Spatial representation in the hippocampal formation: a history

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Main text (without Box, Figure Legends, and References: 10,818 words

8 figures (including timeline), 1 Box

Acknowledgments. The work was supported by two Advanced Investigator Grants from the European Research Council (GRIDCODE – grant no. 338865 to E.I.M.; 'ENSEMBLE', Grant Agreement no. 268598, to M.-B.M.), the Centre of Excellence scheme of the Research Council of Norway (Centre for Neural Computation, grant number 223262 to M.-B.M. and E.I.M.), the Kavli Foundation (M.-B.M. and E.I.M.), and National Science Foundation Grant 1631465 to B.L.M.

ABSTRACT

Since the first place cell was recorded, and the subsequent formulation of the cognitive-map theory, 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 the generation of 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. How specialized cell types of these systems work together is now investigable 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 history of the study of spatial coding did not begin there, but rather with the parietal cortex, in the form of early observations on patients with parietal damage[1,2], and 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 and pre- 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 realization that there is a system in the brain which 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[10].

Also key to the emergence of a paradigm for spatial representation was a gradual understanding of the role played by different spatial reference frames and their interactions. There exist three reference frames in which space can be represented: 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 they 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 the establishment of 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 and grid cell firing or plays an equal or subordinate role to the integration of information from external stimuli[24-26].

Finally, a discussion of paradigm shifts would not be complete without some realization of the role that technology has played (Fig. 4). Key technical advances have been the shift from recording single cells in restrained, usually anesthetized, animals to 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 micro-machined 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 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 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 explained 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 leitmotiv 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 encoding 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, the 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. 2ab). In the 1971 paper, the number of place cells, and the evidence for localized firing, was limited, but a lot more substantial data were presented by O’Keefe in 1976[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. 4cd). 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 was 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 re-interpreted 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 (e.g., 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 that place cells not only continued to fire in the 'correct' location in total darkness; fields could also be formed when animals were introduced to an environment in darkness and they 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 they were rotated between sessions[68,71].

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 salience[79] but varied systematically along the septo-temporal 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 septo-temporal axis was strongly correlated with the gain of physiological speed signals[86].

In spite of gradually accumulating evidence for an in many ways 'non-sensory' 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 high-order integrators of sensory data, perhaps endowed with memory properties. This sensory-integration approach changed, literally overnight, however, when James Ranck brought a video of a recorded head direction cell to the 1984 SfN meeting[87] (Fig. 3). Head direction cells are cells that fire specifically when the animal faces a certain direction[5-7] (Fig. 3ab). Ranck first encountered these cells in the dorsal presubiculum – almost by accident in an experiment where 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]. At 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 were formed by integration of salient sensory inputs, independently of movement. One of the main observations presented in favour of this concept was 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, but 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 towards 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 where 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 travelled 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].

'Remapping': global, partial, local and rate

In the late 1980's, 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 radically 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 the situations in which only fields near a specific, manipulated, cue changed from the situation in which there was a general (partial or complete) rearrangement of fields throughout the environment, as is often seen when the animal is placed in non-uniform environments[104,105], or as in the cases of deficient plasticity 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 re-scaled. In contrast, when the recordings took place in identical apparati 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 vs. 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 pre-trained 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 non-spatial code on top of the place code ("rate remapping") is consistent with dozens of studies, starting already in the 1980s, which show 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 non-spatial 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 non-spatial 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 familiarized 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[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 MEC is effectively silenced[128-30]. 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)[131], which may provide hippocampal cells with path integration-independent sensory inputs necessary for efficient rate coding[132]. However, even under conditions where MEC inactivation does not impair hippocampal place selectivity, the intervention causes instant remapping[133,134], suggesting that MEC is obligatory for activating the correct place map. This does not preclude, of course, that place maps are stored also in the CA3 network (e.g., the 'charts' of Samsonovich and McNaughton[90]), and 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 1990's, 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 autoassociation, pattern formation and pattern completion[135]. 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[136-138]. 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[139,140]. 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"[139]. For a long time, however, these pioneering 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 be 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 their firing fields were broad and dispersed, with little spatial selectivity in standard laboratory environments, and the fields seemed not to remap between environments[22,139,141]. This, together with the observation that CA1 place fields persisted following large lesions of the dentate gyrus[142], 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[143].

Given the uncertainty about how CA3 contributed to the CA1 place signal, Brun and colleagues[144] 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 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[143], the study found, in 2002, that CA1 place cells do not require input from CA3 to maintain reasonably selective spatial firing. This suggested that place fields were either generated within the limited circuitry of the CA1 itself, or place cells in CA1 received spatial input from the entorhinal cortex via temporo-ammonic projections that survived the CA3-CA1 transection. These observations were made only a few years after theoretical studies[3,21,90,145] proposed that the path integrator might located outside the hippocampus – in the 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 re-visit.

An important additional inspiration for the renewed interest in entorhinal cortex was Menno Witter's extensive review of entorhinal-hippocampal systems[146]. 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 medial entorhinal cortex (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 where histology was available[22,141], 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[8,146], 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 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 were 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). The cells were coined grid cells. For each cell, the grid could be assigned a phase (the *xy* 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[9,147]. The spatial periodicity of the pattern was so striking that the authors were concerned, initially, that it was some sort of artefact. However, the grid pattern soon appeared in other labs too[131,148].

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 travelled 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[147]. It should be added, for the sake of balance, that stable grid fields have not yet been identified in darkness in mice[149,150]. The reason for the possible species difference is not known. Associations between path integration coordinates and stationary cues may be weaker in mice[151], 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[152].

