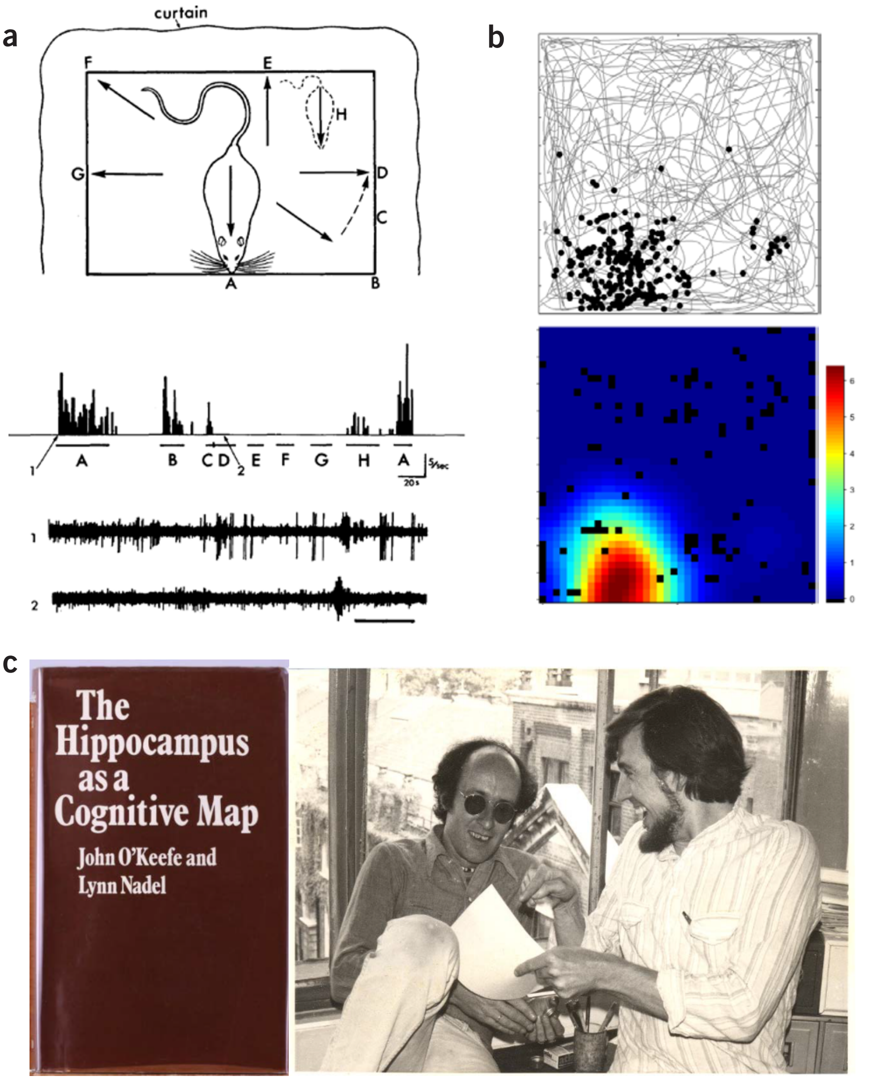


Figure 2 Place cells. (**a**) First place cell described[4]. Arrows and letters mark positions at which the animal was restrained as it was pushed or coaxed around the test platform. Firing rate of the unit is illustrated by the frequency histograms in the middle of the figure. Letters correspond to positions, and lines indicate periods of restraint. Bottom lines show spikes at the onset of the unit response at A (1) and during the absence of a response at D (2). Calibration bar, 400 ms. Note that the cell responds selectively at only a few positions. O'Keefe and Dostrovsky reported 8 units of 76 recorded hippocampal cells that responded solely or maximally when the rat was situated in a particular part of the testing platform and facing in a particular direction. Note that the single-electrode technology available to the authors at the time likely precluded regular good isolation of cells, which may have limited the number of clear 'place' responses observed. (**b**) A place field as typically displayed today. Top: rat's trajectory in gray; spike locations superimposed as black dots. Bottom: color-coded rate map; dark red is maximum rate; blue is silence. Regions not visited in black. (**c**) Left: the book by John O'Keefe and Lynn Nadel was long a 'bible' in the study of spatial coding in the hippocampal formation. Right: Nadel (left) and O'Keefe (right) during preparation of the book. Photo taken by Dulcie Conway around 1975, reproduced here courtesy of John O'Keefe[264]. Panel **a** reproduced with permission from ref. 4, Elsevier.

The foregoing studies were soon followed by a number of observations that cast further doubt on the external sensory origin of place fields: most place fields had asymmetric firing fields in an environment with a symmetric cue configuration[72]; place fields could dynamically shift between a reference frame defined by a reward box that moved relative to the laboratory reference frame and the lab reference frame itself[73,74]; the location and orientation of place fields followed the rat when the rat was rotated independently of the environment[75,76]; place cells and head direction cells exhibited coordinated drift error in a cylindrical environment[77,78]; the size of place fields was almost completely independent of local cue density, spatial frequency, or

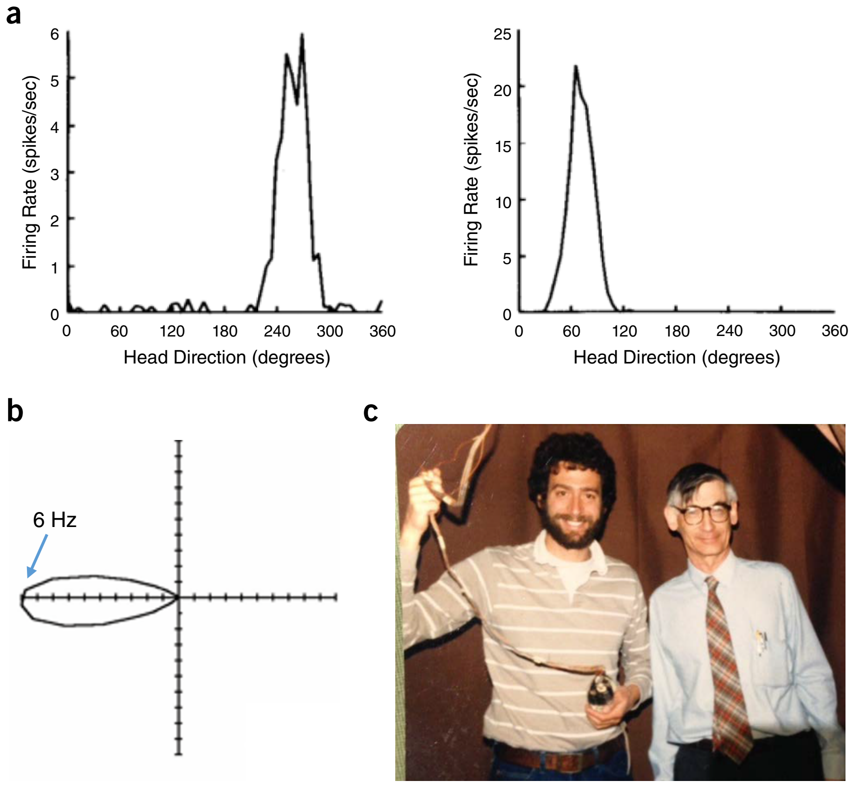


Figure 3 Head direction cells[6]. (**a**) Firing rate as a function of head direction for two representative cells from two different animals. (**b**) A head direction cell firing rate in polar coordinates. Peak firing rate, in the left orientation, is 6 Hz. (**c**) Jeffrey Taube (left) and James B. Ranck Jr. (right), at SUNY Downstate Medical Center in Brooklyn., N.Y., in 1987. Photo courtesy of Jeffrey Taube. Panel **a** reproduced with permission from ref. 6, "Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis," J.S. Taube, R.U. Muller & J.B. Ranck Jr., 1990, in *Journal of Neuroscience*, Vol. 10, pages 420–435.

salience[79] but varied systematically along the septotemporal axis of the hippocampus[80,81]; in rats with age-related memory impairment[82] or with NMDA receptors blocked[83], place fields appeared perfectly normal in a novel environment but could be completely rearranged when the animals were returned to the same environment after even a short delay; the place field map as a whole dynamically expanded when motor and vestibular information about movement speed was disrupted, in the absence of changes in landmark inputs[84]; place cells shut off completely when animals were restrained from locomotion[85]; and finally, the variation in scale of place fields along the hippocampal septotemporal axis was strongly correlated with the gain of physiological speed signals[86].

In spite of gradually accumulating evidence for an, in many ways, nonsensory origin of spatial receptive fields in the hippocampus, the lack of proper quantification prevented a general acceptance of this idea, and much of the initial effort was thus spent on proving that the signal was indeed spatial. As this skepticism was gradually overcome, investigators began to focus on how place cells might be synthesized as higher-order integrators of sensory data, perhaps endowed with memory properties. However, this sensory-integration approach changed, literally overnight, when James Ranck brought a video of a recorded head direction cell to the 1984 Society for Neuroscience meeting[87] (**Fig. 3**). Head direction cells are cells that fire specifically when the animal faces a certain direction[5–7] (**Fig. 3a**,**b**). Ranck first encountered these cells in the dorsal presubiculum—almost by accident, in an experiment in which electrodes targeted to the subiculum went astray[87]—but they were later observed across a wide network of cortical and subcortical regions[88,89]. In the same way that place cells covered all locations of an environment, the preferred firing directions of head direction cells were distributed evenly around angular space, enabling precise read-out of head direction in neural networks downstream of head direction cells. If the brain was endowed so clearly with an internal compass, as suggested by Ranck's 1984 movie, the idea that it also had a map became much more palatable. However, the first full publication on the basic properties of head direction cells did not appear until 1990, in joint work by Ranck, Taube, and Muller[6,7]. By that time, it was already recognized that the basis of the head direction signal was likely integration of head angular velocity, and the outline of a model for how this integration was performed using conjunctive head direction × head angular velocity cells (observed in dorsal presubiculum and parietal cortex) was proposed[18].

To many investigators, the foregoing observations collectively pointed almost inescapably to the hypothesis that the primary determinant of the cognitive map is some form of coordinate system in which head angular velocity and linear velocity are integrated over time to express displacement and orientation from a starting point (path integration)[19–21,90,91] (**Fig. 5**). According to this view, the path-integration mechanism assigns place fields based on motion integration. In the absence of external stationary input, errors from noise in the self-motion integration process accumulate, and place fields (and head direction tuning curves) would start to drift. However, in environments with salient cues, rapidly formed associations between cues and place cells enable stabilization of the firing fields, and previously formed maps can be recalled from session to session[10,19–21,90], possibly cued by landmark information conveyed through the dorsal presubiculum[92]. Nevertheless, there is also some support for the idea that place cells are formed by integration of salient sensory inputs, independently of movement. One of the main observations presented in favor of this concept is that place fields could be seen to expand[71] or stretch[93] in response to corresponding distortions of the enclosure in which recordings took place. However, such distortions do not occur when the animal is introduced *ab initio* into the distorted environment, only when the animal has first experienced the undistorted version. Stretching or expanding can thus be seen as a result of the external inputs attempting to correct the path integrator based on prior associations[90].

During the past decade, virtual environments have enabled investigators to dissociate with increased rigor the relative contributions of self-motion inputs and stationary landmarks. Typically, head-fixed mice or rats run on an air-cushioned ball or a circular treadmill while visual flow is projected onto an immersive screen at a rate that directly reflects the animal's running speed and direction, emulating the sensory-motor coupling of the real world[39,40]. When the virtual environment is linear, as on a treadmill, hippocampal place cells exhibit firing fields that depend on distance moved[94,95] or stationary cues on the screen[94], with some variation between cells[94]. Reducing the gain of ball-to-virtual-scene movement causes place fields to move toward the start of the virtual track, as expected if firing locations are determined by self-motion, but the shift is generally smaller than expected from movement distance alone, pointing to an additional role for visual inputs[94]. The dual dependence on self-motion cues and external cues confirms earlier studies in which these sets of inputs were disentangled in real environments[73,74,93]. However, when the virtual environment is made two-dimensional and movement of the head remains restricted, localized firing breaks down, although a small influence of distance traveled is detectable[96]. In contrast, when body and head rotation is unconstrained, stable position coding persists[97]. Together these studies point to vestibular signals (which are impoverished during head fixation) as a critical source for integrating velocity and direction signals into a coherent two-dimensional representation, in agreement with earlier work showing that place fields are disrupted following inactivation or lesions of the vestibular system[98,99].

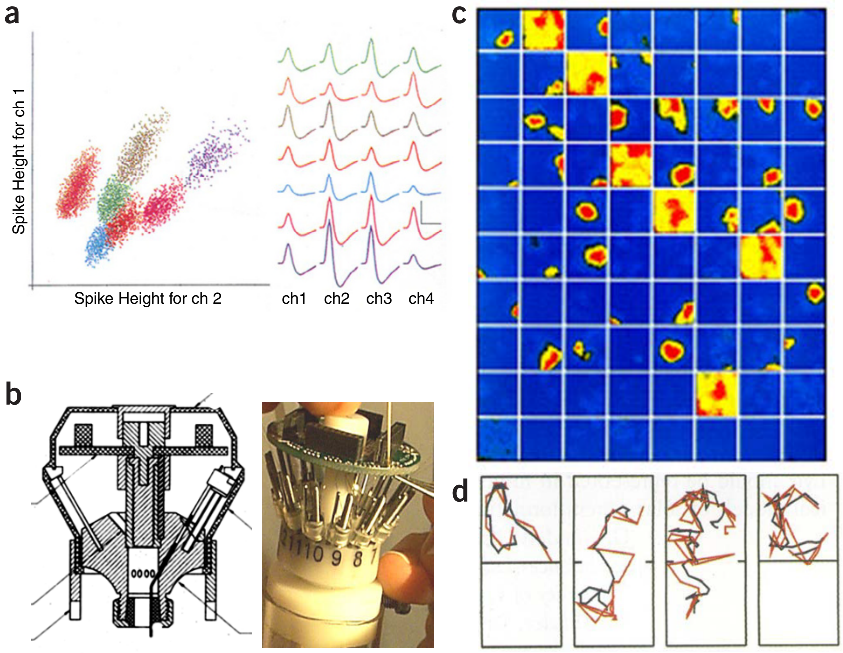


Figure 4 Ensemble recording technology. (**a**) The principle of tetrode recording proposed by McNaughton *et al.*[32] exploits the variation in extracellular spike height as a function of distance to the recording site to resolve multiple single units in structures such as hippocampus, where the neurons are fairly tightly packed. Example of spike amplitude clusters from a tetrode recording showing two of the four spike-amplitude dimensions. The corresponding spike waveforms are shown on the right. (**b**) A 48-channel, 12-tetrode probe array (hyperdrive) from ca. 1995. This system exploited the flexibility of wire tetrodes, which allowed researchers to advance them by pushing them through gently curving tubes (like a mosquito proboscis). (**c**) Multitetrode recording made it possible to record from more than 100 hippocampal neurons simultaneously. Here we show 80 firing rate maps from simultaneously recorded CA1 cells as the rat ran in a 70 × 70-cm arena[33]. Firing rate is color-coded from blue (silent) to red (maximum rate). Note that many CA1 cells were virtually silent in this particular arena, whereas about 40% had place fields. Six of the recorded cells correspond to fast-spiking cells (interneurons), which have much less spatial selectivity. (**d**) Examples of the actual (blue) spatial trajectory of the rat and the trajectory reconstructed from the population firing-rate vector (red). Panel **a** reproduced with permission from ref. 80, "Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat," M.W. Jung, S.I. Wiener & B.L. McNaughton, 1994, in *Journal of Neuroscience*, Vol. 14, page 7347–7356. Panels **c** and **d** reproduced with permission from ref. 33, AAAS.

Remapping: global, partial, local, and rate

In the late 1980s, Muller and Kubie began a series of investigations on the effects of changing the most salient visual cues in a cylindrical environment and introducing various local cues[71,72,100–102] (**Fig. 6**). As alluded to above, cue-card rotations, changes in the size or color of the cue card, or even removal of the cue card altogether rarely changed the radial coordinate of the field but could change the angular coordinate, completely unpredictably in the case of complete removal of the cue card when the rat was not present (**Fig. 6b**). They coined the term 'remapping' to describe any manipulation-induced changes in the firing of place cells. These could include mild changes in the firing characteristics in a few cells, such as when new objects or walls were placed in a cell's place field, up to radical changes in the location of firing, including the disappearance of a field altogether, which was sometimes observed when the environmental shape was changed or visual cues substantially altered.

Whether sets of place cells remapped completely or only partially depended on the experimental conditions. The terms 'global', 'partial', and 'local' remapping were introduced by Knierim and McNaughton[103] in an attempt to distinguish situations in which only fields near a specific, manipulated cue changed from situations in which there was a general (partial or complete) rearrangement of fields throughout the environment. Such limited remapping is often seen when the animal is placed in nonuniform environments[104,105] or in cases of deficient plasticity as discussed above[82,83]. The concept of remapping was clarified considerably by several experiments that followed. In 2005, Leutgeb *et al.* showed that, when the cues in the recording chamber or its shape were radically changed between sessions that took place in the same physical location, CA1 and CA3 place cells underwent substantial changes in their firing rates, without changing their firing locations[106] (**Fig. 6c**). These changes could be sufficient to make a field appear to be present in only one condition, unless the rate map graphs were rescaled. In contrast, when the recordings took place in identical apparatus located in two separate rooms, the place field distributions became completely uncorrelated. Leutgeb *et al.* made the distinction between 'rate remapping' for the former situation and 'global remapping' for the latter. Thus, it appears that, under conditions in which the path-integrator coordinates likely remain consistent, changes in external input or, indeed, internal variables such as motivation, working memory, or action plans, can result in dramatic changes in firing rate while firing location remains unaltered[107–110]. Leutgeb *et al.* suggested that rate remapping might be the cause of apparent partial remapping or direction dependency on linear tracks. The role of the path-integrator coordinates in governing rate versus global remapping was fairly decisively demonstrated by Colgin *et al.*[111], who showed that when environmental shape was gradually morphed between a circle and a square, abrupt, global remapping only occurred if the rats had previously been allowed to locomote between a circle and a square via a connecting tunnel. When rats were pretrained on the two shapes in the same location, only rate remapping was observed. Thus, it was the path integrator that determined whether global or rate remapping was observed.