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[153]. 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"[154]. 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[155] 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[148,156], in concert with either scaling or remapping in hippocampal place cells[157]. However, these distortions of the grid pattern were recorded when the environment was changed after the animal was already familiarized 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[158] or in irregular geometric shapes[159], 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[159,160], causing distortions and rotations that can be described effectively as a shearing process[160]. The common existence of fragmented and distorted grids have raised questions about whether grid cells are useful as a source of metric information[159]. Speaking against 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[161]. 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 differed from place cells in more than one way. Not only did they have periodic firing fields but also the relationship between the firing fields of different cells followed 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[106,155,162-164], the ensemble activity of grid cells is normally maintained coherently from one environment to the next, without changing phase or orientation relationships between cells[147,165], 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[156]. A similar degree of coherence is present among head direction cells[6,7,77,78,166] as well as in the more recently discovered populations of entorhinal border cells and speed cells[167,168]. The coherence of grid cells and head direction cells is state-independent and persists during sleep[169-171]. Collectively, these findings point to a fundamental difference between hippocampal and entorhinal spatial maps: hippocampal circuits are high-dimensional, 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[162,172,173] 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[91,174]. In 2007, Barry and colleagues showed with a small cell sample that values of grid spacing were not evenly distributed[148]. 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 if grid cells clustered in groups with similar properties[156]. 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[156], confirming the prior predictions[91,174], 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[175,176].

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[91,177]. This summation mechanism might be facilitated further by coordinated gamma-frequency oscillations in MEC and CA1 cells[178]. 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[179-182]. 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[128,129], and in young animals, place cells acquire stable firing fields before sharp periodic firing patterns emerges in grid cells[183,184]. Inactivation or damage of the MEC is not sufficient to disrupt place-cell firing in the hippocampus[130,133,134,185]. However, neither of these observations rule 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 non-periodic firing patterns[186], as well as weakly place-tuned cells in the LEC[131]. 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 to place or place to grid 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 pre- and parasubiculum years before[5-7,188]. The directional tuning curves of many entorhinal head direction cells were found to be broader than in pre- 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 pre- 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[167,190] (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[167]. Border cells intermingled with grid cells and head direction cells, particularly in layers II and III of MEC[167,], 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 observed also 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 more sparse than grid cells and head direction modulated cells, and may comprise less than 10% of the local principal cell population[167], 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 and Burgess and their 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, the latter lack distance tuning, firing only along the borders 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 centre 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, similar to entorhinal border cells[196]. Regardless of whether border cells fulfil 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[159,160], 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 presence of head direction cells and border cells, it became clear that grid cells have local access to information about direction, needed for the angular component of path integration, as well as 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 time scale 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 from 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 travelled[208], and distance travelled 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. Already in 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[168]. We now know that the entorhinal cortex has a distinct population of cells whose firing rates increase linearly with speed[168,209]. In the large majority of speed-tuned MEC cells[168], firing rates increase linearly as a function of speed up to 30-40 cm/s. A small but significant number of cells have negative speed-rate relationships[168]. 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[168]. 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[168]. In CA1, the gain of speed tuning varies systematically along the septo-temporal 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 where position, direction and distance are encoded at 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 to date 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 location 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, the 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[131,132,211,212]. 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 towards a salient goal positioned centrally in the environment. Although the preferred orientation of the cells spanned the full 360-degree range relative to the direction to the goal, a large proportion of the cells in this category fired when the animal was heading directly towards 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[221]. 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[73,222-226], and the finding of goal orientation cells in both parietal cortex and hippocampus begs the question of which region is 'copying' which. It remains for the future to determine if 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[167,168,,187,227]. Conjunctive cells are recognized to be essential ingredients of the 'hidden layer' for almost any type of coordinate transformation or conditional association network[18,228-230]. 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 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. Already in 1949, Hebb proposed that activity may self-sustain in networks of recurrently connected neurons[231]. 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[232]. In such an 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[233], Zhang[234], and Redish and Touretzky and colleagues[235], 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 competing models have not surfaced. In mammals, the reciprocally connected network of the dorsal tegmental nucleus and the lateral mammillary area has been proposed as a location for the ring attractor[236], 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 underlie firing in neurons that represent orientation relative to landmarks[237,238].

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[19,90,234,239,240] (Fig. 5cd). 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 – that 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[90,241] but nonetheless raises the question of whether a single network matrix, expressed in all environments, would not be more efficient[21,240]. A few years later it became apparent that such a low-dimentional architecture exists in the entorhinal cortex.

When grid cells entered the research arena in 2005[9], it was quite obvious that the dynamics proposed for localized firing in place cells might take place also in parahippocampal regions[91,153,240], as alluded to already by Samsonovitch and McNaughton[90]. In the first models proposed after the discovery of grid cells[91,153], 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[153], 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[242-245].

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[91,174]. Experimental evidence suggests that such a modular functional organization is indeed present[148,156]. A second observation consistent with a path integration-dependent attractor architecture is the maintenance of a single grid-phase structure across environments and tasks[147,165], which would be expected if MEC neurons are organized as strongly interconnected networks where 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[246,247] 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[248-251]. 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[252]. As the animal moves through the field, the theta phase moves progressively forward also in space, in fact with a stronger correlation to location than time[252,253]. 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-degree intervals onto three separate dendrites[248-250]. 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[254], the sensitivity to period irregularity[255], the persistence of grid patterns in the absence of theta oscillations[219,256], as well as the presence of a ramping depolarization and the absence of a theta interference oscillation in intracellular recordings from MEC cells[257,258], 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[253]. Indeed, as recognized by several investigators soon after phase precession was discovered[253,259,260], 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 feed-forward networks where 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[261]. Thus, competitive Hebbian plasticity offers an alternative mechanism for grid formation, although this mechanism may co-exist with attractor-network architectures[262]. Regardless of mechanism, accounts of grid formation must consider not only intrinsic MEC dynamics but also how external inputs from the hippocampus[243], the medial septum[128,129], and locomotor[204-207,263] and head-direction circuits[264] 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 first subsequent 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 at which spatial functions can be studied in the hippocampal formation of a number of mammals has made the study of the positioning system 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 to 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.