The presence of a nonspatial code on top of the place code (rate remapping) is consistent with dozens of studies, starting in the 1980s, showing that place cells encode more than space. Cells with clear place fields in one task were shown in other tasks to respond in a time-locked manner to various nonspatial features of the environment or the experience, such as odors[112–114], textures[115], conditioned tones[28,116,117], or temporal stages of the experiment[118]. However, in combination with the remapping studies, these observations suggest that hippocampal cells respond conjunctively to spatial and nonspatial variables, with the latter represented as changes in the rate distribution. Experience-related changes in rate distribution can also account for moment-to-moment variability of firing rates within place fields (overdispersion)[119]. The conjunctive nature of spatial and event-related firing is demonstrated elegantly in a more recent study of hippocampal activity after systematic variation of location, food cups (objects), and color or pattern of the recording box (context)[120]. The majority of cells in this study fired at specific locations but with rates depending on context and objects. Thus, when location is clamped, unique constellations of cues give rise to unique rate patterns, implying that each experience is characterized by its own hippocampal–neocortical output, even when those experiences occur at a fixed location. This uniqueness is a necessary condition for the widely held view that hippocampus may provide an index that links memory attributes distributed widely over neocortex[121–123]. The wide range of stimulus configurations that activate hippocampal firing, over and above space, has been taken as evidence for a broad involvement of the hippocampus in episodic memory, where space is just one of several attributes of the encoded representation[48].

Lest one conclude from the foregoing that the phenomenon of remapping or the necessity or dominance of path integration is now fully understood, it is necessary to consider some remaining flies in the ointment. First, Tanila, Shapiro, and Eichenbaum[124,125], and later Knierim[126], have shown that, when an animal is highly familiar with the local and distal cues in an environment, rotating these cue sets relative to each other can cause some CA1 cells to follow the local set while others simultaneously follow the distal set (still others may remap). Such discordant responses are stronger in CA1 than CA3 (ref. 127). These effects are not inconsistent with a path-integration-based origin of the place fields, if one assumes that the subsequent, plasticity-dependent association between cues and place cells that leads to robust rate-remapping is also strong enough in some cases to move the fields independently, depending on which type of inputs dominate the synaptic input vector of a given cell. The fact that this effect occurs predominantly in CA1, which lacks the potential stabilizing effects of reciprocal excitatory connections present in CA3, tends to support such a view[127]. A second possible challenge is the fact that place fields can be expressed in CA1 under conditions in which the medial entorhinal cortex (MEC) is completely lesioned[128]. This suggests that localized firing may itself be generated from alternative inputs, such as from weakly spatially modulated neurons in the lateral entorhinal cortex (LEC)[129], which may provide hippocampal cells with path-integration-independent sensory inputs necessary for efficient rate coding[130]. However, even under conditions in which MEC inactivation does not impair hippocampal place selectivity, the intervention causes instant remapping[131,132], suggesting that MEC is obligatory for activating the correct place map. This does not preclude, of course, that place maps are also stored in the CA3 network (for example, the 'charts' of Samsonovich and McNaughton[90]), or that, in the absence of a strong MEC input, CA3 attractor dynamics may result in the recall of some previously constructed chart in the novel context.

Moving from hippocampus to entorhinal cortex

Until the 1990s, for primarily technical reasons, most recording studies had been confined to CA1 of the dorsal hippocampus, in spite of the fact that hippocampal subfields may have distinct computational functions. David Marr had, in the early 1970s, already pointed to the unique properties of area CA3 as a recurrent network capable of auto-association, pattern formation, and pattern completion[133]. His work was followed by theoretical investigations pointing to the possible role of the dentate gyrus in pattern-separation processes needed to counteract memory interference at subsequent stages of the hippocampal circuit[134–136]. An additional, striking property that was discovered to differentiate between hippocampal subfields was coding sparsity. Contrary to some expectations, in the successive transformations from CA3 to CA1 to subiculum, mean firing rates increased, and coding became less sparse and less spatially selective[137,138]. This observation led Barnes *et al.* to conclude that "discrete spatial representations are constructed within early stages of the process, for some purpose intrinsic to the hippocampus itself, possibly that of rapid information storage" and that "the information leaving the hippocampus through the subiculum seems to consist of much more highly distributed representations, constructed perhaps through the convergence and disjunction of a number of unrelated hippocampal place cells"[137]. For a long time, however, these ideas did not fully catch the attention of the place cell community, which, with few exceptions, retained its focus on the readily accessible CA1 area.

In a similar manner, until the 1990s, there was minimal focus on computational operations outside the hippocampus and computations underlying place-field formation were at risk of being erroneously attributed to the hippocampus itself. The focus on a hippocampal origin of the place cell signal was further influenced by the observations of a relatively small set of tetrode studies in the entorhinal cortex, the major cortical input to the hippocampus. These studies showed that entorhinal cells were spatially modulated but that their firing fields were broad and dispersed, with little spatial selectivity in standard laboratory environments, and the fields seemed not to remap between environments[22,137,139]. This, together with the observation that CA1 place fields persisted following large lesions of the dentate gyrus[140], pointed to the remaining associative networks of CA3 as one possible origin for the formation or learning of the sharply localized place signals seen in CA1. The validity of this interpretation was questioned, however, by the fact that partial inactivation of CA3 cells, following inhibition of septal inputs, failed to remove spatial firing in CA1[141].

Given the uncertainty about how CA3 contributed to the CA1 place signal, Brun and colleagues[142] decided to record place cells in CA1 after the CA3 input to these cells had been entirely removed by excitotoxins or by knife cuts that completely separated CA1 from CA3 as well as from dentate gyrus and subcortical afferent regions. Retrograde tracer injections in CA1 verified that no input was spared. Confirming the interpretation of the septal-inactivation work[141], the study found, in 2002, that CA1 place cells do not require input from CA3 to maintain reasonably selective spatial firing. This suggested either that place fields were generated within the limited circuitry of the CA1 itself or that place cells in CA1 received spatial input from the entorhinal cortex via temporoammonic projections that survived the CA3–CA1 transection. These observations were made only a few years after theoretical studies[3,21,90,143] proposed that the path integrator might located outside the hippocampus—in the

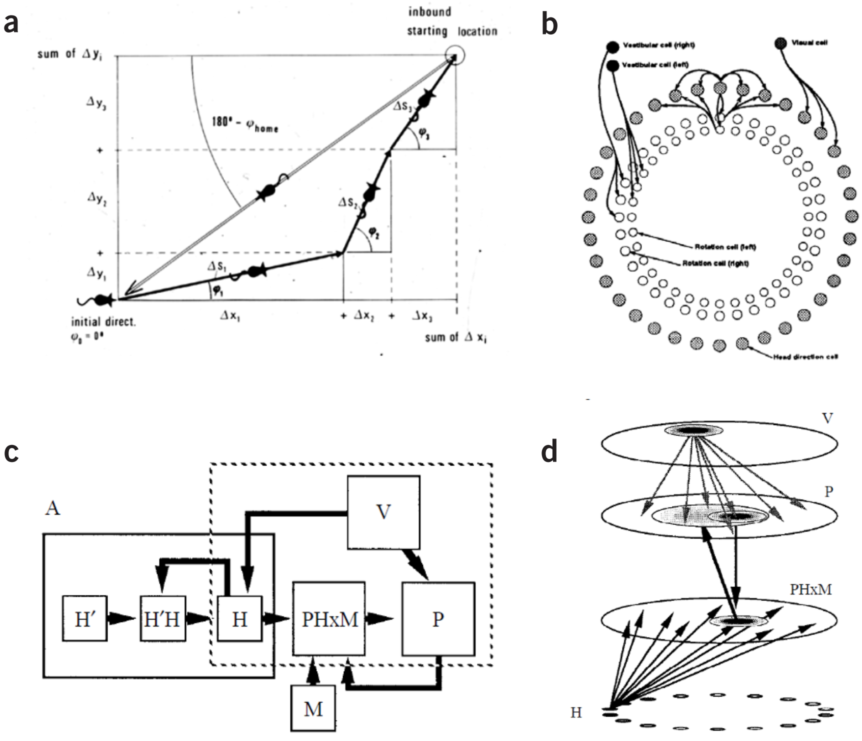


Figure 5 Path integration. (**a**) Illustration of the Mittlestaedt & Mittlestaedt 1980 experiment[12]. This experiment showed that rodents can perform angular and linear path integration. A female mouse returns directly to her nest after finding a lost pup in total darkness but makes a heading error if she is rotated below vestibular threshold before starting the inbound journey. (**b**) The Skaggs *et al.* continuous-attractor model from 1995 proposed to explain how head direction cells arise through integration of head angular velocity signals from the vestibular system[18,232]. Updates in the head direction (attractor) layer were performed by a hidden layer of cells conjunctive for head angular velocity and starting head direction, whose return projections to the head direction layer are offset according to the sign of rotation. Such conjunctive cells have been found in several regions of the brain. (**c**,**d**) The continuous-attractor model for path integration in two dimensions, as proposed by McNaughton *et al.* in 1996 (ref. 19) and simulated by Samsonovich and McNaughton in 1997 (ref. 90). H′, head angular velocity; H′H, conjunctive cells; H, head direction; P, place cells; M, speed cells; PH×M, cells conjunctive for place and head direction and modulated by speed; V, external sensory inputs that were assumed to associatively bind to both H cells and P cells to enable correction of drift error in the path integrator and to enable resetting of the integrator upon entry to a familiar environment. Panel **a** reproduced with permission from ref. 91, Nature Publishing Group. Panel **b** reproduced with permission from ref. 232, MIT Press. Panels **c** and **d** reproduced with permission from ref. 90, "Path integration and cognitive mapping in a continuous attractor neural network model," A. Samsonovich & B.L. McNaughton, 1997, in *Journal of Neuroscience*, Vol. 17, page 5900–5920.

subiculum, the entorhinal cortex, or both—because correlations between firing fields in these regions appeared to be invariant across contexts[22,23], as might be expected for a path-integration-based representation. At this time it was clear that the entorhinal cortex, the main cortical input to the hippocampus, was worth a revisit.

An important additional inspiration for the renewed interest in entorhinal cortex was Menno Witter's extensive review of entorhinal–hippocampal systems[144]. Witter pointed out that dorsal and ventral regions of the hippocampus receive inputs from and project back to different regions of the entorhinal cortex, in a topographical manner, with increasingly dorsal hippocampal regions mapping onto areas that were increasingly closer to the rhinal sulcus, or increasingly more dorsal within the MEC. In 1990, based on his review and after direct consultation with Witter, two of us (M.-B.M. and E.I.M.) realized that in earlier MEC recordings for which histology was available[22,139], cells had been recorded quite far outside the area of MEC that receives most visual–tactile information and projects most extensively to the dorsal hippocampus, where the most sharply tuned place cells of the hippocampus are located[80,81]. This led us, eventually, after the turn of the millennium, to target tetrodes to the dorsal MEC, the origin of the majority of inputs to the dorsal hippocampus[8,144], a region of MEC so far not touched by electrodes *in vivo*.

Grid cells: a metric for space?

Recordings in dorsal MEC soon showed that cells in this region have sharply defined firing fields, much like those in CA1 of the dorsal hippocampus, except that each cell had multiple firing fields, distributed all over the environment[8]. These findings, reported in 2004, pointed to the MEC as a key element of a circuit for space, but the nature of the entorhinal representation remained elusive.

A striking characteristic of many spatially modulated MEC cells was that the distribution of the multiple firing fields of each cell was more regular than expected by chance[8]. When the data from MEC were presented at the 2004 Society for Neuroscience meeting, they created considerable excitement. Among those who were most excited was Bill Skaggs, who thought he saw hexagonal symmetry, inspiring the Mosers and their students, Hafting, Fyhn, and Molden, to increase the size of the recording arena and visualize the firing pattern once and for all. Using a newly constructed 2-m-wide circular recording cylinder, these authors found, in a substantial fraction of MEC superficial-layer cells, that the firing fields of individual cells created a grid-like periodic hexagonal pattern tiling the entire space available to the animal[9] (**Fig. 7a**). These cells were designated as grid cells. For each cell, the grid could be assigned a phase (the *x*,*y* locations of the grid vertices), a wavelength or spacing (the distance between the vertices), and an orientation (how much the axes through the vertices were tilted compared to an external reference line). In addition, the peak firing rates varied between fields[9,145]. The spatial periodicity of the pattern was so striking that the authors were concerned, initially, that it was some sort of artifact. However, the grid pattern was soon found by other labs too[129,146].

One of the most striking aspects of the grid cell finding was that the spatial periodicity was maintained despite constant changes in the animal's running speed and running direction. The cells fired at the same vertices regardless of how much time and space the rat had traveled between each crossing, implying that grid cells had continuous access to information about distance and direction moved. The persistence of grid fields[9] and place fields[70] when rats run in darkness is consistent with the primary role that such self-motion information might have in determining firing locations, as is the fact that grid patterns unfold immediately in new environments[9] and are expressed with similar phase relationships between cell pairs in all environments tested[145]. It should be added, for the sake of balance, that stable

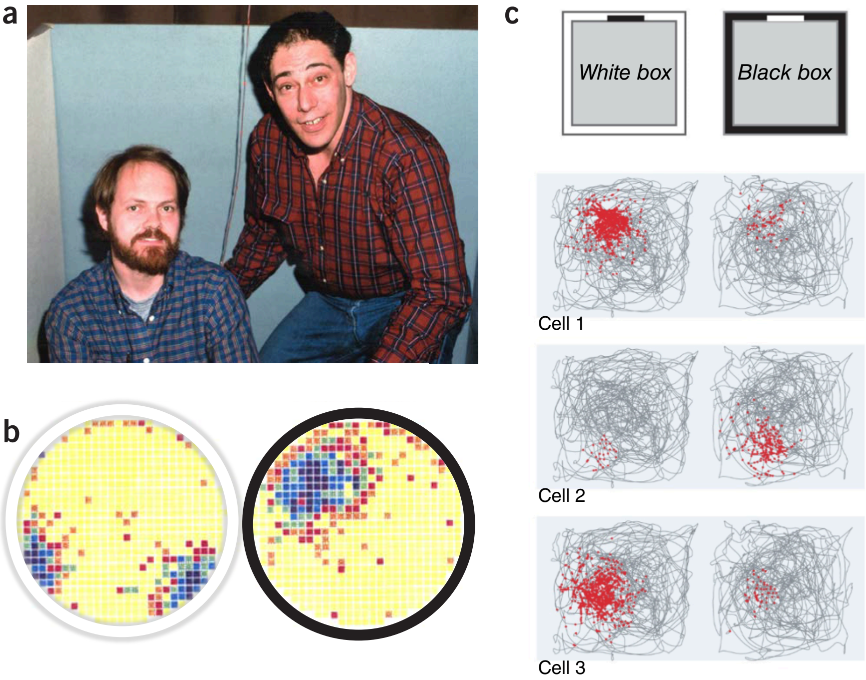


Figure 6 Remapping. (**a**) John Kubie and Robert Muller from SUNY Downstate Medical Center, NY. Picture courtesy of John Kubie. (**b**) Global remapping apparently induced by changing only the color of the recording environment[100]. Rate maps are shown for the same place cell recorded in a white cylinder (left) and a black cylinder (right). Firing rate is color-coded from yellow (no firing) to dark blue or black (high rate). The cell fires in different regions of the cylinder (some cells are active in only one cylinder) despite changing only the color of the box. We note that the authors later confirmed, anecdotally, that they had pretrained the animals in the white and black cylinder in two different rooms, which would have allowed differences in path-integrator coordinates to control the global remapping, as later shown by Colgin *et al.*[111]. (**c**) Rate remapping induced by changing the color of the recording environment while keeping its location constant[106]. The rat's trajectory in a white box and a black box is shown for three cells, with spikes superimposed as red dots. Note that changing only the color of the box causes substantial change in the distribution of firing rates across cells, but firing locations are retained. Rate maps in **a** adapted with permission from ref. 100, Wiley. Panel **c** adapted with permission from ref. 265, Elsevier.

grid fields have not yet been identified in darkness in mice[147,148]. The reason for the possible species difference is not known. Associations between path-integration coordinates and stationary cues may be weaker in mice[149], or grid fields of mice may simply be harder to visualize at times of increased jitter, given their smaller field size and shorter grid spacing compared to rats[150].

Based on the possible role of self-motion information in the formation of grid patterns, the three of us suggested, in 2006, that grid cells are part of an intrinsic path-integration-based metric for space[91]. A similar proposal was made the same year by a different group of investigators[151]. Both concepts bore similarities to the mechanism proposed a decade earlier from studies of place cells[19,90]. In fact, by implementing their attractor map model for path integration on a torus, Samsonovich and McNaughton[90] indirectly predicted periodic place fields, although, at the time, the idea seemed to them too preposterous to publish, and an attempt to discover such periodicity in CA1 by running rats down a long hallway concluded that "place field distributions can best be described by a random selection with replacement"[152]. A decade later, with the new data from the entorhinal cortex, it was clear that grid cells may supply the brain's spatial map with a coordinate system not available from place cells in the hippocampus, given the apparently random allocation of place fields to position[153] and the related extreme remapping across environments.