In memoriam

In memoriam, Howard B. Eichenbaum (1947-2017; Fig. 8). The field of hippocampal and memory research mourns the loss of our friend and colleague Howard, who passed away unexpectedly recently. Howard's contribution to the field was immense both scientifically and in service. His research was mostly focussed 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].

Figure Captions

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

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 msec. Note that the cell responds selectively at only a few positions. O'Keefe and Dostrovsky reported 8 units out of 76 recorded hippocampal cells that responded solely or maximally when the rat was situated in a particular part of the testing platform facing in a particular direction. It should be noted that the single electrode technology available to the authors at the likely precluded regular good isolation of cells, which may have limited the number of clear 'place' responses observed. Reproduced from ref. 4, with permission.

b) A place field as typically displayed today. Top rat’s trajectory in grey; 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. Picture taken by Dulcie Conway around 1975. Picture courtesy of John O’Keefe[265]

Figure 3: 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 4 spike-amplitude dimensions. The corresponding spike waveforms are shown on the right. Reproduced from ref. 80.

b) A 48 channel, 12 tetrode probe array (hyperdrive) from ca. 1995. This system exploited the flexibility of wire tetrodes to enable them to be advanced by pushing them through gently curving tubes (like a mosquito proboscis).

c) Multi-tetrode recording made it possible to record from more than 100 hippocampal neurons simultaneously. Here is shown 80 firing rate maps from simultaneously recorded CA1 cells as the rat ran in a 70x70 cm arena[33]. Firing rate is color-coded from blue (silent) to red (maximum rate). Note, 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. Reproduced from ref. 33.

d) Examples of the actual (blue) spatial trajectory of the rat and the trajectory reconstructed from the population firing rate vector (red). Reproduced from ref. 33.

Figure 4: Head direction cells[6]. a) Firing rate as a function of head direction for 2 representative cells from 2 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), SUNY Downstate Medical Center in Brooklyn., N.Y., in 1987. Panel a reproduced from ref. 6, with permission. Picture courtesy of Jeffrey Taube.

Figure 5: Path integration.

a) Illustration of 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 prior to starting the inbound journey. Reproduced from ref. 91.

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[18,228]. Updating in the head direction (attractor) layer was 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. Reproduced from ref. 233.

c & d) The continuous attractor model for path integration in 2-D proposed by McNaughton et al. in 1996[19] and simulated by Samsonovich and McNaughton in 1997[90]. H'=head angular velocity; H'H = conjunctive cells; H = head direction; P = place cells; M = speed cells; PH x 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 resetting of the integrator upon entry to a familiar environment. Reproduced from ref. 90.

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 only changing 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 (and other cells are active in only one cylinder) despite changing only the color of the box. It is interesting to know that the authors later confirmed anecdotally that they 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]. Rate maps adapted from ref. 100, with permission.

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 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. Adapted from ref. 106.

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[9]. Left, trajectory of the rat (black) with superimposed spike locations (red). Middle: color-coded rate map with peak rate indicated. Right: spatial autocorrelogram, color-coded from blue (r = - 1) through green (r = 0) to red (r = 1). Reproduced from ref. 9.
b) Sagittal section of the rat brain showing the hippocampus and the MEC (red area) and grid cells of different scales recorded at three locations on the dorsal – ventral axis (trajectories with spike locations as in a). Note expansion of grid cell from dorsal to ventral MEC. Adapted from ref. 91.
c) Grid cell modules[156]. Top: autocorrelation plots showing grid patterns at successive positions along the dorsoventral axis of MEC. Bottom: grid size, defined as 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 square root of two. 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]. Adapted from ref. 156.
d) Head-direction cell in layer V of MEC. Adapted from ref. 187.
e) Conjunctive grid × head-direction cell in layer III of MEC. Adapted from ref. 187.
f) Border cell[167]. Color-coded rate maps showing cell with selective firing along one of the walls of the recording environment. Top: open environment. Bottom: rate map following 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. Adapted from ref. 167.

Figure 8: Howard Eichenbaum (1947-2017). Few 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.

Box 1

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 ref. 237 and 238 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 similarly tuned MEC cells, 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 non-topographical[9,270] grid-cell network of the adult MEC (Fig. 8 of ref. 91)? Tools for targeted analysis of functional identity and connectivity of discrete developmental cell populations have been developed, 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 contain the majority of them[257,258,272-275]. 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[161,175,176,276]. 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[277] 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 towards 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[278]. 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[279] as well as observations in compartmentalized laboratory environments[158]? If the latter is true, how are they connected? And how is space coded in large and three-dimensional environments[278]? In flying bats, place cells have spherical firing fields[280] 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[281,282].

6. Representation of time

Understanding space 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[283] or on a treadmill[284], 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 medial entorhinal cortex[285]. 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 tasks with different delays[284], suggesting that hippocampal ensembles encode temporally organized information much the same way as 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 the animal[286] or changing the speed of the treadmill[287], 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[288-290], as well as cell populations in LEC[291], 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 already by O'Keefe and Nadel[65]? Evidence for such an extension of functions has been reported recently in a task where rats press a lever to alter the frequency of a sound on a continuous scale, hippocampal and entorhinal cells display frequency fields resembling place fields during navigation of physical space[292]. 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[256,293,294]. 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[295,296], grid cells may take on functions in conceptual mapping[297]. 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 capacity for imaginary navigation[49,65,298,299]. 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[300].

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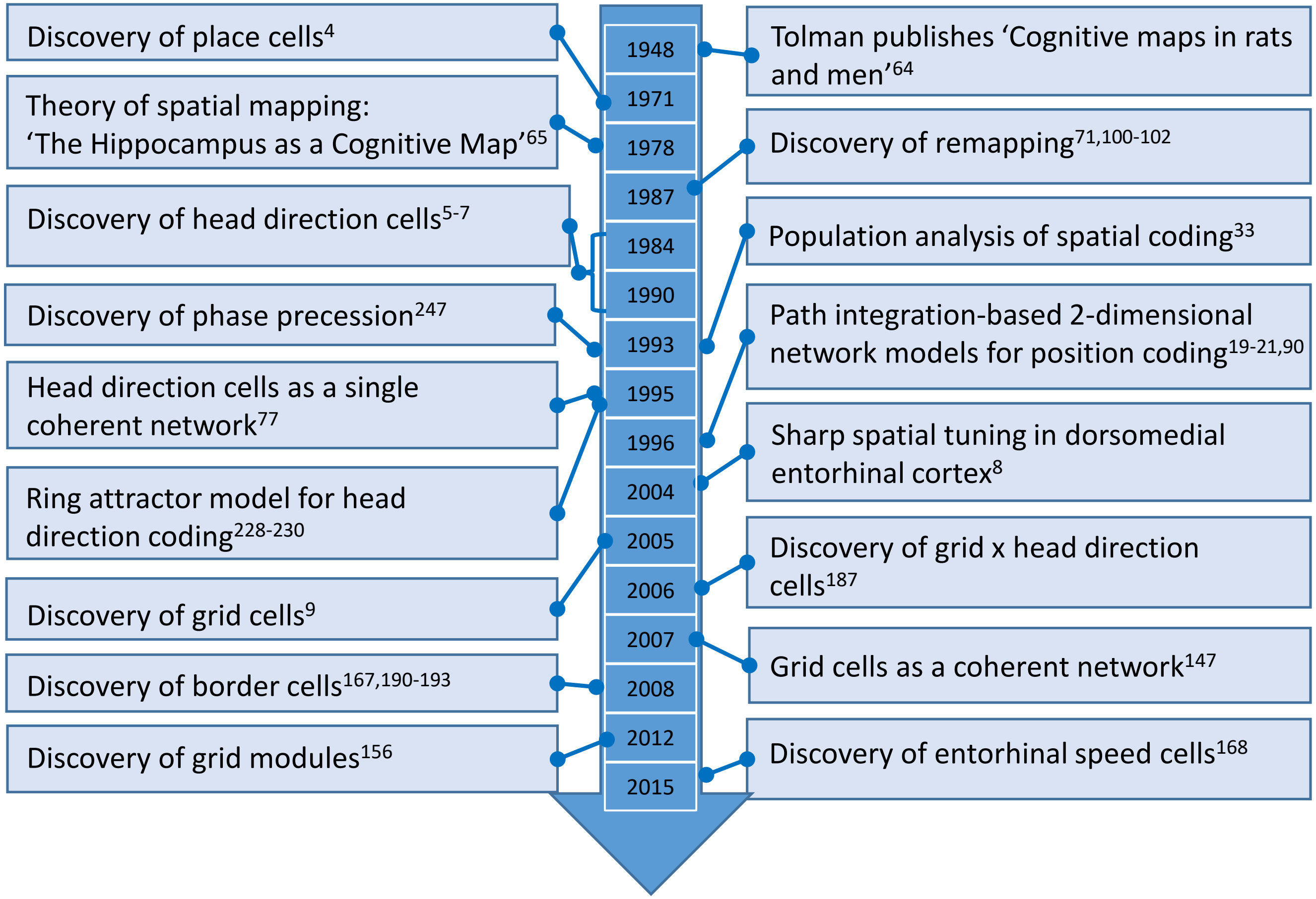
Figure 1



Discovery of place cells[4]

Theory of spatial mapping: 'The Hippocampus as a Cognitive Map'[65]

Discovery of head direction cells[5-7]

Discovery of phase precession[247]

Head direction cells as a single coherent network[77]

Ring attractor model for head direction coding[228-230]

Discovery of grid cells[9]

Discovery of border cells[167,190-193]

Discovery of grid modules[156]

Tolman publishes 'Cognitive maps in rats and men'[64]

Discovery of remapping[71,100-102]

Population analysis of spatial coding[33]

Path integration-based 2-dimensional network models for position coding[19-21,90]

Sharp spatial tuning in dorsomedial entorhinal cortex[8]

Discovery of grid x head direction cells[187]

Grid cells as a coherent network[147]

Discovery of entorhinal speed cells[168]