It soon turned out that if grid cells supply a metric, this metric is not always constant over time or locations. Experiments showed that when environments were stretched or rescaled, the spacing of the grid increased in the extended direction[146,154], in concert with either scaling or remapping in hippocampal place cells[155]. However, these distortions of the grid pattern were recorded when the environment was changed after the animal was already familiar with it, suggesting that grid maps might be formed by path integration but linked to external cues in such a way that the latter can override the path-integration dynamics[90]. Yet under some conditions, grid cells appear to be fragmented or distorted even after extended training in a constantly shaped environment. When rats are tested in environments with discrete compartments[156] or irregular geometric shapes[157], the strict periodicity of the grid pattern is often gone. In particular, it has been shown that walls exert strong local influences on the grid pattern[157,158], causing distortions and rotations that can be described effectively as a shearing process[158]. The common presence of fragmented and distorted grids has raised questions about whether grid cells are useful as a source of metric information[157]. Countering these doubts, theoretical analyses have shown that precise symmetry may not be necessary for accurate population-based decoding of position, distance, and direction if the grid cells are all distorted in the same way[159]. Direct behavioral evidence is needed, however, to establish how well spatial metrics can be decoded from distorted grid patterns.

Network properties of grid cells

Grid cells differ from place cells in more than one way. Not only do they have periodic firing fields but the relationship between the firing fields of different cells also follows a different rule. Whereas place cells often remap completely between environments and multiple fields can appear in large environments, with no more overlap in the subset of active cells than expected by chance[106,153,160–162], the ensemble activity of grid cells is normally maintained coherently from one environment to the next, without changing phase or orientation relationships between cells[145,163], much like in early recordings from MEC cells before grid cells were discovered[22]. The coherence of the grid map is particularly strong within ensembles, or modules, of similarly scaled grid cells[154]. A similar degree of coherence is present among head direction cells[6,7,77,78,164], as well as in the more recently discovered populations of entorhinal border cells and speed cells[165,166]. The coherence of grid cells and head direction cells is state-independent and persists during sleep[167–169]. Collectively, these findings point to a fundamental difference between hippocampal and entorhinal spatial maps: hippocampal circuits are high-dimensional and capable of storing a very large number of patterns, while MEC maps are low-dimensional and rigid, expressing the same intrinsic structure in all behavioral contexts, as would be expected for a path-integration-based map that keeps metric properties constant across contexts and environments.

It was clear from the outset that grid cells come in different varieties—with different phases, wavelengths, orientations, and field amplitudes—and that the network of grid cells is anatomically organized according to some but not all of these variables[8,9]. While the phase of the grid pattern appeared to be distributed randomly among cells on the same tetrode, the scale of the grid showed a striking increase from dorsal to ventral recording locations in the MEC (**Fig. 7b**). In both respects, the organization of grid cells was reminiscent of that of place cells, which also appear to have random spatial relationships[160,170,171] but show an increase in scale from dorsal to ventral[80,81]. In the hippocampus, the scale increase is strongly coupled with decreasing gain of self-motion parameters[84,86]. A similar gain-change may underlie the scale change in MEC, consistent with the hypothesis that the overall system parameters are dominated by path-integration mechanisms.

One question that was not settled by the earliest grid cell recordings was whether the scale gradients were smooth and gradual or instead consisted of multiple discrete maps with distinguishable scale and self-motion gain, the latter being a necessary prediction of attractor-map-based models[91,172]. In 2007, Barry and colleagues showed, with a small cell sample, that values of grid spacing were not evenly distributed[146]. In 2012, Stensola and colleagues were able to record activity from up to 180 grid cells in the same animal: enough to determine once and for all whether grid cells clustered in groups with similar properties[154]. Stensola *et al.* found that grid cells were organized in at least four modules, each with their own scale, orientation, and asymmetric distortions (**Fig. 7c**). The scale change across successive grid modules could be described as a geometric progression with a constant scale factor[154], confirming the prior predictions[91,172], as well as theoretical analyses pointing to nested and modular organizations as the most efficient code for representing space at the highest-possible resolution with the lowest-possible cell number[173,174].

The discovery of grid cells cast new light on the mechanisms underlying formation of place cells, the very question that motivated the search for spatially modulated cells in the entorhinal cortex. The periodicity of the firing pattern and the variability of the grid scale suggested early on that place cells may emerge by a Fourier-like linear summation of output from grid cells with similar phase throughout the environment over a range of spatial scales[91,175]. This summation mechanism might be facilitated further by coordinated gamma-frequency oscillations in MEC and CA1 cells[176]. Alternatively, and more in line with the sensory-integration ideas of the 1980s, place fields might be generated from any weak spatial input, so long as the hippocampal circuit contains mechanisms for amplifying a subset of these inputs, either through Hebbian plasticity or through local recurrent networks[177–180]. The merits of these two classes of models remain to be determined. Experimental studies have shown that MEC grid cells are not necessary for the emergence of spatially tuned firing in place cells. Place fields have been reported to persist when the spatially periodic firing pattern of MEC grid cells is compromised by inactivation of septal inputs[181,182], and in young animals, place cells acquire stable firing fields before sharp periodic firing patterns emerge in grid cells[183,184]. Inactivation or damage of the MEC is not sufficient to disrupt place cell firing in the hippocampus[128,131,132,185]. However, neither of these observations rules out grid cells as a key determinant of spatially selective firing in the hippocampus. The hippocampus receives input from multiple spatially tuned entorhinal cell types, including not only grid cells but also border cells and spatially modulated cells with nonperiodic firing patterns[186], as well as weakly place-tuned cells in the LEC[129]. Place fields may be formed from any of these inputs, by more than a single mechanism. Even pure rate changes among the MEC inputs are sufficient to completely alter the activity distribution among place cells in the hippocampus[185]. The mechanism for grid cell to place cell or place cell to grid cell transformation may have many faces, and understanding it may require that circuitry is disentangled at a higher level of detail, possibly in terms of inputs and outputs of individual cells.

A zoo of cell types

Grid cells are abundant, especially in the superficial layers of the MEC, but not all cells are grid cells. As early as 2006, it was clear that in layers III–VI of the rat MEC, a number of cells respond to head direction[187] (**Fig. 7d**), very much like the head direction cells reported in the neighboring presubiculum and parasubiculum years before[5–7,188]. The directional tuning curves of many entorhinal head direction cells were found to be broader than in presubiculum and parasubiculum, and many head direction cells responded conjunctively to location, expressing grid-like firing fields but discharging within each grid field only when the rat's face pointed in a certain direction[187]. Head direction cells intermingled with grid cells and conjunctive grid × head direction cells (**Fig. 7e**) throughout MEC layers III–VI, as well as in presubiculum and parasubiculum[189], pointing to a computational mechanism for imposing the angular component of path integration on grid cells[19,91].

Shortly after head direction cells were observed in recordings from the MEC, another cell type appeared on the entorhinal stage. These cells, named border cells, fired exclusively along geometric borders of the local environment: along one or sometimes several walls of the recording enclosure or along the edges of a platform[165,190] (**Fig. 7f**). Border cells were distinct from grid cells—a border cell could never be transformed to a grid cell or vice versa—but there was overlap between border cells and head direction cells, i.e., some (conjunctive) border cells fired within their border fields only when the animal was running in one direction[165]. Border cells intermingled with grid cells and head direction cells, particularly in layers II and III of MEC[165], suggesting that the three types of cells interact. However, while grid cells and head direction cells seemed to be confined to parahippocampal—and not hippocampal—regions, cells with border-like firing fields were also observed in the hippocampus[191] and the subiculum[192,193], raising the possibility that firing patterns of entorhinal border cells are inherited by at least subsets of neurons in the hippocampus and subiculum[93,194], or vice versa.

Border cells are sparser than grid cells and head direction modulated cells, and they may comprise less than 10% of the local principal cell population[165], but this does not negate a significant role in shaping hippocampal–entorhinal representations. The discovery of border-like properties in several regions of the hippocampal formation confirmed, to some extent, predictions from computational models dating back to the observation that the location and shape of place fields are determined by local boundaries of the recording environment[93]. Based on this observation, O'Keefe, Burgess, and colleagues proposed a model in which place fields are formed by summation of tuning curves from upstream 'boundary vector cells', cells with firing fields tuned to the animal's distance from a particular wall or boundary in the environment[93,192,194]. Boundary-vector-like cells, with distance-dependent tuning curves, were reported in the subiculum[193], but, given the unidirectional wiring of the hippocampal circuit, these cells are unlikely to provide major input to hippocampal place cells. Such inputs might instead come from border cells in the MEC. On the other hand, border cells in MEC lack distance tuning, firing only along the bor-

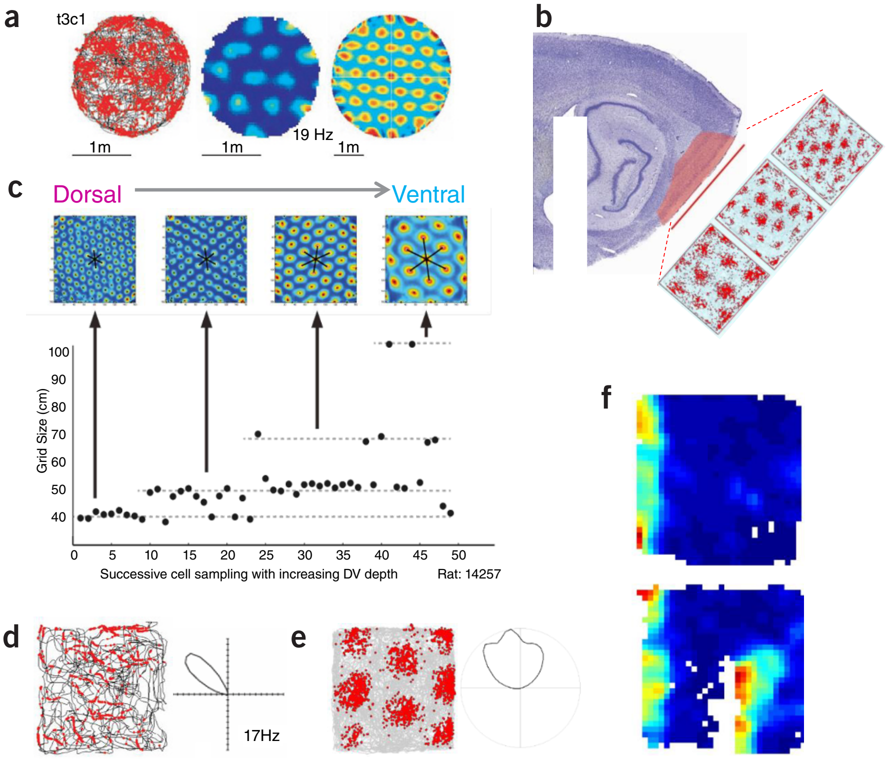


Figure 7 Grid cells and other functional cell types of the MEC. (**a**) Firing fields of one of the first grid cells reported in 2005 (ref. 9). Left: trajectory of the rat (black) with superimposed spike locations (red). Middle: color-coded rate map with peak rate indicated (red, peak rate; dark blue, no firing). Right: spatial autocorrelogram, color-coded from blue ($r = -1$) through green ($r = 0$) to red ($r = 1$). (**b**) Sagittal section of the rat brain showing the hippocampus and the MEC (red) and grid cells of different scales recorded at three locations on the dorsoventral axis (trajectories with spike locations as in **a**). Note the expansion of grid scale from dorsal to ventral MEC. (**c**) Grid cell modules[154]. Top: autocorrelation plots showing grid patterns at successive positions along the dorsoventral axis of MEC. Bottom: grid size, defined as the distance between grid vertices, as a function of position along the dorsoventral MEC axis (positions rank-ordered). Note that the increase in grid size is not linear but discretized, following a geometric order with a factor of approximately $\sqrt{2}$. Mean grid size for each module is indicated by stippled lines. Such modularization is an essential prediction of the attractor map theory if it is to account for variable spatial scaling[91]. (**d**) Head direction cell in layer V of MEC. (**e**) Conjunctive grid × head direction cell in layer III of MEC. (**f**) Border cell[165]. Color-coded rate maps showing a cell with selective firing along one of the walls of the recording environment. Top: open environment. Bottom: rate map following the insertion of a wall. Note that the border cell responds to the same side of the wall insert as the main wall in the environment. Panel **a** reproduced with permission from ref. 9, Nature Publishing Group. Panel **b** adapted with permission from ref. 91, Nature Publishing Group. Panel **c** adapted with permission from ref. 154, Nature Publishing Group. Panels **d** and **e** adapted with permission from ref. 187, AAAS. Panel **f** adapted with permission from ref. 165, AAAS.

ders and not away from them. If border cells provide input to place cells, their influence might be limited to cells with firing fields in the periphery of the recording enclosure, near boundaries and not in open spaces. There is some indirect evidence for this possibility as, in juvenile rats, place cells with fields in the center of an open recording environment mature at the same slow rate as grid cells[195], which acquire adult-like hexagonal symmetry only late in juvenile development[183,184]. Place cells near the borders of the recording box appear at an earlier age, similarly to entorhinal border cells[196]. Regardless of whether border cells fulfill criteria for boundary vector cells or not, the existence of border cells, as well as the strong asymmetries in grid patterns caused by environmental boundaries[157,158], point to a significant role for boundaries in defining the location of firing in place cells and grid cells, consistent with behavioral studies identifying geometry of the environment as a determinant of the animal's perception of self-location[13,197,198]. However, these observations are not at variance with a path-integration-based account of spatial firing of grid cells. Boundaries may serve as references for path-integration-based position estimates, with resetting of the path integrator and subsequent reduction of error taking place regularly near major boundaries or landmarks[19–21,90]. The increased variability of grid field locations in open spaces compared to locations near the walls[199], as well as the instability of place fields in open spaces when spatially stable information is available only from border cells[195], speak in favor of a reference function for environmental boundaries, where grid and place representations are reset and corrected from drift each time the animal encounters a salient boundary.

With the identification of head direction cells and border cells, it became clear that grid cells have local access to directional information, needed for the angular component of path integration, as well as to information about the geometry of the environment needed to prevent drift in the path-integrator coordinates. Head velocity signals upstream of head direction cells, in the lateral mammillary nuclei[200] and further upstream in the dorsal tegmental nuclei[201,202], might enable head direction cells to infer direction at the timescale of behavior. However, if grid cells express path integration, they must also have access to information about moment-to-moment changes in the animal's speed. Such information was known early on to be present in the hippocampus, where both place cells and fast-spiking interneurons exhibit speed tuning[30,86,203]. Speed-responsive cells have similarly been observed in subcortical areas directly or indirectly connected with hippocampal and parahippocampal regions[204–207]. These cells might feed into the brain's path-integration system. Speed tuning of hippocampal theta rhythm amplitude is sufficient to enable accurate reconstruction of distance traveled[208], and distance traveled might be decoded by integrating the net discharge rate of a population of hippocampal cells or afferents of the hippocampus.

The observation of speed coding in the hippocampus and subcortical areas motivated the search for speed information locally within the MEC circuit. By 2006 it was observed that some information about speed is present in a subset of grid cells, especially in layer III and deeper[187], but the correlations between firing rate and speed in these cells were weak and would require decoding from large cell numbers to yield a reliable momentary speed signal[166]. We now know that the entorhinal cortex has a distinct population of cells whose firing rates increase linearly with speed[166,209]. In the large majority of speed-tuned MEC cells[166], firing rates increase linearly as a function of speed, up to 30–40 cm per s in rats. A small but significant number of cells have negative speed–rate relationships[166]. As in the hippocampus, many of these are fast-spiking cells[210]. The rates of these cells are tuned so strongly to running speed that speed can be decoded with extreme accuracy from just half a dozen cells[166]. Tuning profiles (slope and y-intercept of the speed–rate relationship) vary between speed cells but remain constant across environments and persist in the absence of visual cues, pointing to speed cells as yet another component of a low-dimensional path-integration-based position map in the MEC[166]. In CA1, the gain of speed tuning varies systematically along the septotemporal axis in register with the change in spatial scale[86]. This has yet to be confirmed in MEC, but if verified it would strongly support the idea that speed cells convey the necessary information to set the grid scale.

Taken together, these observations point to a network of entorhinal and hippocampal neurons in which position, direction, and distance are encoded with sufficient accuracy to enable dynamic representation of the animal's location in an empty enclosure. However, most real-world environments differ from experimental settings, in that the available space is cluttered with objects. Salient objects may serve as references for navigation, but little is known about whether and how objects are included in the representation of self-position in the MEC. It has been shown that a subset of neurons in the LEC respond specifically at the locations of discrete objects in the recording enclosure[211,212]. These neurons increase firing whenever the animal encounters an object at a certain location, regardless of the exact identity of the object. In a subset of these object cells, firing even persists for minutes, days, or weeks after the object is removed[212]. Whether and how these cells contribute to representation of the animal's own location has remained elusive. Theoretical models from the 1990s postulated the existence of cells with place fields, defined by the animal's vectorial relationship to salient landmarks in allocentric coordinates[213], and such cells are indeed found in small numbers in the hippocampus[214]. These cells encode direction and distance from one or a small number of discrete objects placed at different locations in the recording arena. Now new data suggest that a class of MEC cells has more general vectorial properties. These 'object vector cells' have firing fields defined by distance and direction from an object, regardless of the object's location in the environment and regardless of what the object is[215]. Thus, one main difference between object vector cells in MEC and in CA1 appears to lie in their object specificity. Perhaps, like rate remapping of hippocampal place cells, the coordinate information in CA1 is inherited from MEC, whereas the identity information is added after the fact, possibly from LEC[129,130,211,212]. Like rate remapping in place cells[216], at least some of the CA1 object vector cells appear to require extended experience[214].