Figure 2

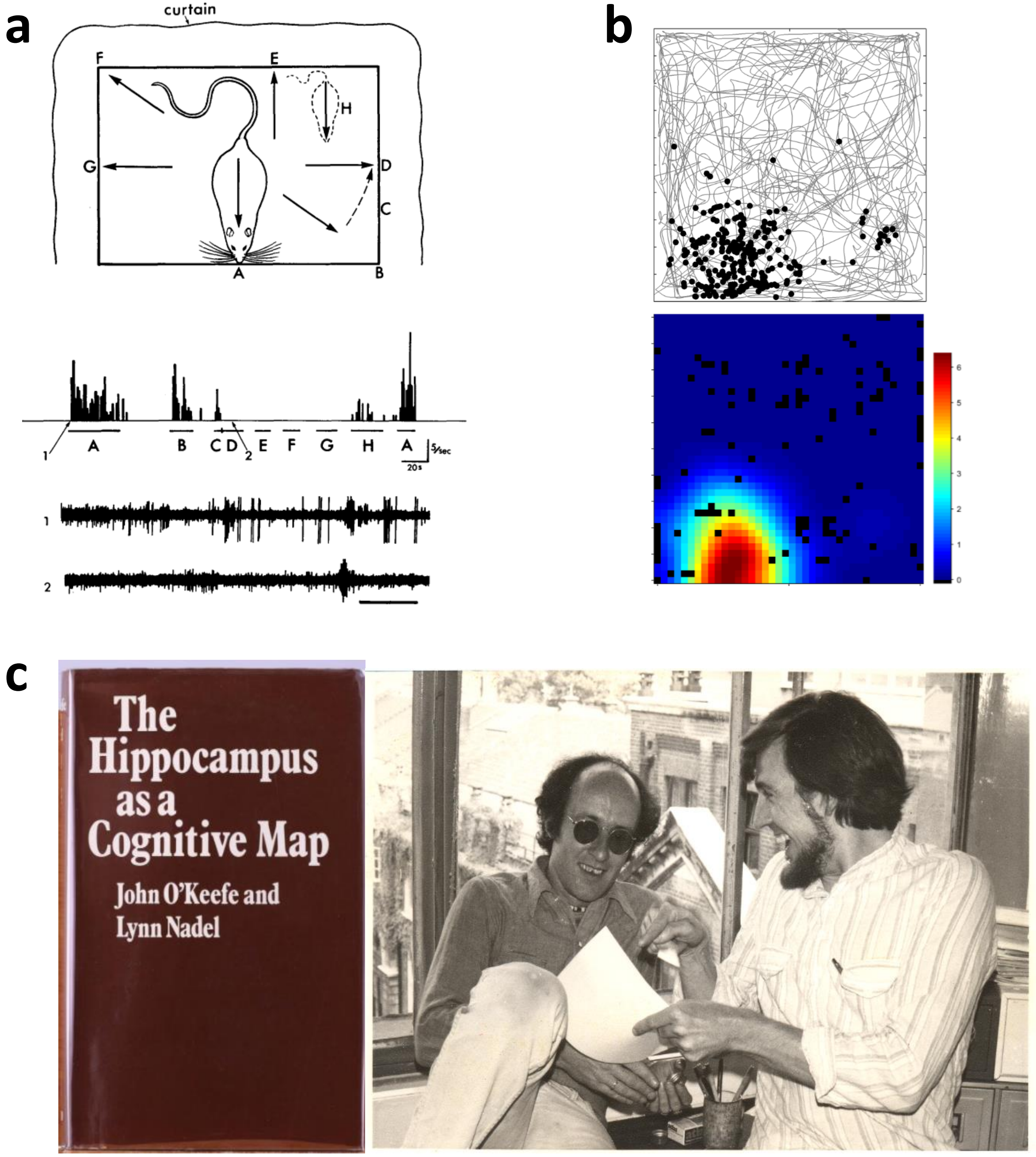

a
curtain
F
E
H
G
D
C
A
B
1
A
B
C D
2
E
F
G
H
A
5/sec
20s
1
2
b
6
5
4
3
2
1
0
c
The Hippocampus as a Cognitive Map
John O'Keefe and Lynn Nadel

Figure 3

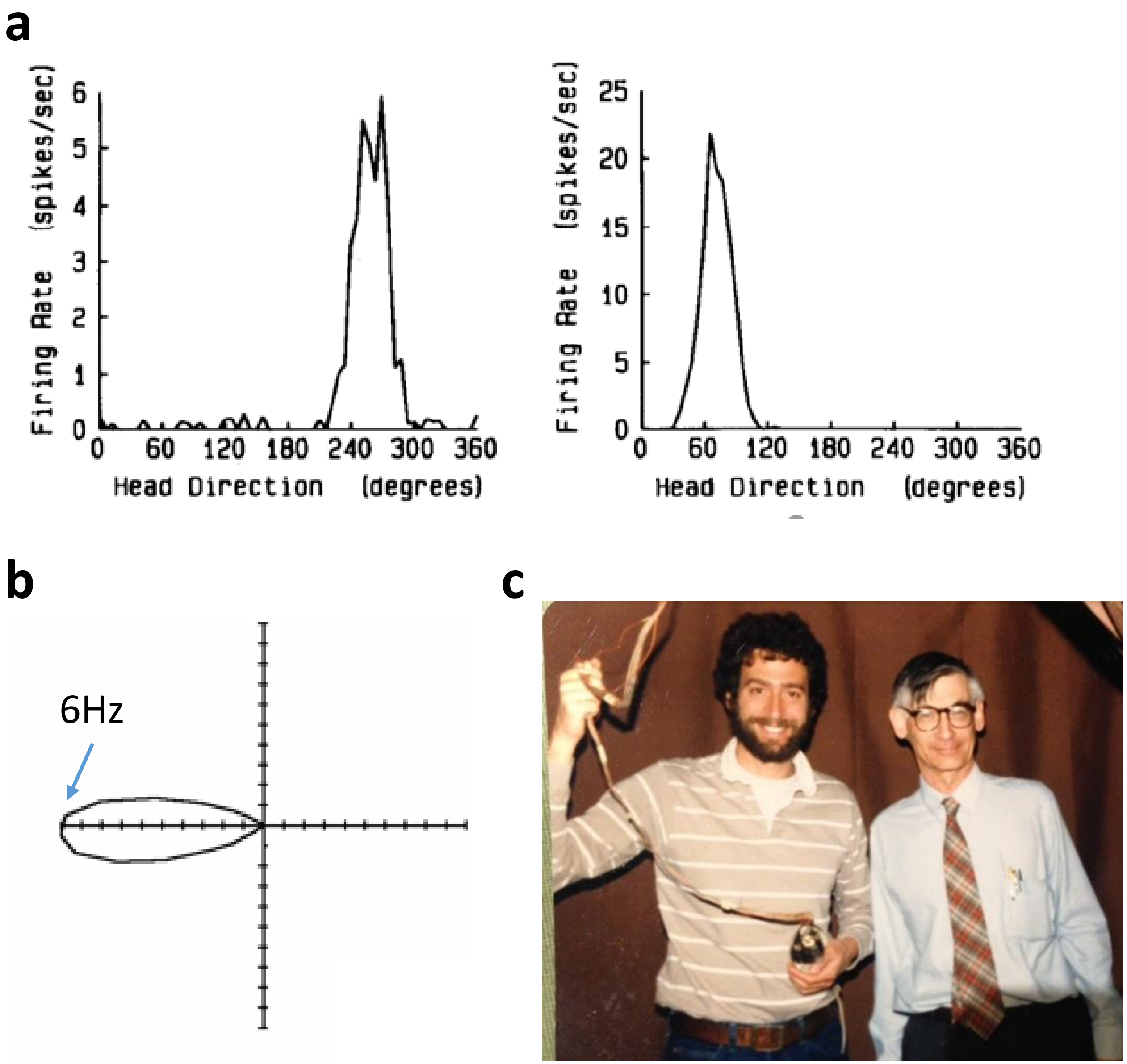

a
Firing Rate (spikes/sec)
0
1
2
3
4
5
6
0 60 120 180 240 300 360
Head Direction (degrees)
Firing Rate (spikes/sec)
0
5
10
15
20
25
0 60 120 180 240 300 360
Head Direction (degrees)
b
6Hz
c

Figure 4

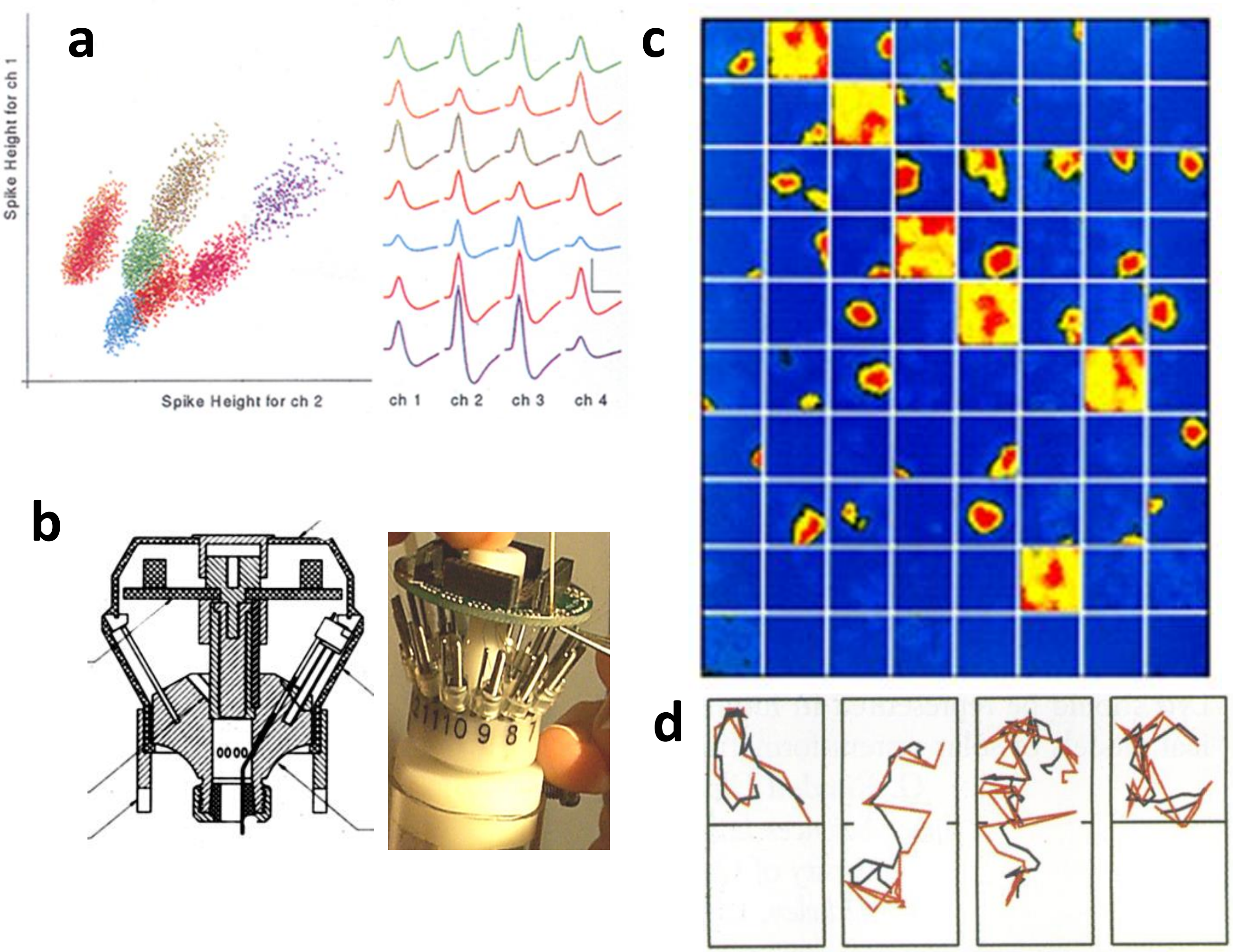

a
Spike Height for ch 1
Spike Height for ch 2
ch 1
ch 2
ch 3
ch 4
b
0000
11 10 9 8 7
c
d