Finally, investigators have identified a population of hippocampal cells with activity defined by the animal's egocentric orientation to a goal location. Sarel *et al.*[217] recorded from the CA1 region of flying bats, which have hippocampal–parahippocampal spatial representations similar to that of rodents[218–220]. The investigators identified a set of cells that responded as a function of the animal's orientation toward a salient goal positioned centrally in the environment. Although the preferred orientation of the cells spanned the full 360° range relative to the direction to the goal, a large proportion of the cells in this category fired when the animal was heading directly toward the goal, ramping up their firing as the bat approached the goal. A little more than half of the cells were also place cells, but a substantial fraction did not have any significant tuning to place. Cells with essentially the same characteristics were recently reported in posterior parietal cortex[17]. Goal-vector cells are reminiscent of cells reported in rats in earlier hippocampal studies, in which neural firing increased in the proximity of a goal[73,221–225], and the finding of goal-orientation cells in both parietal cortex and hippocampus begs the question of which region is 'copying' which. Future research may determine whether similar cells are also present in the MEC circuit and whether they remap between goals and environments, like place cells, or maintain intrinsic spatial and directional relationships, like all medial entorhinal functional cell types characterized so far.

The multitude of functionally specialized cell types in the entorhinal–hippocampal space circuit is striking; however, equally striking is that many cells still express more than one type of information, particularly in the intermediate and deep layers of MEC, where many grid cells fire conjunctively for position and head direction, or position and speed, and many border cells are direction-selective[165,166,187,226]. Conjunctive cells are recognized as essential ingredients of the 'hidden layer' for almost any type of coordinate transformation or conditional association network[18,227–229]. A challenge for future work will be to determine how this variety and mixture of differently tuned cell types enable a dynamic representation of self-position that can be read out to guide navigation and memory for a wide variety of environments.

The role of theory: mechanisms of place cells, head direction cells, and grid cells

The abundance of functionally dedicated cell types in the entorhinal–hippocampal system has prompted investigators to look for the neural mechanisms that enable their characteristic firing patterns. Mechanisms have been sought in the properties of single cells as well as in neural networks. While details remain elusive, the preceding sections of this review have already emphasized how circumstantial evidence points to path-integration-based attractor-network properties as a key contributor to pattern formation in the entorhinal–hippocampal space system.

Attractor networks have provided starting points for models of localized firing since the earliest studies of hippocampal function. In 1949, Hebb proposed that activity may self-sustain in networks of recurrently connected neurons[230]. In 1977, Amari took a giant step by showing that localized firing can be maintained in networks of neurons arranged conceptually on a ring with Mexican-hat connectivity[231]. In such architecture, each neuron has strong excitatory connections to its nearest neighbors, with excitation decreasing with distance along the ring, in contrast to inhibition, which is maintained at longer distances. Almost 20 years later, Skaggs and McNaughton and colleagues[232]; Zhang[233]; and Redish, Touretzky, and colleagues[234] showed, independently, how the concept of a ring attractor with local (Gaussian) connectivity and global recurrent inhibition could be used to explain the emergence of directionally specific firing in head direction cells (**Fig. 5b**). The connectivity created a self-maintained activity bump, which could be induced to move around the ring in accordance with external angular velocity signals that were transmitted through a hidden layer of conjunctive head direction × angular velocity cells[18]. The model explained a number of features of head direction cells, including the persistence of directional phase relationships across conditions and environments. Today, more than 20 years after its proposal, the key concepts of the ring-attractor model for head direction cells remain unchallenged, which is remarkable for theoretical models in systems neuroscience, and no competing models have surfaced. In mammals, the reciprocally connected network of the dorsal tegmental nucleus and lateral mammillary area has been proposed as a location for the ring attractor[235], and in *Drosophila*, the concept of a ring attractor for directional tuning has received its first experimental support in studies of central body neurons, where a circular anatomical arrangement has been shown to

Box 1 Questions for the future

We have listed some outstanding problems in entorhinal–hippocampal space circuits that we believe can be addressed with state-of-the-art systems neuroscience tools.

1. Path-integration networks and mechanisms of grid cells and head direction cells

The performance of attractor network models for space relies on a unique and testable connectivity between functionally similar cells. With state-of-the-art tools for neural imaging, genetic tagging, and structural analysis, it may soon be possible to examine directly, in large MEC populations, the probability of connections between functionally identified neurons with various degrees of feature similarity and dissimilarity. On a longer time scale, one may hope for a direct visualization, with *in vivo* microscopy, of activity flow between connected mammalian neurons in a way that matches the animal's movement in space (similar to refs. 236,237 in flies).

2. Development of spatial network architectures

How is the specificity of the hippocampal–entorhinal spatial neural network architectures achieved during development of the nervous system? Excitatory neurons from the same radial glial progenitor are known to have stronger interconnections than other cells[266,267]. Might such connectivity between clonally related cells underlie a possible preferential coupling between MEC cells with similar spatial or directional tuning, in the same way that cells from the same clone exhibit similarities in orientation preferences (and possibly preferential coupling) in the visual cortex[268,269]? Does the young MEC have a topographically arranged teaching layer, with connections between clonally related cells, that during early postnatal development gives way to the largely nontopographical[9,270] grid cell network of the adult MEC (Fig. 8 of ref. 91)? Tools have been developed for targeted analysis of the functional identity and connectivity of discrete developmental cell populations, allowing these questions to be resolved in the near future[271].

3. Including the entire entorhinal–hippocampal circuit

A key objective for a more complete understanding of entorhinal–hippocampal function will be to determine how cell types with different functional correlates map onto the variety of morphological or neurochemical cell types and their unique connectivity patterns. Recent data suggest that, in layer II of MEC, both stellate and pyramidal cells can be grid cells, although stellate cells may comprise the majority of them[256,257,272–275]. If so, are grid patterns created independently in these two cell classes, or does one of them inherit the grid from the other?

4. Read-out

Position can be decoded from grid cells and place cells, with greater accuracy in grid cells than place cells if the population is multimodular and scaled in particular ways[159,173,174,276]. Whether neural circuits decode information in the same way remains to be determined, however. Do neurons have access to grid cells with different phase relationships or different spacing; do they integrate information from grid cells with information from border cells or head direction cells? If so, where are these neurons and how do they communicate with neocortical regions involved in strategy formation and decision-making? Most research on the mechanisms of spatial coding in hippocampus has focused on the nature of the inputs that contribute to it, and less is known about the impact of hippocampal output on coding dynamics in the widespread regions of neocortex and other areas to which the hippocampal formation projects. The impact of outputs from the entorhinal–hippocampal circuit will perhaps constitute a new frontier in the study of this system.

5. Moving toward naturalistic environments

Natural environments are large, three-dimensional, compartmentalized, nested, and full of objects. Ultimately, studies of the hippocampal–entorhinal circuit should explore how cells map environments of shapes, sizes, and content more comparable to the animal's natural habitat[277]. Are grid cells, head direction cells, and place cells used only for local mapping, in the range of a few meters, or is the entorhinal–hippocampal network used also for extended spaces, and if so, how? Is there a single continuous map, or are there different maps for different local spaces, as proposed by theoretical studies[278], as well as observations in compartmentalized laboratory environments[156]? If the latter is true, how are the map fragments connected? And how is space coded in large and three-dimensional environments[277]? In flying bats, place cells have spherical firing fields[279] and head direction cells are tuned to all three axes of orientation[220]. Whether such volumetric coding extends to terrestrial animals remains unsettled, although experimental data suggest that, in rats, head direction is encoded not only by classical azimuth-sensitive head direction cells but also by cells in the lateral mammillary bodies that respond to head pitch[200]. Observations in rats also suggest that the tilt of a surface is factored into hippocampal and entorhinal representations of space[280,281].

6. Representation of time

Understanding space and memory requires understanding time. Direct representation of the passage of time was not observed in hippocampal neurons until the Buzsáki and Eichenbaum groups showed that, when animals run for a known interval at a steady location, in a running wheel[282] or on a treadmill[283], hippocampal neurons fire successively at distinct times during the interval, following the same order on each trial. Cells with similar properties are present in the MEC[284]. Most of these 'time cells' have discrete place or grid fields in standard spatial foraging tasks. Different assemblies and sequences of hippocampal time cells are active in different task configurations[283], suggesting that hippocampal ensembles encode temporally organized information much the same way they represent space. The observation of time cells is a provocative finding that may share properties with mechanisms underlying path-integration-based representation of location, but the temporally confined firing fields of time cells do not disappear when time and distance are decoupled by restraining

(continued)

Box 1 (continued)

the animal[285] or changing the speed of the treadmill[286], suggesting that sequences do not exclusively reflect the number of steps at the task location. Certainly the relationship between representations of space and time and the role of time cells in perception and recall of time require further study. While time cells have firing fields in the order of a few seconds, and assemblies of time cells can represent events at the scale of tens of seconds, encoding of longer temporal distances may require different mechanisms. One may speculate that the spontaneous drift over hours and days in the firing properties of place cells in CA2 and (to a lesser extent) CA1 (refs. 287–289), as well as cell populations in LEC[290], may possess the power to encode temporally distant events as distinguishable memories.

7. Beyond physical space

Do grid cells and other spatially modulated cells encode information beyond physical space, as suggested by O'Keefe and Nadel[65]? Evidence for such an extension of functions was reported recently in a task in which rats press a lever to alter the frequency of a sound on a continuous scale; in this experiment, hippocampal and entorhinal cells display frequency fields resembling place fields during navigation of physical space[291]. Further functional expansion might be expected in primates. Indeed, in monkeys, hippocampal and entorhinal cells fire in patterns defined not by the animal's location in space but by where it moves its eyes on a visual scene[255,292,293]. This observation raises the possibility that place and grid cells create a map of visual space using eye movement signals instead of locomotor information to support coordinate transformation, without having to change any other computational elements of the circuit. In humans[294,295], grid cells may take on functions in conceptual mapping[296]. The possible adoption of grid cells as a metric for navigating abstract spaces would be consistent with the idea that hippocampal circuits first evolved for representation of space and later acquired the capacity for imaginary navigation[49,65,297,298]. This expansion of functions would be reminiscent of the way cortices originally involved in object recognition formed the basis for a visual word form area during the evolution of written language processing in the human cortex[299].

underlie firing in neurons that represent orientation relative to landmarks[236,237].

Only a year after the introduction of velocity-driven ring attractors to models of head direction cells, it was acknowledged that a similar integration mechanism might apply for position mapping in two dimensions, as expressed in hippocampal place cells[19,90,233,238,239] (**Fig. 5c**,**d**). In the position version of the model, neurons were arranged conceptually according to their location of firing in two-dimensional space. A matrix of recurrent connections was generated, in which excitation decreased with the distance between neurons on the sheet. In combination with global inhibition, self-excitation between similarly tuned cells maintained localized firing. A path-integration mechanism moved the activity bump across the network in accordance with the animal's position in the environment, using conjunctive head direction × place cells, in the same way that angular velocity inputs moved the bump in the ring attractor for head direction cells. The model was proposed to apply for any neural architecture of the hippocampal system, but with the knowledge that existed in the 1990s, the implementation was focused on area CA3 of the hippocampus. This explained a number of properties of place cells but faced one major challenge: the subset of active hippocampal neurons remaps across environments and circumstances[71,100–102]. For position to be computed in place cells, some sort of independent architecture for each environment would then be required. This is computationally possible[90,240] but nonetheless raises the question of whether a single network matrix, expressed in all environments, would not be more efficient[21,239]. A few years later it became apparent that such low-dimensional architecture exists in the entorhinal cortex.

When grid cells entered the research arena in 2005 (ref. 9), it was quite obvious that the dynamics proposed for localized firing in place cells might take place also in parahippocampal regions[91,151,239], as alluded to already by Samsonovitch and McNaughton[90]. In the first models proposed after the discovery of grid cells[91,151], cells were arranged on a matrix according to the phase of the grid. A bump of activity was formed when cells with similar phases were connected through excitatory connections, in the presence of global inhibition. Competitive network interactions led to multiple activity bumps[151], or toroidal connectivity caused a single bump that returned periodically to the same location[91]. Under certain conditions, in the presence of tonic excitatory input, a radius of inhibitory connectivity was sufficient to generate hexagonally patterned firing, without intrinsic excitatory connections[241–244].

Whether a path-integration-based attractor-network architecture exists in MEC remains to be determined, but there is indirect evidence for this possibility. First, correspondence between movement and displacement on the neural sheet can only be maintained so long as the participating grid cells have a common scale and orientation. Grid cells exist at a range of scales, suggesting that, to maintain the correspondence, grid cells must be organized in functionally independent grid modules, all with their own spacing and orientation[91,172]. Experimental evidence suggests that such a modular functional organization is indeed present[146,154]. A second observation consistent with a path-integration-dependent attractor architecture is the maintenance of a single grid-phase structure across environments, tasks and brain states[145,163,168,169], which would be expected if MEC neurons are organized as strongly interconnected networks in which external inputs recruit the same subset of neurons under a wide range of starting conditions. The strongest prediction of the attractor models, however, is perhaps that grid cells with similar grid phases have enhanced connectivity. Statistical analysis of firing patterns in simultaneously recorded grid cells confirm this prediction[245,246], but direct measurements of connections between functionally verified cell types are still missing.

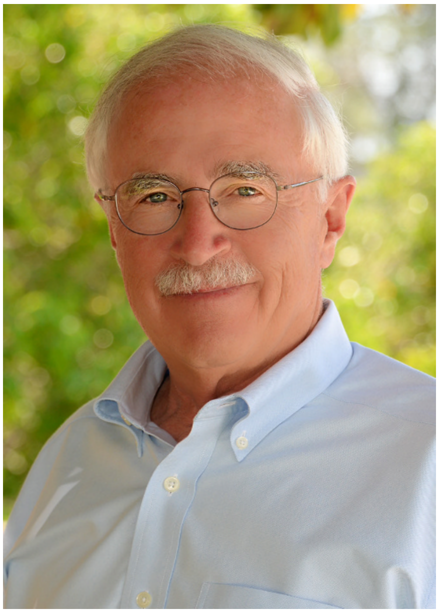
Attractor models do not provide the only possible explanation of how grid patterns might be created. For several years, a competing class of models, based on properties of the hippocampal theta-frequency network rhythm[60–62], suggested that grid patterns were generated as a result of wave interference between a constant global theta oscillation and a velocity-controlled cell-specific theta oscillation[247–250]. The model can be traced back to O'Keefe and Recce's observation, in the early 1990s, that, as animals move through the place field of a place cell on a linear track, the spike times of the cell move forward across the cycle of background theta oscillations[251]. As the animal moves through the field, the theta phase of the spikes moves progressively forward also in space, and is in fact more strongly correlated with location than with time[251,252]. This observation suggested to O'Keefe and colleagues that position could be calculated from the interference pattern between the global theta rhythm and a velocity-dependent oscillator specific to the cell. If position reflected peaks of the interference pattern, however, the firing positions should be periodic, which, for place cells, they were not. With the discovery of grid cells, the model was instantly revised and grid patterns were suggested to emerge from interference with velocity-controlled oscillators controlled by the projection of velocity in three directions separated by 60° intervals onto three separate dendrites[247–249]. Interference with the global oscillator led to a band-like spatial-activity pattern along each orientation, and the combination of bands led to a hexagonal pattern. The oscillatory interference models guided some of the most influential studies of grid formation, but in the end, accumulating evidence, such as the biophysical implausibility of independent dendritic oscillations[253], the sensitivity to period irregularity[254], the persistence of grid patterns in the absence of theta oscillations[219,255], the presence of a ramping depolarization, and the absence of a theta interference oscillation, in intracellular recordings from MEC cells[256,257], suggested that oscillatory interference is not the mechanism of the grid pattern. Yet phase precession is a reliable observation. Although it may not explain periodicity in grid cells, phase precession causes sequences of place cell activation to be replicated, in compressed format, within individual theta cycles, an effect that may be used by hippocampal circuits to store temporal sequences in addition to mere locations[252]. Indeed, as recognized by several investigators soon after phase precession was discovered[252,258,259], theta rhythm and phase precession may exist precisely to enable memory for spatial and temporal sequences.

The evidence against the oscillatory-interference model did not, however, rule out single-cell properties as determinants of the grid pattern. Kropff and Treves[24] showed how hexagonally patterned firing may arise through competitive Hebbian plasticity in a path-integration-independent manner in feedforward networks in which neurons undergo neuronal fatigue or adaptation. Because the emergence of grids in this model required many iterations, it was proposed that the adaptation mechanism contributed particularly to development of the network in young animals and that the coherence of phase and orientation relationships across environments was the result of recurrent connections that were added as the cortex matured[260]. Thus, competitive Hebbian plasticity offers an alternative mechanism for grid formation, although this mechanism may coexist with attractor-network architectures[261]. Regardless of mechanism, accounts of grid formation must consider not only intrinsic MEC dynamics but also how external inputs from the hippocampus[242], the medial septum[181,182], and locomotor[204–207,262] and head direction circuits[263] contribute to the emergence of grid patterns (**Box 1**).

Perspective

The search for a hippocampal positioning system began with the discovery of place cells in 1971. We have illustrated how the next few decades were characterized by attempts to find the determinants of spatially localized firing, with a focus on the sensory sources. As we entered the 1990s, the discovery of head direction cells and the turn to population dynamics prepared the field for more-targeted investigation of the circuit operations underlying place field formation and spatial mapping. The 1990s showed how ensembles of simultaneously recorded hippocampal neurons encoded functions that could not be read out from the activity of individual neurons. From around 2000, with increasing awareness that these ensembles likely extended beyond the hippocampus, investigators entered the entorhinal cortex, and an intricate circuit of grid cells and other specialized cell types was discovered there. The investigation of space has been brought to a new level, where it is possible to ask questions about how functions emerge through interactions within extended networks of heterogeneously connected cell types and subsystems.

While we will certainly learn more about the neural origins of spatial cognition during the years to come (**Box 1**), studies of spatial representation and navigation are informative about cortical functions in a wider sense. The ease with which spatial functions can be examined in the hippocampal formations of a number of mammals has made the study of the positioning system an area in which investigators pioneer the development and testing of sophisticated computational neural-network models. Few other areas of systems neuroscience have benefited so strongly from the interplay between computational and experimental neuroscience. Place cells and their entorhinal counterparts have helped open the cortex to studies of neural computation, allowing researchers to identify generic circuit motifs that may be expressed not only in the spatial circuits of the hippocampus and entorhinal cortex but across widespread regions of the brain. Almost 50 years after place cells were discovered, place cells and their parahippocampal counterparts have become one of the most powerful tools we have for understanding cortical computation and spatial mapping, and navigation may become one of the first cognitive functions to be understood in mechanistic terms.



Howard Eichenbaum (1947–2017). Few individuals have contributed more to the modern understanding of hippocampal memory function, with place cells as a key component, than Howard Eichenbaum, who sadly passed away, far too early, before the publication of this article. Photo credit: photographer Dan Kirksey, KDKC Photos, Escondito, CA.

IN MEMORIAM

In memoriam, Howard B. Eichenbaum (1947–2017). The field of hippocampal and memory research mourns the loss of our friend and colleague Howard, who passed away unexpectedly recently. Howard's contributions to the field were immense, both scientifically and in service. His research was mostly focused on one of the major aspects that we have explicitly not covered in this review: the role of the hippocampus in memory. Over the years, his position evolved from that of an unafraid and much-needed devil's advocate against the pure spatial map hypothesis towards what is now the general consensus view that spatial coding provides a foundation on top of which sensory and event-specific memory is superimposed, and he became a pioneer in the study of how time and temporal order also play a role. His thinking on hippocampal–cortical interactions in memory organization and control is beautifully summarized in his 2017 *Annual Review of Psychology* article[47].

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NEUROSCIENCE

CHEMOKINE—OPIOID CROSSTALK

A painful conversation

Is this map the right way up?

Navigation strategies on multiple scales

Spatial cognition in bats and rats: from sensory acquisition to multiscale maps and navigation

Maya Geva-Sagiv[1,2], Liora Las[1], Yossi Yovel[3] and Nachum Ulanovsky[1]

Abstract | Spatial orientation and navigation rely on the acquisition of several types of sensory information. This information is then transformed into a neural code for space in the hippocampal formation through the activity of place cells, grid cells and head-direction cells. These spatial representations, in turn, are thought to guide long-range navigation. But how the representations encoded by these different cell types are integrated in the brain to form a neural 'map and compass' is largely unknown. Here, we discuss this problem in the context of spatial navigation by bats and rats. We review the experimental findings and theoretical models that provide insight into the mechanisms that link sensory systems to spatial representations and to large-scale natural navigation.

> *"A journey of a thousand miles must begin with a single step."* Lao Tzu

Many animals (including humans) can navigate over thousands of miles, and yet research into the neural basis of navigation has been conducted almost exclusively in the confined spaces of laboratories. How do we find our way to far-away destinations? What are the neural mechanisms underlying our mental maps of complex, natural environments? No definitive answers to these questions exist, in part because spatial navigation and the neural encoding of space in the brain have been studied by two very different research traditions over the past century.

Research originating from the fields of ethology and ecology has examined animal navigation in the wild over large spatial scales (from tens of metres to thousands of kilometres). This approach has focused on non-mammalian species — including birds[1–3], lobsters[4], ants[5–7], honeybees[8] and sea turtles[9] — and has been limited mostly to behavioural studies, with relatively few studies of the underlying brain mechanisms[10–12]. This research tradition is dominated by the 'map-and-compass' theory of navigation[1–4,8,9,13].

In a second approach, psychologists and neuroscientists have studied the navigation of mammals — mostly rats — in mazes and small experimental arenas, and characterized the activity of neurons that might underlie their navigation. The brain area that has been most extensively studied is the hippocampal formation, which contains place cells[14–23], grid cells[24–30] and head-direction cells[28–34]. However, the link between these spatial cell types and the map-and-compass navigation strategy remains conjectural. It is unknown whether the activity of place, grid and head-direction cells, as recorded in laboratory-sized environments, is relevant to large-scale navigation and spatial memory in the real world (over kilometres). Thus, there is a fundamental conceptual gap between these two parallel approaches. This gap encompasses different experimental methodologies, different species studied, and an emphasis on natural behaviours versus highly controlled set-ups, as well as a major gap in the spatial scales studied by each approach.

Here we propose a synthesis between the two research approaches. We focus on an animal with extraordinary navigation abilities — the bat — and make comparisons with findings from laboratory rats. Bats are the only mammals that have been studied extensively using both of the research approaches described above. We consider how the bat's 'active sensing' systems (echolocation, vision, olfaction and somatosensation) shape the spatial information available to the animal, and translate this into a neural representation of space via hippocampal spatial cells. In particular, we discuss evidence that the spatial resolution of these cells is determined by the resolution of the sensory information available. We suggest that the need to orient and navigate across multiscaled natural environments[35–41] must be reflected in multiscale neural codes for space, and argue that the neural representation of large-scale space is unlikely to be a simple scaled-up

Place cells
Hippocampal neurons that become active whenever the animal traverses a specific location in the environment, called the 'place field'. The dimensions of the place field govern the spatial resolution of a single place cell; and together, multiple place cells are thought to represent a mental map of absolute (allocentric) space.

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version of laboratory-sized environments. We review recent theoretical models of multiscale neural coding[42–46] and describe the limited experimental evidence that is available to support these unconventional neural coding schemes.

Sensory perception in bats

Active sensing systems, in which an animal actively interacts with the environment to control sensory information acquisition, are widespread in the animal kingdom. Primate vision, for example, is influenced strongly by eye movements[47]; olfactory perception in both rats and humans is influenced strongly by sniffing[48–50]; and neural activity in the rat somatosensory system is influenced by whisker movements[51]. Bat echolocation (or 'biosonar') is another classical example of a mammalian active sensing system[35] (FIG. 1; BOX 1).

Echolocating bats emit brief sound pulses through their mouth or nostrils, and use the returning echoes to forage and navigate[35,52,53]. Bats compute target direction with a resolution of 2° to 3° by comparing the sounds arriving at each of their two ears[54–56]. They compute the distance-to-object by measuring the time delay between the emitted pulse and returning echo (FIG. 1a), with an accuracy of ~10 mm (REF. 57) (and can sometimes reach a super-resolution of <1 mm (REF. 58)). Several bat species use the Doppler effect to measure target velocity[59] and even to detect wing movements that enable them to identify an insect species[60,61]. Furthermore, bats use the structure of returning echoes to infer the detailed shape and texture of an object[62–66], which allows them to use trees and rocks as acoustic landmarks for navigation. Thus, echolocation provides the bat with a rich and detailed three-dimensional image of the world.

When approaching an object, bats dramatically change their echolocation pulses, in order to control the acquired image of the world (BOX 1): they decrease pulse duration and increase pulse bandwidth[67,68], which improves the accuracy of range measurements[69]; concurrently, they increase the pulse emission rate (sensory-update rate)[53,67–69]. Interestingly, many other mammalian sensory systems exhibit similar dynamics when approaching objects of interest. For example, rats increase their whisking rate when approaching an object[70–73] (BOX 1), and humans increase the rate of eye saccades when examining objects of interest[74]. In these active sensing systems, the increase in sensory update rate is thought to allow faster behavioural responses and finer object identification[53,67,68,70–74].

There are many other variables in echolocation that the bat can tightly control (BOX 1). Of particular importance for spatial perception is the bat's ability to change the sonar beam's shape and angular width, and to steer the spatial direction in which it emits the beam, both of which are used to optimize object detection or object localization[55,56,75,76] (BOX 1, see the figure part c).

Although echolocation is a primary sensory modality in most bats, it is not the only one. Indeed, because ultrasonic sounds quickly attenuate in air[77], echolocation has a limited maximal range of a few metres for small insects[78,79], and up to 100 metres for large landscape objects[78,80] (landmarks). Therefore, bats rely on other senses, such as vision, for longer-range orientation and navigation[79,81,82,83]. Indeed, many bat species have excellent vision, much better than that of rats or mice[35,84,85]. Old-world fruit bats, for example, have visual acuity that is better than that of humans at light levels equivalent to an overcast night (FIG. 1b). Moreover, in several bat species, vision provides a better angular resolution than echolocation[56,84]. These differences in sensory resolution are important when considering sensory contributions to hippocampal place cells and navigation (see below, and BOX 2).

Four additional sensory systems contribute to long-range bat navigation: olfaction[86] (FIG. 1c), somatosensation[87] (FIG. 1d), the vestibular sense[88], and magnetosensation[89–91]. Olfaction is particularly important in fruit bats, which can detect fruit-associated odours at very low concentrations[92] (FIG. 1c). Somatosensation was recently suggested to contribute to flight control, as well as to the self-speed measurement that may support 'path integration'[87] (FIG. 1d; BOX 3). The vestibular sense is crucial for intact directional coding by head-direction cells in rodents[93], and probably has a similar role in bats. Magnetosensation also contributes to bat spatial orientation and navigation[89–91]. Thus, bats possess a suite of superb sensory systems that enable them to negotiate the challenging nocturnal environment.

From perception to spatial codes

Most sensory modalities for bats and rats — vision, olfaction, echolocation (bats) and whisking (rats) — are represented in the coordinate frame of the head (egocentric coordinates); that is, sensory perception rotates with the animal's head and eyes. By contrast, spatial representation in the hippocampal formation is coded in absolute-space coordinates (allocentric coordinates). How do bats and rats transform the incoming sensory information into spatial representation, spatial memory and navigation?

Building blocks of spatial codes in the brain. The hippocampus, entorhinal cortex and surrounding regions contain four types of spatial cells thought to underlie absolute-space representation: place cells, grid cells, border cells and head-direction cells[34,94,95] (FIG. 2a).

Place cells[14,96] are hippocampal neurons that become active whenever the animal passes through a specific location in the environment, called the place field. A population of several-dozen place cells can be used to precisely read out the animal's location[15,97]. Moreover, the hippocampal circuit can store multiple maps in parallel. Thus, although a given place cell may be active in several different environments, its place field will often differ from one setting to another[98,99]. Even subtle changes in sensory input may induce remapping[99] (a change in the mental map represented by the population of place cells). Thus, hippocampal place cells can be thought of as storing a dynamic map of the external environment[100].

Grid cells, found in the medial entorhinal cortex and the pre- and parasubiculum[24,28], become active whenever the animal traverses one of the vertices of a periodic hexagonal or triangular lattice that tiles the

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Grid cells
Neurons in the medial entorhinal cortex (and some adjacent regions) that become active whenever the animal traverses one of the vertices of a periodic hexagonal or triangular lattice that tiles the environment.

Head-direction cells
Neurons found in multiple brain areas, which become active whenever the animal's head points to a specific absolute (allocentric) direction, thus providing a compass signal.

Doppler effect
The change in wave frequency for an observer that is moving relative to the wave source. For example, when an ambulance with a siren approaches an observer, a high-pitched sound (high frequency) is heard, but the perceived frequency drops when the ambulance passes and drives away. Bats know their own emitted frequency, and thus can use the perceived shifted frequency of the echo (Doppler shift) to compute the relative velocity of the target.

Magnetosensation
The ability to detect the Earth's magnetic field and use it to compute direction or spatial position. Utilizing magnetosensation for navigation purposes has been described in many animals, including some rodents and bats.

Egocentric coordinates
Coordinates that are given relative to the body axis; for example, '1 km to your left'.

Allocentric coordinates
Coordinates that are independent of the observer's orientation; for example, '1 km North of Tel Aviv'. Also known as absolute-space coordinates.

Border cells
(Also known as boundary cells.) Neurons that become active when the animal is close to a salient border of the environment, thus signalling the environmental geometry.

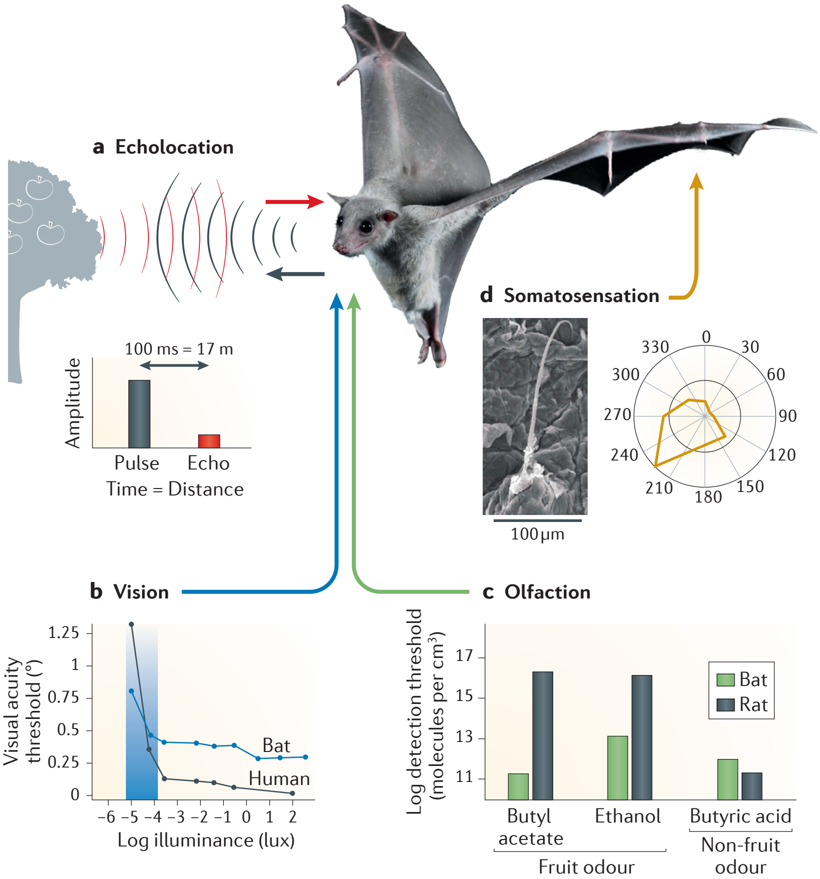


Figure 1 | **Sensory modalities of bats.** Bats use a variety of sensory modalities to orient and navigate in the environment. **a** | Echolocation provides detailed information about the distance (range), velocity, size, shape and texture of nearby objects. Target range is determined by measuring the time difference between the pulse and echo (multiplied by the speed of sound). For example, the 100-ms pulse–echo delay shown here indicates a range of 17 m (REF. 83). **b** | Vision provides information for long-range sensing and navigation[79]. The graph shows that the visual acuity of the greater Indian fruit bat exceeds human acuity at ecologically relevant low light levels equivalent to an overcast night sky (blue shaded area). Data from REFS 188,189. **c** | Excellent olfactory abilities are exhibited by fruit-eating bats, such as Seba's short-tailed bat: as shown in the graph, the olfactory detection thresholds for some fruit-related odours are up to 100,000 times better in these bats than in rats (data from REFS 92,190,191). **d** | Somatosensory abilities in bats have been neglected for many years, but recent findings demonstrate that thousands of micro-hair cells covering the bat's wings (shown in the scanning electron microscope image) enable it to detect changes in air flow, which in turn may be translated into information about its movement (air speed)[87]. Graph shows normalized directional tuning to different directions of air flow for a multi-neuron cluster in the wing area of the bat's somatosensory cortex[87]. The angle of air flow (in degrees) is indicated along the periphery and the firing rate is indicated by the distance from the centre. The image of an Egyptian fruit bat is reprinted with permission from Haim Ziv, Weizmann Institute of Science, Israel. Part **d** is adapted with permission from Sterbing-D'Angelo, S. *et al.* Bat wing sensors support flight control. *Proc. Natl Acad. Sci. USA* **108**, 11291–11296 (2011).

environment (FIG. 2a). The spatial scale of the grid can differ between grid cells: therefore, combining multiple grid cells with different scales could allow accurate decoding of the animal's position[42–45,101,102]. Thus, the mammalian brain employs two fundamentally different neural codes for representing the animal's position in the environment; the 'place code' and the 'grid code'[42–45].

Border cells, found in medial entorhinal cortex and subiculum[27,103,104], fire when the animal is located along one or several borders of the environment (FIG. 2a). These neurons may thus represent the environmental geometry and could anchor the spatial map to the surrounding borders.

Head-direction cells, found in dorsal presubiculum[31,34], anterodorsal thalamus[32,105] and multiple additional brain regions[34], become active whenever the animal's head points in a specific absolute direction relative to its environment (FIG. 2a). Head-direction cells are thought to underlie the animal's mental compass[34,106], allowing it to maintain an internal sense of direction. A directional signal is also carried by a subset of grid cells[25] and by hippocampal CA1 place cells[107].