Figure 5

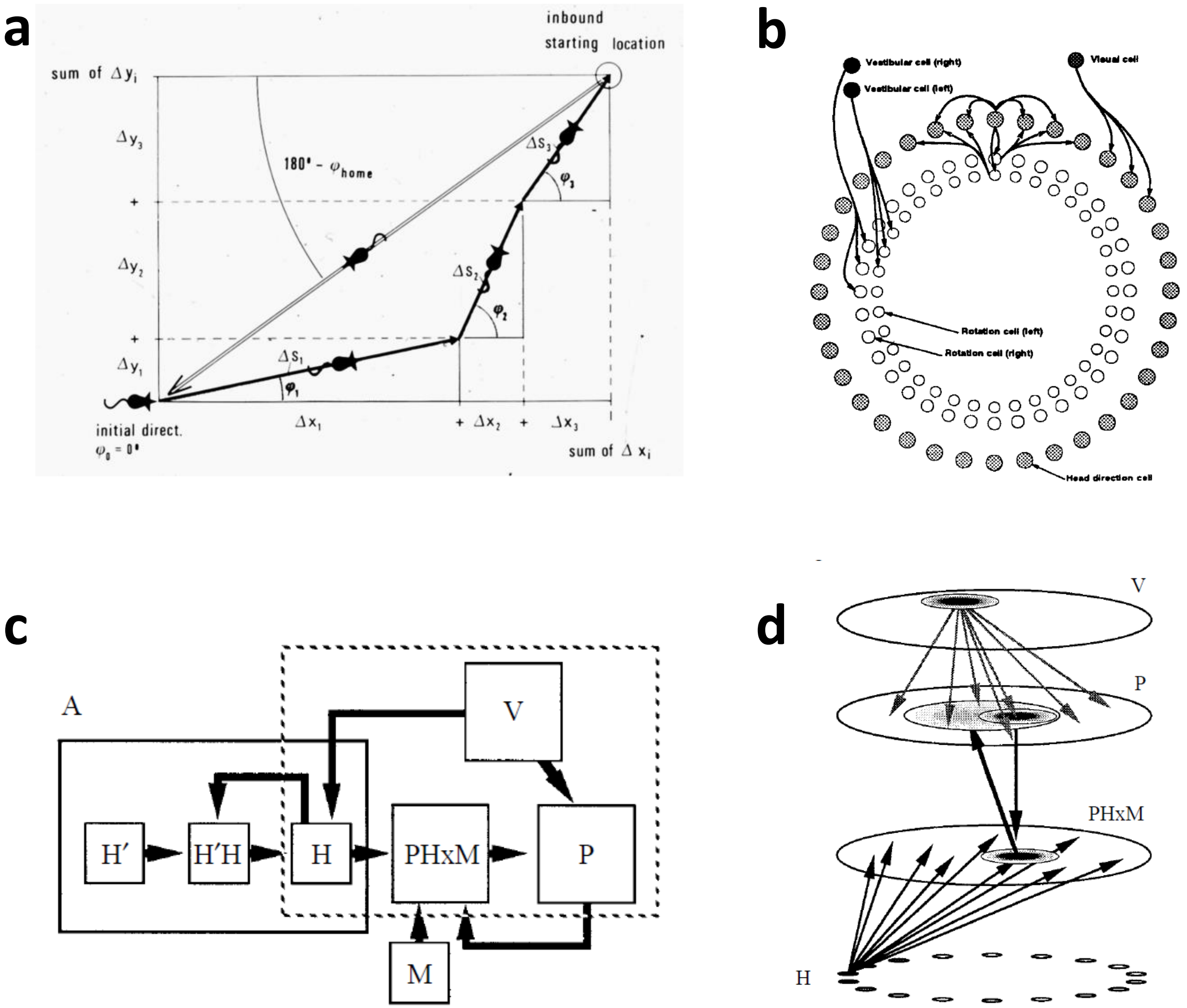

a
inbound
starting location
sum of Δy_i
Δy_3
$180° - \varphi_{home}$
Δs_3
φ_3
+
Δy_2
Δs_2
φ_2
+
Δy_1
Δs_1
φ_1
initial direct.
$\varphi_0 = 0°$
Δx_1
+ Δx_2 +
Δx_3
sum of Δx_i
b
Vestibular cell (right)
Vestibular cell (left)
Visual cell
Rotation cell (left)
Rotation cell (right)
Head direction cell
c
A
V
H′
H′H
H
PHxM
P
M
d
V
P
PHxM
H