These four spatial cell types may implement navigation mechanisms. Two of the main theories of animal navigation — the cognitive map theory[14,108] and the map-and-compass theory[2,13] — require neural mechanisms for a map and a compass (BOX 3). Place cells, grid cells and border cells may implement the neural map, while head-direction cells may function as a neural compass.

Although these four cell types (FIG. 2a) were discovered and mainly studied in rats and mice[96,109], subsequent studies established their existence in other mammalian species[110–114], and all four cell types are found in bats[23,30,114] (FIG. 2a, bottom).

Transforming sensory inputs to spatial maps. How are hippocampal spatial maps formed? Two types of information can underlie the tuning properties of hippocampal spatial neurons. The first are external sensory inputs (FIG. 1), which can be further subdivided into distal senses (such as vision and biosonar) that provide information about remote landmarks, and proximal senses (such as somatosensation) that provide information about nearby cues. The second type of information is provided by self-motion cues (for example, proprioceptive and vestibular). The integration of self-motion information (known as path integration) enables animals to compute location and direction in the absence of external cues, at least over short distances[102,115]. The contribution of path integration to short-range navigation and small-scale spatial maps in the brain has been reviewed elsewhere[102]. Over long distances, however, path integration accumulates noise and produces large positional errors[116–118] (BOX 3). Therefore, we focus here on the contributions of external sensory inputs to long-range navigation.

Most studies on the influence of sensory input on place-cell tuning have emphasized the contribution of vision. For example, rotation of prominent distal landmarks causes place fields to rotate accordingly[18,99]. Likewise, when a rectangular arena is stretched, many place fields also stretch[16]. These and similar results have led to the development of several theoretical models that describe the formation of place-tuned activity from distal sensory inputs, and make some key predictions about the transformation of sensory inputs into a cognitive map. In particular, the models have been used to consider the mechanisms that determine the location of place fields and the resolution of the map.

Box 1 | Echolocation in bats

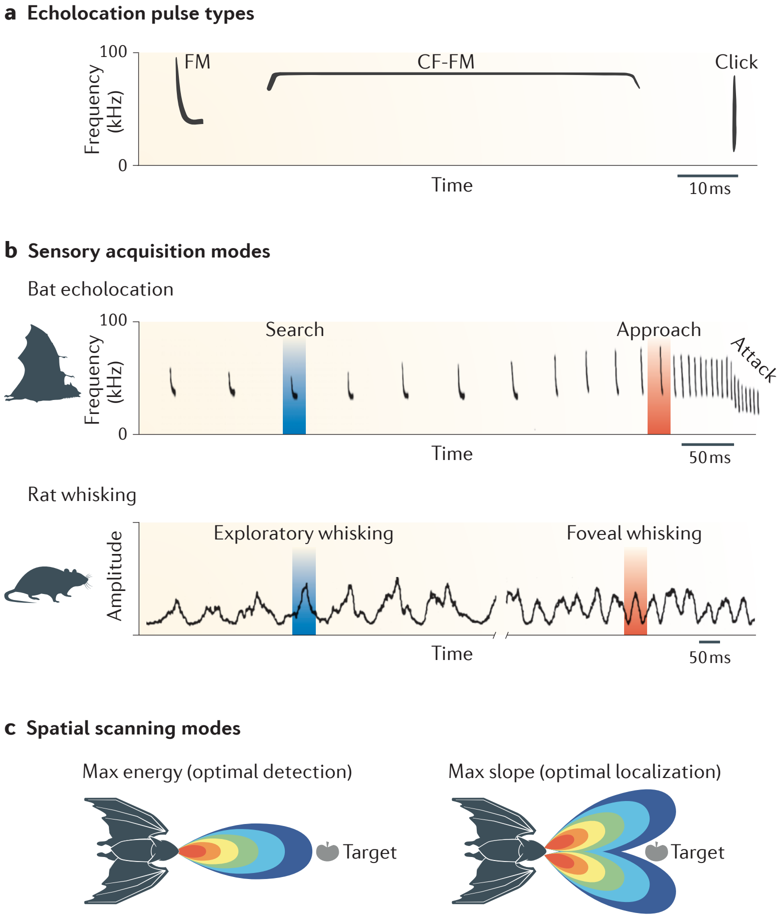
Bat echolocation pulses can be classified into frequency-modulated pulses, constant-frequency pulses, and ultra-short clicks (see the figure, part **a**). Each pulse design provides specific signal-processing advantages that match the bat's foraging strategy and habitat[53,165]. Bats can rapidly change their pulse design to optimize sensory acquisition[35,53,166,167]. Researchers have defined three phases of bat echolocation (see the figure, part **b**): the 'search phase' (which in the absence of targets, optimizes detection); the 'approach phase' (which localizes a target, enabling approach); and the 'attack phase' (or 'terminal phase'; which occurs just before reaching the target). The transitions between phases are characterized by a dramatic increase in the pulse emission rate (thus providing a higher temporal resolution when manoeuvring towards a target), an increase in the pulse bandwidth (which improves the resolution of range measurement[69]), and a decrease in pulse duration (which avoids temporal overlap between emitted pulse and received echo, thus preventing auditory masking[53,165]). This transition illustrates a classical trade-off. The long, low-bandwidth pulses of the search phase provide more energy for the auditory system's narrow-frequency filters and are thus ideal for target detection at longer distances[53,165]. By contrast, the high-bandwidth approach pulses are ideal for target localization, at the expense of detection range. Thus, bats rapidly change their perception of the world from a blurry long-range acoustic image to a sharp yet short-range image.

There are several parallels between the active-sensing systems of bats, rats and other mammals. Many of these sensory systems, including bat echolocation, rodent whisking and sniffing, and primate eye saccades, are rhythmic[48–50,70–73,168], and these sensory-acquisition rhythms occur broadly around the 'theta' frequency band (4–11 Hz)[48–50,53,67,70–73,78,168]. Similarly, many active-sensing systems exhibit an increase in sensory update rate (such as an increase in rat sniffing or whisking rate) near objects of interest[70] (see the figure, part **b**). Moreover, rats change the dynamics of individual whisks[71–73], perhaps analogous to the changes in pulse shape exhibited by bats[53,67,68].

Bats can also alter pulse intensity and spectrotemporal shape, each with its own sensory trade-offs[35,53]. In addition, they widen their sonar beam when approaching a target[75], which may prevent them from losing sight of a rapidly manoeuvring insect. Several bat species also exhibit sophisticated strategies of steering their sound beams to optimize sensory acquisition[55,56,76]. For example, Egyptian fruit bats that need to detect a target under low signal-to-noise conditions direct the part of their beam containing the maximal energy towards the target, thus optimizing detection[56] (see the figure, part **c**, left). However, when localizing a target under high signal-to-noise conditions, they instead aim the edge of their beam towards the target[56] (see the figure, part **c**, right). At the edge (maximal slope) of the beam, the beam intensity changes fastest as a function of the angle to target: thus, every change in the angle to target results in the largest possible change in echo intensity, which optimizes localization (see the figure, part **c**, right; and REF. 56). The ability to switch on-the-fly between optimal detection and optimal localization provides yet another example of the bat's sensory flexibility.

The extensive literature on the mathematical theory of sonar and radar[69,169] provides a theoretical understanding of why bats change their sonar pulses. This theoretical background, together with the experimenter's ability to monitor and manipulate the dynamics of echolocation[56,58,63,76], make the bat an ideal animal model for studying spatial perception via active sensing.

In the figure, part **a**, the click is adapted with permission from Ulanovsky, N. and Moss, C. F. What the bat's voice tells the bat's brain. *Proc. Natl Acad. Sci. USA* **105**, 8491–8498 copyright (2008) National Academy of Sciences, U.S.A.; and the frequency-modulated (FM) and constant-frequency frequency-modulated (CF-FM) calls are reprinted from *Curr. Biol.* **15**, Jones, G. Echolocation R484–R488 copyright (2005) with permission from Elsevier. The figure part **b**, top, is reprinted from *Trends Ecol. Evolut.* **18**, Schnitzler, H. -U., Moss, C. F. and Denzinger, A. From spatial orientation to food acquisition in echolocating bats 386–394 copyright (2003) with permission from Elsevier. The figure part **b**, bottom, is adapted with permission, from Berg, R. W. and Kleinfeld, D. Rhythmic whisking by rat: retraction as well as protraction of the vibrissae is under active muscular control. *J. Neurophysiol.* **89**, 104–117 (2003).



One sensory-based model of place-field formation is the boundary vector cell (BVC) model, which posits that place fields are created by summing inputs from a population of boundary-sensitive cells. The firing fields of these boundary-sensitive cells create bands in the environment[16,104,119,120] (FIG. 2b), akin to those of the border (boundary) cells that were discovered later experimentally[27,103,104] (FIG. 2a). However, it is important to note that most of these experimentally identified cells fire along walls and very few actually fire at a distance from

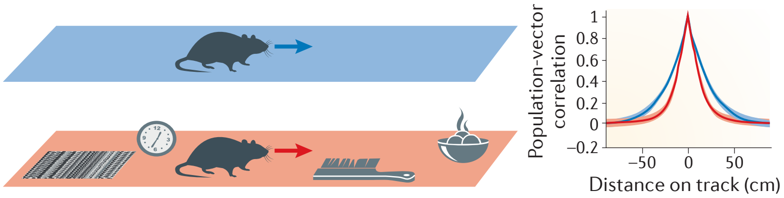
Box 2 | Sensory resolution affects spatial-map resolution

Although it is commonly thought that hippocampal place-field sizes are relatively uniform in a given environment (possibly reflecting path-integration processes that are largely independent of external sensory cues[102]), two theoretical sensory-based models for place-cell generation — the boundary vector cell (BVC) model (FIG. 2b) and the view-based model (FIG. 2c) — predict that changes in sensory resolution should affect the size of hippocampal place fields. This prediction is supported by several experimental findings in rats and bats. Two recent studies showed that rat place fields were significantly smaller when visual landmarks were present than when they were absent[171,172]. In a different experiment, rats were tested on a smooth featureless running track or on a track that contained a rich set of somatosensory and olfactory cues. Place fields were significantly smaller in the latter condition[173] (see the figure, part **a**; in the right panel, the width of place fields is indicated by the width of the population-vector decorrelation). In addition, place fields in rats tend to be smaller for locations near the walls of the arena during open-field exploration[174], which may result from the higher whisking rate near the walls[70] (BOX 1). Finally, in big brown bats, place fields are small when tested immediately after each echolocation pulse, when the animal receives rich echoic sensory information, but rapidly diffuse within a few hundred milliseconds[175] (see the figure, part **b**, for an example (left panels) and for population data (right panel) showing place-field widening after each sonar pulse). The place fields then shrink back upon arrival of a new pulse carrying sensory information[175]. All of these results are consistent with the notion that sensory resolution determines spatial resolution.

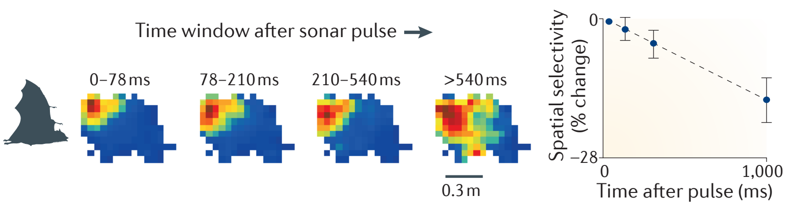
Several additional experiments in bats could test this prediction more directly. First, the sonar signal-to-noise ratio could be reduced by parametrically varying the levels of background acoustic noise. According to the BVC and view-based models, this should increase the place-field size. Second, place-field size could be examined near walls and goals, where bats use high-bandwidth sonar pulses (BOX 1), and we might therefore expect[53,69,176] smaller place-field size. Third, place-field sizes could be compared under conditions in which the bat uses pure vision versus pure echolocation. Vision in Egyptian fruit bats provides a better angular sensory resolution than echolocation[56,84]. We would therefore predict that in these bats, place fields will be systematically smaller when using vision than when using echolocation. These three proposed experiments may cleanly isolate the effects of variations in sensory resolution, and how it translates to hippocampal spatial resolution.

The figure, part **a**, right, is adapted with permission from REF. 173, Society for Neuroscience; part **b** is adapted with permission from REF. 175, © Wiley-Liss, Inc.

a Spatial coding sharpens in cue-rich versus cue-poor environments



b Place fields broaden with time after each sonar pulse



a wall. The BVC model further assumes that distances to geometrical boundaries are continuously available to the animal; an assumption that could perhaps hold true for indoor laboratory experiments, but seems less likely for rats navigating through borderless agricultural fields[121], or for bats flying at a height of 500 m (REF. 82).

A very different model — the view-based model[122,123] — takes as its input a realistic full retinal image (along with path-integration information). This, via several interconnected populations of neurons, eventually drives the firing of place cells and head-direction cells (FIG. 2c). In this model, positional and directional information are derived directly from the raw retinal image, without using any abstract geometric or landmark information or an external compass input. The model utilizes the rich information available in natural panoramic visual scenes: this makes the model relatively insensitive to specific details of the image, and thus allows robust spatial representation and navigation even in the absence of prominent landmarks[122,124]. This highlights the need to examine more closely the level of abstraction that animals use for real-life navigation: for example, one question is whether mammals use the full retinal image, as was proposed for some insects[124]. In the case of bats, could they use an analogous mechanism based on the full echoic soundscape? Or perhaps animals primarily use abstracted geometric borders or isolated landmarks?

Many animals dynamically change their sensory sampling rate (BOX 1, see the figure part b), thus altering the resolution of the incoming sensory information. Therefore, for both of these models, one question is how changes in sensory resolution would affect the size of place fields (BOX 2). This question has been addressed in the BVC model by simulations in which the sensory tuning was degraded, which led to wider BVC activity bands and, in turn, increased place-field size (FIG. 2b). For the view-based model, place-field size has been compared for high-resolution visual input versus visual input with degraded angular resolution: these simulations showed that the average place-field size increases substantially when the visual input is blurred (FIG. 2c). Thus, both of these sensory-based models predict that sensory resolution affects the size of hippocampal place fields, which in turn determines the resolution of the spatial map. This prediction is indeed supported by several experimental studies (BOX 2).

Finally, we note that spatial resolution can be improved by pooling information across neurons[15]. Thus, if specific spatial locations are over-represented by a larger number of neurons, the ensemble resolution at that location will be higher even if individual place-field sizes are constant across the arena. Non-uniform densities of place fields near 'important' locations (such as the location of hidden food rewards or the hidden platform in a water maze) were indeed found in several laboratory studies[17,125]. This might imply that navigational accuracy is improved at such over-represented locations; this prediction awaits experimental testing.

From maps to real-world navigation

So far, the spatial cells described above have been tested only in small-scale, artificial laboratory environments that are also impoverished in sensory cues compared to the natural environment. Are these cell types relevant to real-life navigation (BOX 3)?

Box 3 | **Theories of animal navigation**

Egyptian fruit bats navigate dozens of kilometres to a specific fruit tree, and return night after night to forage in the same individual tree[82]. The figure, part **a**, shows global position system (GPS) tracking of a single bat over 7 consecutive nights (flight tracks of this bat on different nights are shown in different colours; data collected using methods similar to those described in REF. 82). How do animals accomplish such navigational feats? Five main types of (not necessarily mutually exclusive) navigational strategies have been proposed[2,14,177].

Beaconing: navigation directly towards a distant sensory cue, such as a visual object, a sound, or an odour. Visual beaconing was proposed for greater spear-nosed bats in Trinidad, which use the central mountain range of the island as a beacon[81] (see the figure, part **b**). Auditory beaconing was demonstrated in big brown bats, which beacon toward the sounds of a swamp frog chorus[178].

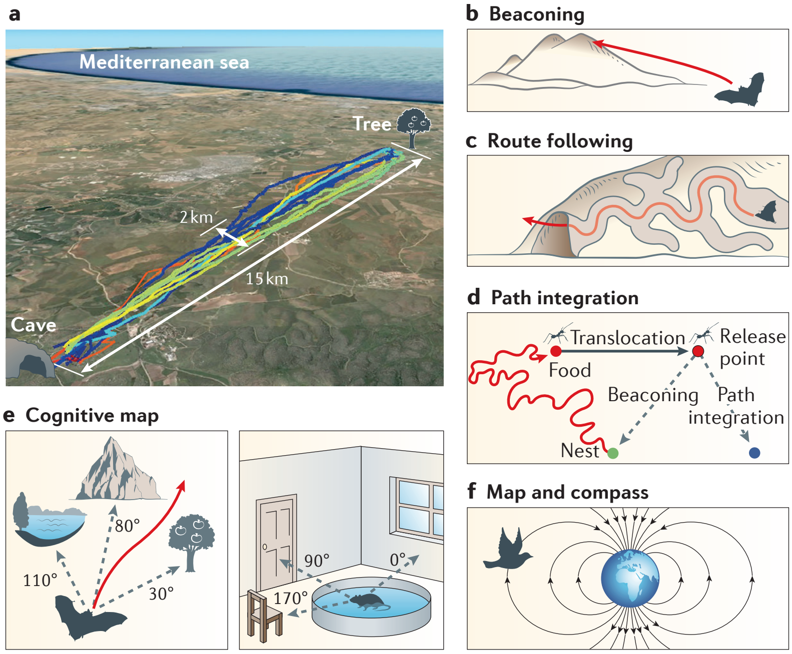
Route following (route guidance): Navigation along a complex physical route, where movement course changes at specific landmarks. This is how humans navigate when driving in cars, turning left and right at specific intersections. Bats also exhibit route-following along forest paths[165], or through complex kilometre-long underground passageways[179] (see the figure, part **c**).

Path integration: navigation based on an online computation of the present location from the past trajectory[115,180]. Path integration (also known as 'dead reckoning' (REF. 177)) does not require any external landmarks and relies only on integrating the animal's own movements. Path integration over short distances is tested by letting an animal wander away from its nest, and then translocating the animal: if it uses path integration, the animal will move directly to where the nest should have been (see the figure, part **d**, rightmost dashed line), as indeed was found in desert ants[181,182]. Notably, path integration is unreliable because it accumulates noise and produces extremely large errors within a few seconds[117,118]: behavioural studies demonstrated that when rodents forage in an arena, their path-integration may deteriorate after one 360° rotation[116,183], and fails completely after more than three full rotations[116]. Bats can path-integrate over very short distances (1–2 m)[184,185], but it is unlikely that they (or any mammal) could path-integrate over ethologically relevant large distances.

Cognitive map: a navigation strategy that relies on a mental map of the environment, which allows flexible navigation without the need to pass through familiar waypoints. This is the most sophisticated navigational strategy and seems to require the highest cognitive abilities. Cognitive map theory[14,108], originating from laboratory studies in psychology, emphasizes the need to combine self-motion (path-integration) cues with sensory information arising from multiple distal landmarks, to yield self-triangulation[14] (see the figure, part **e**). Although there have been intense debates on whether animals possess fully detailed cognitive maps[14,177,186], it is noteworthy that some of the navigational abilities of bats are consistent with a map, or a map-like mechanism over a 100-km scale. For example, Egyptian fruit bats[82] that were displaced to several release sites at different directions and distances from their cave nearly always navigated straight back to their cave or favourite fruit tree (see REF. 82 for details).

Map and compass: a navigation strategy that allows animals to return from unfamiliar release points, using either self-triangulation or stimulus–place associations that are based on universal gradients of olfactory odorants or magnetic fields[2,9,86,187] (see the figure, part **f**). The map-and-compass theory[2,13] originated from studies of bird ethology[13], and was later applied to study navigation in a variety of species[2,4,9]. Although map-and-compass and cognitive-map theories differ in the proposed sensory stimuli used, they share substantial similarities in navigational processes: in particular, both theories utilize self-triangulation, and both allow flexible navigation without the need to pass through familiar waypoints. Interestingly, homing pigeons, whose ability to return from unfamiliar areas has provided much of the experimental support for the map-and-compass theory[2], were also shown to use cognitive-map-like navigation within familiar environments[2].

Animals often use different navigational strategies in different circumstances, or even switch strategies while navigating. It remains unknown what the implications of such navigational switches are for our understanding of the neural basis of navigation.



Distal senses
Senses that provide long-range information to the animal. For rats, vision is the primary distal sense. Bats have two distal senses, echolocation and vision, when considering a small environment like a cave or a room. However, echolocation range is limited to < 100 m, so on a scale of kilometres, echolocation may be classified as proximal, while vision remains a truly distal sense. In both species, olfaction is a proximal sense in enclosed spaces (cave, burrow), but may serve as a distal sense outdoors where winds can carry odours from afar.

Proximal senses
Senses that are restricted to a short range. For rats, somatosensation (whisking) and olfaction are the primary proximal senses.

Bats possess outstanding spatial memory and navigational abilities[35]. At long ranges, some bat species migrate annually up to 2,500 km, returning year after year to the same roosting location[35–39]. At medium ranges, Egyptian fruit bats navigate dozens of kilometres to forage at the same individual fruit tree night after night[82] (BOX 3, see the figure part a); and moreover, these bats can return straight back to their cave after a 100-km translocation[82], suggesting that they possess a detailed spatial map of their environment over a 100-km range. There is evidence that Egyptian fruit bats use ultra-distal visual landmarks (such as mountains, sea, cities and factories) to visually guide this precise navigation[82]. At short ranges (metres), bats rely on spatial memory of echo-based landmarks[126], and can even remember the three-dimensional position of objects with an accuracy of 1 to 2 cm (REF. 35). Thus, bats seem to have multiple mental maps of their environment on different spatial scales.

Wild rodents also have excellent navigational abilities: they can find goals with 1-cm accuracy[127,128], and some species routinely navigate distances of several kilometres[121,129]. For example, Norway rats and jerboas have been shown to navigate every night up to 2 km away from their burrow, and back[121,129]. This suggests that some wild rodents possess a detailed mental map of their environment, and this map represents spatial scales from ~1 cm to several kilometres[121,127–129].

The question of how the brain supports this large-scale navigation remains largely unanswered. Are the principles and spatial cell types discovered in small-scale navigation applicable to large-scale navigation, or is the neural basis of natural navigation entirely different? In particular, is the hippocampal formation involved in large-scale navigation? Several studies showed that homing pigeons with hippocampal lesions exhibit deficits in homing performance over kilometres[12], and other studies reported correlations between hippocampal volume and large-scale navigational load in birds[130], rodents[131], bats[132] and humans[133]. Therefore, our working hypothesis is that the hippocampus is indeed involved in large-scale navigation. This leads to two additional questions. The first concerns the encoding of spatial information on multiple scales. Is there one mega-map of the environment, or are there many fragmented maps for different regions of space, possibly at different resolutions? That is, does the hippocampal formation contain detailed high-resolution representations for important locations but sparser representations for less important locations (FIG. 3a)? Second, how does the mammalian brain represent spatial information on very large scales (kilometres)? Laboratory-sized place fields increase with the size of the experimental environment[16,19], but can place fields scale up to 1 km or even 1,000 km, to support a real-world cognitive map? If not, what are the alternative possibilities for neural coding of very large spaces?

Spatial representation on multiple scales. Consider a bat in its cave, or a rat in its burrow. These confined environments are highly important to both animals, and hence they pay close attention to the abundant sensory cues, such as tree roots, rocks and crevices. Therefore, place fields are expected to be comparable in size to those recorded in small laboratories. Place fields recorded in ~1 × 1 m laboratory setups have a typical diameter of ~20 cm for rats[94] and bats[23,30] in one- or two-dimensional environments (FIG. 3b). However, three-dimensional place fields recorded in bats flying in a 5.8 × 4.6 × 2.7 m flight room had a ~1-m diameter[134] (FIG. 3c, top). At some point after sunset, the bat and rat will exit their roost to forage[82] (FIG. 3a). Should we expect the place fields along the bat's flyway to have the same size as the tiny place fields in the cave? This is unlikely, for several reasons.

First, it is important to consider the total number of neurons needed to tile a typical 20-km flyway (BOX 3, see the figure part a), which (at 2 km width and 500 m height[82]) has a total volume of 20,000,000,000 m^3. To cover this flyway with laboratory-sized 1-m^3 place fields[134], with a few tens of neurons overlapping at each location[15,97], would require ~1,000,000,000,000 place cells; a million times more neurons than the total cell count in the hippocampus[42,135]. This discrepancy can be fully accounted for if place fields in the middle of the flyway have a millionfold larger volume (that is, a diameter 100 times larger) than place fields within the cave: that is, a place-field diameter of 100 metres, or more.

Second, it can be argued that the bat's cave needs to be encoded at high resolution, whereas there is no behavioural need for such high resolution if a bat is flying at a ~500 m altitude with speeds of 40 to 60 km per hour[82]. In such a 'mid-air void', we might expect place fields with a size of a few hundred metres simply because the bat does not need any better resolution. Thus, different locations in the environment may be represented at very different spatial resolutions, depending on their behavioural relevance to the animal.

Third, if we consider the sensory resolution of the view-based model of place fields[122,123] (FIG. 2c) and assume a certain angular visual acuity that is determined by properties of the eye's lens and retina, then the sensory resolution is proportional to the flight altitude above ground. For example, when a fruit bat flies at an altitude of 500 m above ground[82], its visual resolution (in metres) is 100 times poorer than that obtained when flying at an altitude of 5 m. This suggests that place-field volumes at 500 m altitude should be larger by ~100^3 than when flying at 5 m altitude, which would resolve the millionfold discrepancy discussed above.

We therefore reason that the natural habitat of bats and rats is encoded by a multiscale spatial representation (FIG. 3a), reflecting both the behavioural demands and the sensory inputs available to the animal. To experimentally demonstrate such a multiscale representation would require recording hippocampal neurons in a bat or a rat moving in a very large (kilometre scale) environment that has multiple compartments of varying physical scale and/or importance to the animal. This has not been done, to date; however, some laboratory studies lend experimental support for this hypothesis. FIGURE 3b shows place-field sizes for several neurons recorded in the dorsal hippocampus of rats in different arena sizes, demonstrating that — at least in small-scale laboratory environments — place-field size scales up (somewhat sublinearly) with environment size[16,19,136,137] (FIG. 3b, right).

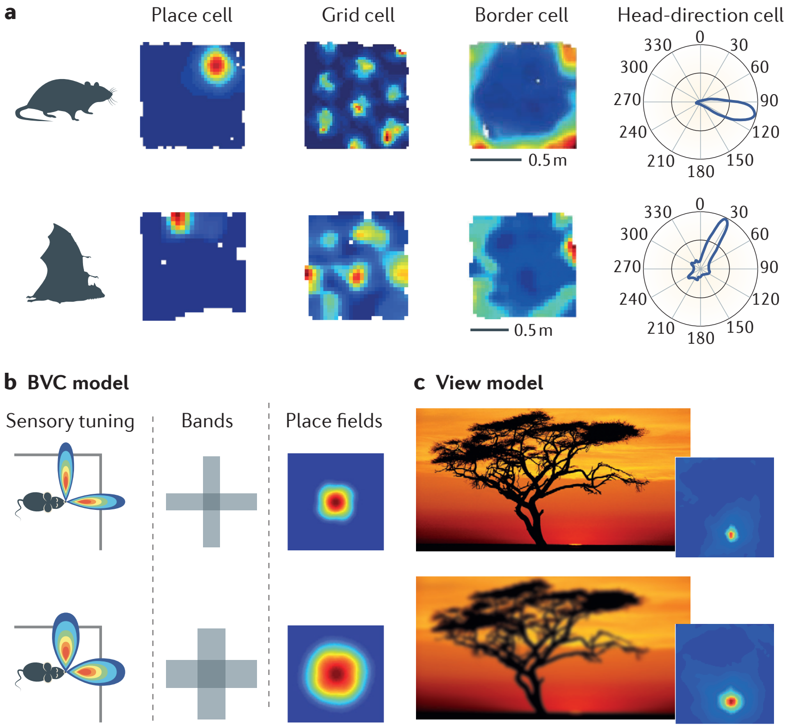


Figure 2 | **Effects of sensory input on spatial representation.** **a** | Properties of spatial cell types in the hippocampal formation of rats and bats. Recordings were made from neurons in animals exploring a square 1 m × 1 m box. Left panels show the firing rate (colour-coded from zero (blue) to maximal rate (red)) of the neuron as function of the animal's position within the box. Right-most panels show the directional tuning curve of a head-direction cell: direction (in degrees) is indicated on the periphery and firing rate is indicated by the distance from the centre. **b**, **c** | Two sensory-based models of place cells predict that degrading the resolution of the sensory input would increase place-field size (BOX 2). **b** | The boundary vector cell (BVC) model[16,119,120]. In this model each boundary cell is tuned to a specific preferred distance and direction from a boundary (left column), and the intersection of the activity bands of several boundary cells forms a place field (middle and right columns). Right panels show simulated place fields for two different sensory resolutions. These simulations used parameters as in REF. 119 but varied the values of the distance resolution and angular resolution. The place-field size for the same neuron increases substantially when the sensory resolution of the input BVC population is degraded. **c** | The view-based model[122,123]. Two images that simulate a retinal image were used as the visual input to the model: the top (sharp) image had a resolution of 500 × 180 pixels, whereas the bottom image was blurred with a 5 × 5 pixel Gaussian filter. Photographs show an example of the type of images used (other examples were used in the simulations) and inset panels show the place fields that were computed. The place-field size for the same neuron increases substantially when the sensory input is blurred. Part **a**, top, grid-cell data were adapted with permission from REF. 28, Nature Publishing Group; the border-cell and head-direction-cell data were reprinted from Solstad, T., Boccara, C. N., Kropff, E., Moser, M.-B. and Moser, E. I. Representation of geometric borders in the entorhinal cortex. *Science* **322**, 1865–1868 (2008) with permission from AAAS; and the place-cell data were adapted with permission from Whitlock, J. R., Sutherland, R. J., Witter, M. P., Moser, M.-B. and Moser, E. I. Navigating from hippocampus to parietal cortex. *Proc. Natl Acad. Sci. USA* **105**, 14755–14762 copyright (2008) National Academy of Sciences, U.S.A. Part **a**, bottom row, adapted with permission from REF. 30, Nature Publishing Group. Simulation results in part **c** reproduced with permission from D. Sheynikhovich, University Pierre and Marie Curie, Paris, France. Photographs in part **c** courtesy of © Royalty-Free/Corbis.

In addition to the scaling of place-field size according to the arena dimensions (FIG. 3b,c), there is evidence that spatial representations with different scales exist simultaneously along the anatomical dorsoventral axis of the hippocampus[19,21,138–140] (FIG. 3d). One study, conducted in rats running on an 18-m track, showed a ~10-fold increase in place-field sizes along the dorsoventral axis of the hippocampus: from ~1-m fields at the dorsal pole to ~10-m fields at the ventral pole[19] (FIG. 3d, blue dots). A somewhat smaller range of place-field sizes was found along the dorsoventral axis of the hippocampus in other studies[21,138] (FIG. 3d, green and orange dots), perhaps owing to the small apparatus sizes used in these studies and the fact that most did not record at the very ventral tip of the hippocampus[138,139]. Combining this dorsoventral 10-fold scaling with the finding that dorsal place-field sizes scale with arena size, we propose that all neurons along the dorsoventral axis scale their place-field sizes together if the environmental size changes (FIG. 3d, ellipses).

The situation with regard to grid cells seems to differ from that of place cells. On one hand, the spacing (wavelength) of grid cells in rats was shown to scale up along the dorsoventral axis of the entorhinal cortex by a factor of ~10-fold[141], with grid spacing increasing in a stepwise manner[26,142]. However, based on experiments conducted so far, the grid scale seems quite resistant to environmental changes: when the arena size is increased, grid spacing also increases[26] (possibly signalling novelty[143]) but then returns to baseline[26,143]. Thus, although grid cells exhibit multiscale representation along the dorsoventral anatomical axis[142], they are quite different from place cells in that their spatial scale seems relatively rigid and does not adapt to environmental changes, other than in a transient manner[26,143]. Therefore, grid cells might have a particularly important role in stably encoding large-scale environments.

As discussed above, over-representation of a specific region by a large number of neurons may improve the ensemble resolution at that location[15]. Therefore, we predict that in natural environments, important locations such as the environs of the bat cave or rat burrow may be represented by many more neurons than locations in mid-air or mid-agricultural-field.

Thus, multiple scales of spatial representation can be obtained by several mechanisms, or a combination of these: an anatomical gradient of spatial scales along the dorsoventral axis of the hippocampus (FIG. 3d); dynamic scaling with changes in environment size (FIG. 3d, different ellipses); and population scaling by increasing the density of place fields for important spatial locations (FIG. 3a).