Figure 6

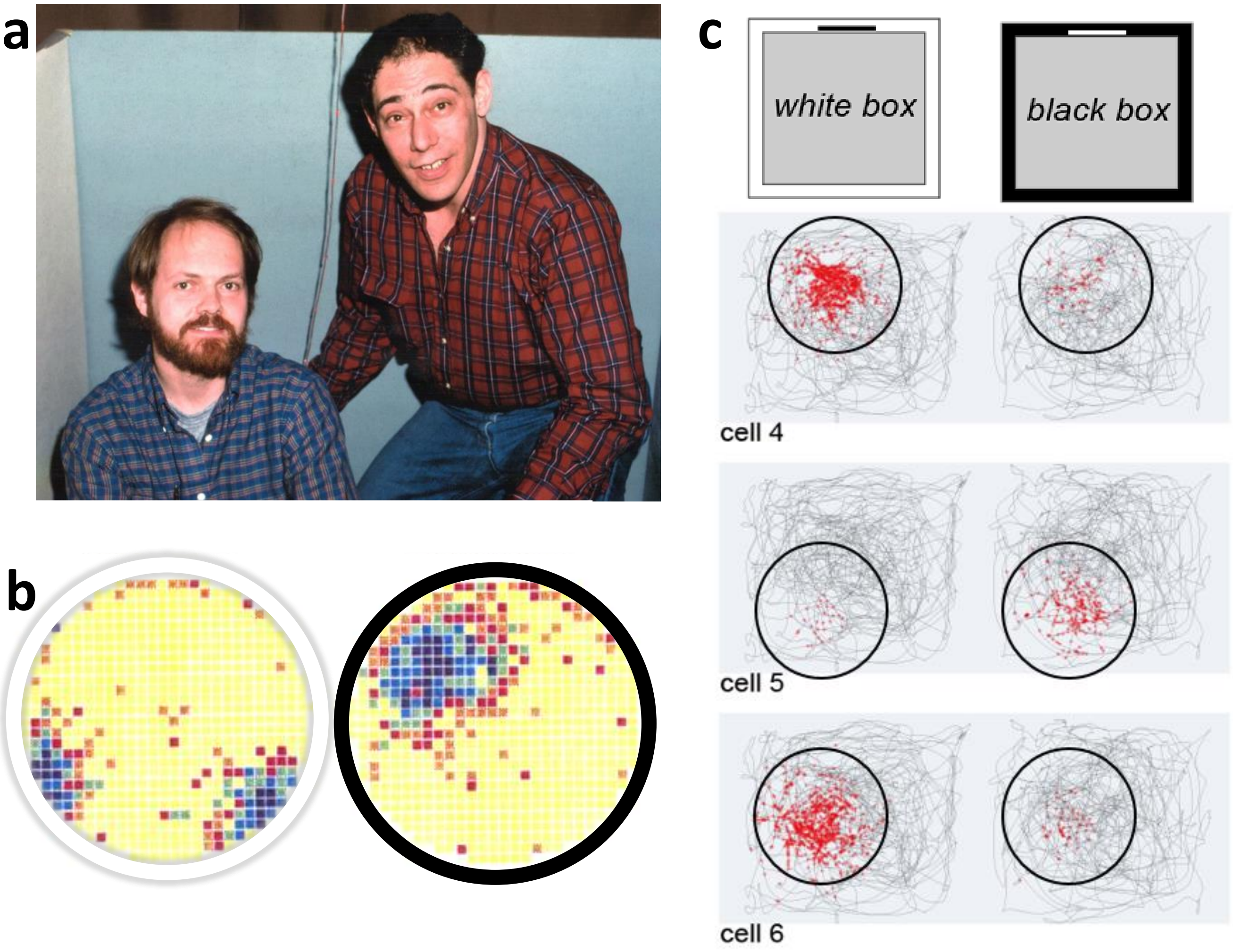
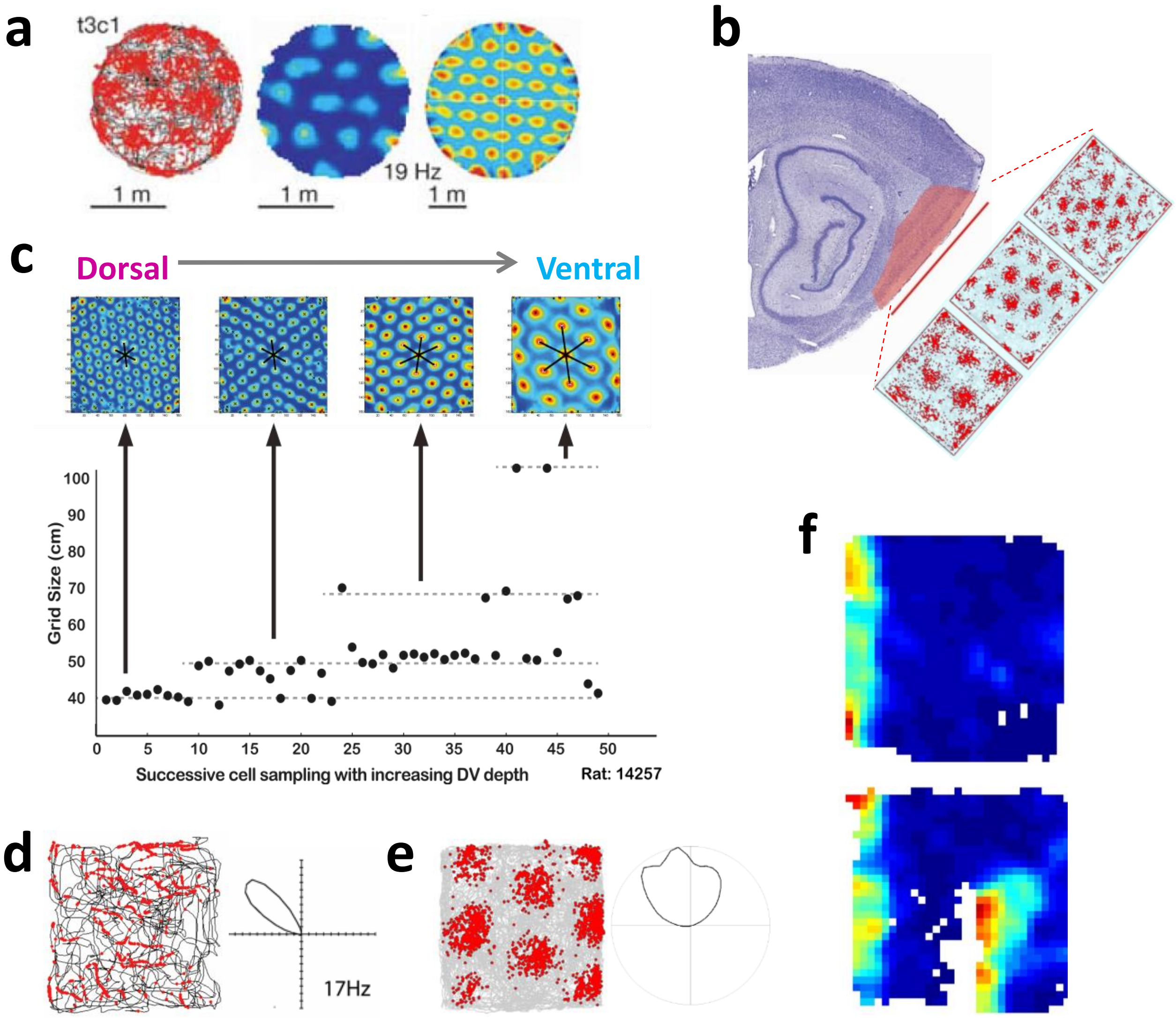


Figure 7


a
t3c1
1 m
1 m
19 Hz
1 m
b
c
Dorsal
Ventral
Grid Size (cm)
100
90
80
70
60
50
40
0
5
10
15
20
25
30
35
40
45
50
Successive cell sampling with increasing DV depth
Rat: 14257
d
17Hz
e
f