Finally, another important question is how different maps are pieced together to allow smooth navigation[100,144,145]. Natural habitats contain multiple compartments, which may have different spatial scales, often without a direct line of sight between the compartments[145] (FIG. 3a), requiring some mechanism for coalescing the compartmentalized maps. One answer to this question comes from human navigation studies, which proposed that navigational strategies differ for different spatial scales[145,146], and that small spaces are navigated using independent maps, which are connected to each other through a graph[145,147]. For example, a city might be encoded as a set of cognitive maps that represent open vista spaces, such as town squares

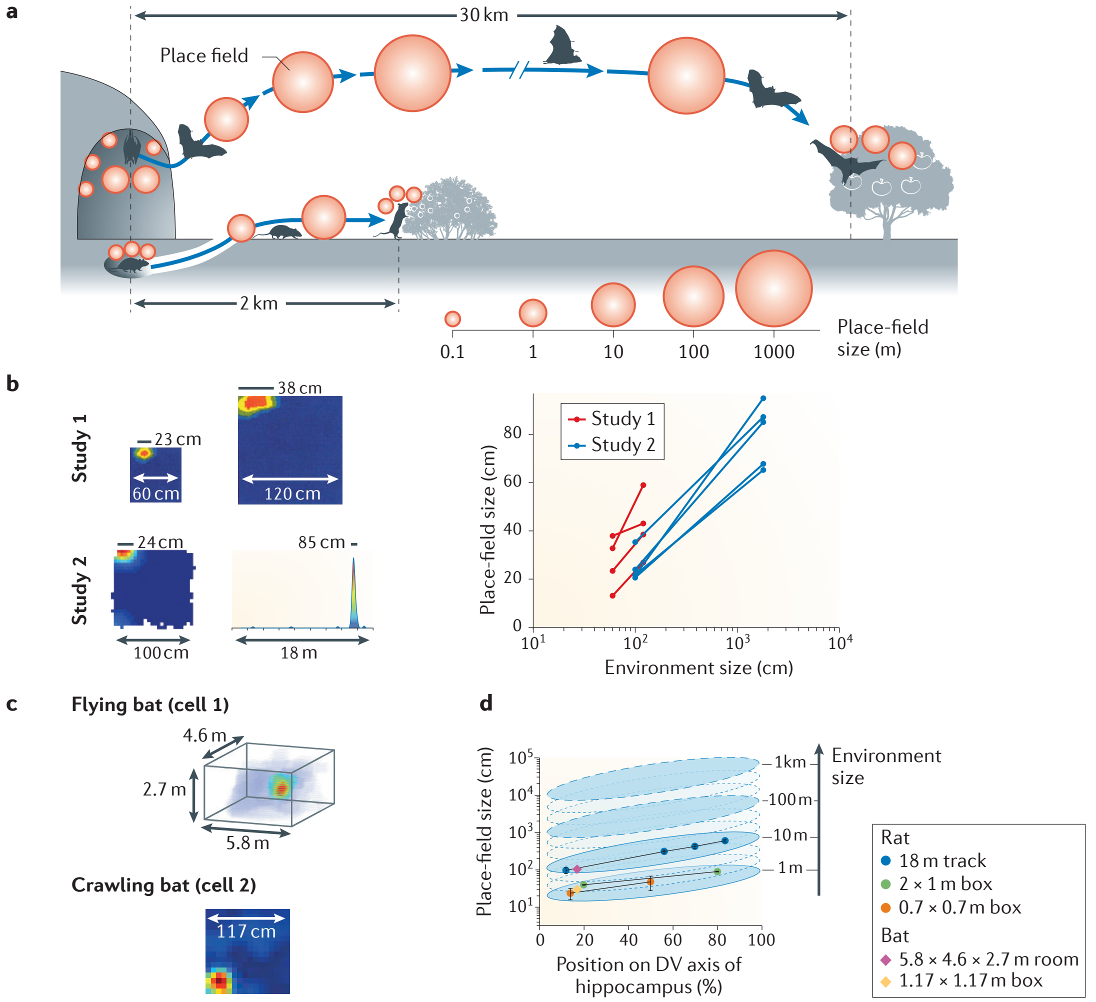


Figure 3 | **Spatial representations on multiple scales.** **a** | Hypothetical schematic showing how the home range of a bat or a rat may be represented on multiple spatial scales. We propose that there may be a higher-resolution representation (smaller place fields) for more important locations such as the cave or burrow, or the feeding tree, and a lower-resolution representation (larger place fields) at less important locations such as at a 500-m altitude in mid-flyway. **b**, **c** | Experimental data from rats and bats showing that place-field sizes of individual neurons increase when the environment's dimensions are enlarged. **b** | Left, place-field sizes of two rat cells, each recorded in two different environments: in study 1 the cell was recorded in a 60 × 60 cm box and a 120 × 120 cm box[16]; in study 2 the cell was recorded in a 100 × 100 cm box and on an 18-m linear track[19]. Right, changes in place-field size in all individual cells for which data are available in each study[16,19]. **c** | Examples of place fields in bats. Top panel, example of a three-dimensional place cell recorded from dorsal hippocampal area CA1 of a flying bat[134]. Bottom panel, example of a two-dimensional place cell recorded in a crawling bat[30,107]. **d** | The spatial scale of the hippocampal representation increases along the anatomical longitudinal axis of the hippocampus. Data shown are population average place-field sizes from a variety of published hippocampal recordings in rats and bats, taken from various dorsoventral (DV) positions; error bars depict mean ± SEM (except the green dots, in which case medians are shown; for two- or three-dimensional place fields, the field size was averaged across dimensions). Data are from REFS 19,21,30,134,138. Neurons near the ventral (temporal) pole of the hippocampus have larger place fields than neurons near the dorsal (septal) pole; the increase in spatial scale along the dorsoventral axis is approximately 10-fold. This anatomical gradient of spatial scales is illustrated by the ellipses, depicting the place-field size versus the dorsoventral position. In addition, the place field of the same neuron also increases with environment size, illustrated by the vertical shift between the different ellipses, with each ellipse corresponding to the larger place fields in the larger environment. We speculate that these relations, as encapsulated by the two bottom coloured ellipses (solid lines), will hold over a continuum of environmental sizes (dotted ellipses), including for very large-scale environments, for which no experiments have been conducted to date (see the uppermost two coloured ellipses with dashed lines). Part **b**, top place-cell example is adapted from REF. 16, Nature Publishing Group; and bottom place-cell example is from Kjelstrup, K. B. *et al.* Finite scale of spatial representation in the hippocampus. *Science* **321**, 140–143 (2008). Reprinted with permission from AAAS. Part **c**, top place-cell example is from Yartsev, M. M. and Ulanovsky, N. Representation of three-dimensional space in the hippocampus of flying bats. *Science* **340**, 367–372 (2013). Reprinted with permission from AAAS. Part **c**, bottom place-cell example is adapted from REF. 107, Society for Neuroscience.

Dorsoventral axis of the hippocampus

The hippocampus of rats and bats is an elongated, banana-shaped structure, and its long axis is referred to as the dorsoventral axis (or septotemporal axis). Place fields increase in size approximately 10-fold along this axis.

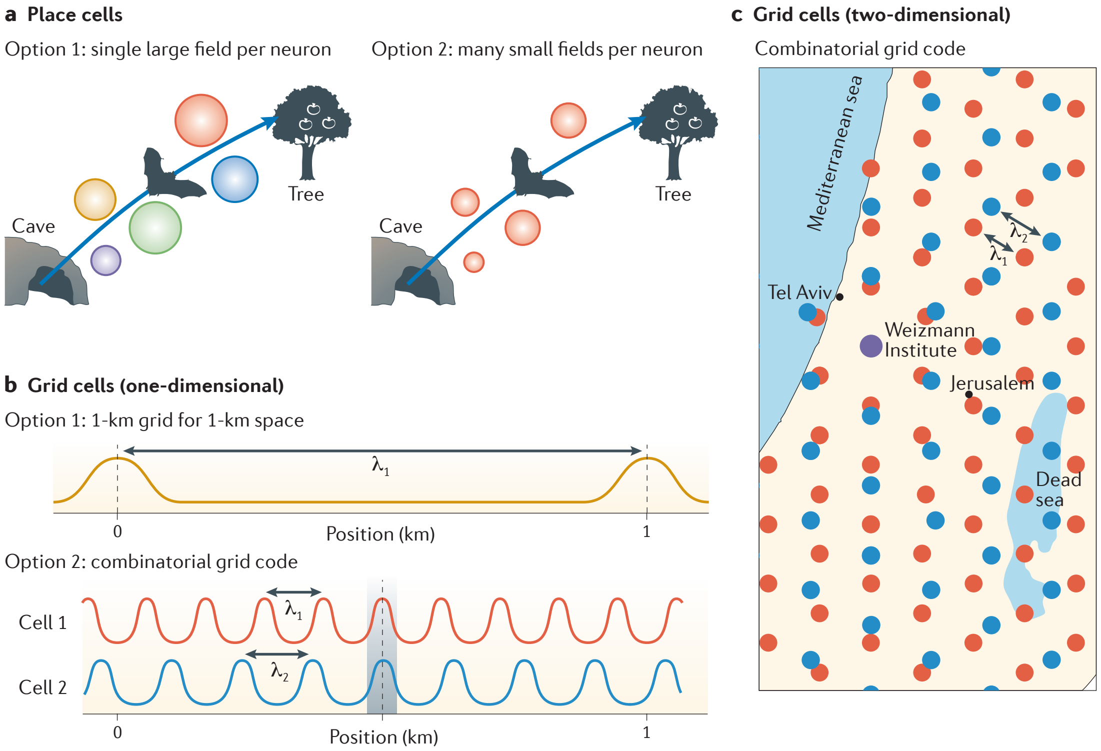


Figure 4 | **Models of large-scale spatial codes.** **a** | Schematic depiction of two options for the representation of a 1-km space by hippocampal place cells. Option 1 is based on scaling up results from the laboratory: it proposes that each neuron might have one large place field (represented by coloured spheres), with field size scaled up to match the environment size. Option 2 is based on laboratory experiments[136] and on a recent theoretical study[46]; the latter study suggested that it may be beneficial, from a decoding perspective, to have dozens of small place fields for each neuron, in order to have more neurons covering each spatial position. This is indicated by all place fields being shown in the same colour (belonging to the same neuron). Combinations of options 1 and 2 are also possible (for example, multiple fields per neuron, with each field having a different size, according to the importance of each location). **b** | Schematic depiction of two options for the representation of a 1-km space by entorhinal grid cells. Option 1 is based on dorsoventral scaling results from the laboratory, suggesting that grid sizes up to 1 km will exist in a 1-km environment. Option 2, as suggested by several recent theoretical studies[42–45], suggests that the animal's position could be encoded by combining grids with different scales, allowing the brain to encode very large spaces using much smaller grid scales[42–45]. In the illustrated example, the two periodic functions represent two grid cells with periods λ_1 and λ_2 slightly larger than 100 m; and these functions coincide only at position = 0.5 km (grey shading): that is, their unambiguous coding range is >1 km (REFS 43,44). **c** | Schematic of a grid code in two dimensions. This illustrates the same concept as in part **b** (option 2) but adapted to two dimensions. The activity of two hypothetical grid cells (red and blue hexagonal grids, with periods λ_1 and λ_2) is shown here overlaid on a map of Israel. The two grids coincide only at one location: The Weizmann Institute of Science, Israel.

and large intersections, which in turn are connected to each other by a network of streets that create a cognitive graph[145–147]. It would be of great interest to search in the hippocampal formation of bats and rats for a neural correlate of such a 'cognitive graph of cognitive maps'.

Computational models of large-scale spatial codes. Spatial scales in the real world span 8 orders of magnitude for a bat — from 1 cm to over 1,000 km — whereas the dorsoventral gradient of place-field sizes in the hippocampus covers only 1 order of magnitude. Similarly, for wild rats, which can navigate several kilometres[121], the dorsoventral gradient is also four to five orders of magnitude too small to support the huge dynamic range of spatial scales that are behaviourally relevant for rats. How does the brain cope with these extreme gaps?

For hippocampal place cells, there are two possibilities (FIG. 4a). First, in very large environments, each neuron might have a single large place field. Second, as proposed in a recent theoretical study[46], place cells in very large environments may have dozens of small place fields per neuron. This would increase substantially the number of neurons that are active at each spatial location and hence encode the animal's position much more precisely[46]. In contrast to the common view, which suggests that one place cell typically has one to two fields[94], this 'multiple fields hypothesis' offers a radically different neural coding scheme: it requires downstream decoders to be much more sophisticated than currently thought. This is akin to proposing that, under natural conditions, V1 visual neurons should have dozens of receptive fields, rather than just one.

Combinations of these two options are also possible. For example, a single place cell may have dozens of place fields, which may vary in size according to the availability of sensory inputs and the importance of different locations. Thus, all of the place fields depicted along the bat's flyway or rat's runway in FIG. 3a may in fact belong to a single hippocampal place cell.

Place-cell recordings are yet to be conducted in kilometre-sized environments, but data from multiscale laboratory experiments so far support both of these possibilities. In one experiment, in rats running on an 18-m linear track, very large place fields of 6 to 10 m were recorded in ventral hippocampus, but each neuron typically had a single field[19]. In another experiment, when an open-field arena was suddenly increased in size, neurons exhibited multiple place fields in the larger arena[136,137]. Multiple fields were found also in rats running on a 48-m zig-zagging track[148] (although the number of fields in that experiment may have been boosted up by the large number of sharp corners on the track, eliciting multiple remappings[149]). In a fourth experiment, conducted in bats (FIG. 3c, top), three-dimensional hippocampal neurons recorded in a larger environment tended to exhibit both a slightly larger number of fields and a larger field-size than those recorded in a smaller three-dimensional environment[134]; consistent with both options. It remains to be seen which of these possibilities holds true in kilometre-sized environments.

In terms of grid cells, there have also been two main proposals (FIG. 4b). First, the largest grids could match the environment size, that is, a 1-km environment will have grids with a 1-km wavelength. A second, very different possibility was recently proposed by several computational studies[42–45], which suggested that two grids with different scales could combinatorially represent a coding range that is much larger than the individual grid wavelengths[42–45] (FIG. 4b, bottom). Although a single grid cell encodes space with a cyclical ambiguity, the combination of two or more grids with different wavelengths — through readout of cells from different grid modules, for example[142] — allows for the coding of space unambiguously within the coding range[42,43]. Furthermore, these theoretical studies demonstrated that this 'combinatorial grid code' produces a highly precise estimate of position, which is exponentially efficient in terms of the number of neurons involved[44,45]; the first example of an exponential neural code proposed for any brain function[44,45].

The combinatorial grid code could be potentially extended to two dimensions, and to very large environments. FIGURE 4c shows how combining two two-dimensional grids with wavelengths that are much smaller than the state of Israel can unambiguously represent a coding range the size of the entire state of Israel. Whether such combinatorial grid codes exist in real brains remains an open question. Although a common view is that grid cells are used primarily for path integration[102], the combinatorial grid code hypothesis proposes that the function of grid cells is to efficiently encode very large environments[42–45] (FIG. 4c). A major challenge for behavioural neuroscience in coming years will be to determine which of these possibilities (or both) captures best the basic function of grid cells.

The need for a neural theory of real-world navigation. We described above the need for mental spatial maps on multiple scales, and discussed experimental results from small environments and theoretical ideas about how these maps may generalize to larger spatial scales. A major open question is how such maps might be used in the process of navigation. The key problem is that place cells, grid cells and head-direction cells (FIG. 2a) may represent a neural map and compass (BOX 3) but are insufficient to navigate from point A to point B. Navigation requires much more than knowing where you are and where North lies: it entails trajectory planning, motor coordination, and decision making at navigational choice points. How does the brain accomplish this? One mechanism that was proposed involves route cells and goal-directed cells, found in the posterior parietal cortex[150–153]. Some of these cells fire along most of the route as a rat navigates in a complex laboratory maze[150]. Route-related codes also exist in the hippocampus itself, where some place cells encode also the future path of the animal[154]. Moreover, ensembles of hippocampal neurons can accurately preplay future trajectories of the animal over distances of 1 to 2 m (REFS 97,155). These studies have been reviewed elsewhere[95,156,157], and may form the starting point for constructing a comprehensive neural theory of real-world navigation (BOX 3).

Future directions

In this Review, we have discussed the neural basis of real-world navigation, focusing on bats and rats as key models. We described some ideas that were proposed for the transformation of incoming sensory information into hippocampal spatial maps, which are used in turn for navigation. We highlighted two key problems. First, there is a requirement to represent very large environments in order to perform real-life navigation. As discussed above, some recent models have proposed fundamentally different views on how very large outdoor environments may be represented in the brain's navigation system. Second, there is a need for multiscale spatial maps that can dynamically adjust their scale to match the variable size of the environment and the changes in behavioural needs. This 'dynamic matching' process seems to be implemented by place cells, but not by grid cells (at least according to the data available to date).

Two further issues are noteworthy here. First, it is possible that laboratory-born animals, which have never experienced 1-km environments, may not display 1-km place fields. Therefore, experiments that aim to test large-scale (kilometre-sized) spatial representations in the mammalian brain should use wild-born rodents, bats or other mammals that have experienced large-scale environments during ontogeny. Indeed, comparing kilometre-scale representations in laboratory-born versus wild-born animals, may illuminate the role of experience in shaping the neural codes for space. Second, the neural matching of place fields to the world's spatial statistics may be similar to the mechanisms by which vertebrate and invertebrate sensory systems adapt their neural responses to match natural stimulus statistics, as was demonstrated, for example, in the visual system[158,159] and auditory system[160–162].

A word of caution is due here: it may be that the neural bases of large-scale representation and navigation are profoundly different from small-scale navigation, with differences much greater than those depicted in FIGS 3,4. For example, it could be that grid cells, which were proposed to result from path-integration processes[24,102,163], will lose their spatial periodicity on large spatial scales, because of the inability to path-integrate over long distances. However, real environments contain a multitude of local landmarks and visual cues[124], including trees, boulders and a variety of textures and strong odour sources, all of which can serve to anchor the path integrator and stabilize the grid; therefore, the richness of real landscapes might be fundamentally different from the emptiness of experimental boxes used to study grid cells in the laboratory. In a similar vein, one may ask whether head-direction cells would convey a similar kind of information in the field as they do indoors; and the same question applies to border cells. For head-direction cells, the answer is probably yes, because these cells encode cyclical variables, either 360° of azimuth[34] or three-dimensional directions in space[164] (360° azimuth × 360° pitch), both of which are independent of spatial scale. For border cells, the answer is less clear, because on the one hand it seems unlikely that animals could measure distances to very distal boundaries such as mountain ranges, but on the other hand, natural landscapes contain also rich sets of elongated local features, such as rock ledges or hedgerows, which could activate border cells similar to their activity in small boxes. Nevertheless, all these classes of cells might also operate completely differently on large scales, or might perhaps not even be involved in real-life navigation; this caveat reinforces the urgent need to conduct electrophysiological studies of the neural basis of long-distance navigation.

Finally, we note that — even if we assume that the same spatial cell types in the hippocampal formation underlie both small-scale and large-scale navigation — we still have a very limited understanding of how the process of long-range navigation may be supported by these neurons. As discussed above, route cells and route preplays might possibly be relevant also for long-range route-following. However, real-world navigation requires much more than that. It requires, for example, the ability to optimize travel distance and/or effort; the ability to perform novel unplanned shortcuts; and the ability to re-orient oneself if the path is lost, or when an unexpected obstacle is encountered. Current models of brain function come short of explaining these complex facets of navigation. A major challenge for future work will be to determine how brain circuits support these feats. Furthermore, pursuing this challenge may help to bridge the gap between the major scientific disciplines of neuroscience and ecology.

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Competing interests statement

The authors declare no competing interests.