REVIEW

A Metric for Space

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ABSTRACT: Not all areas of neuronal systems investigation have matured to the stage where computation can be understood at the microcircuit level. In mammals, insights into cortical circuit functions have been obtained for the early stages of sensory systems, where signals can be followed through networks of increasing complexity from the receptors to the primary sensory cortices. These studies have suggested how neurons and neuronal networks extract features from the external world, but how the brain generates its own codes, in the higher-order nonsensory parts of the cortex, has remained deeply mysterious. In this terra incognita, a path was opened by the discovery of grid cells, place-modulated entorhinal neurons whose firing locations define a periodic triangular or hexagonal array covering the entirety of the animal's available environment. This array of firing is maintained in spite of ongoing changes in the animal's speed and direction, suggesting that grid cells are part of the brain's metric for representation of space. Because the crystal-like structure of the firing fields is created within the nervous system itself, grid cells may provide scientists with direct access to some of the most basic operational principles of cortical circuits. © 2008 Wiley-Liss, Inc.

KEY WORDS: hippocampus; entorhinal cortex (EC); grid cells; place cells; spatial representation; navigation

INTRODUCTION

Studies of the hippocampus have taught us much about the general mechanisms of brain function. More than five decades ago, scientists realized that the strict lamination and unidirectional organization of this brain area made it possible to infer some of its working principles from electrophysiological recordings (Andersen, 1959; Kandel et al., 1961). The first systematic studies of hippocampal field potentials came just a few years after clinical observations in humans identified a possible role for the hippocampus in memory for events of daily life (Scoville and Milner, 1957). Based on the early studies of patient H.M. and other cases, the hippocampus was gradually acknowledged as a major element of the brain's network for encoding and maintaining episodic or declarative memories (reviewed by Squire et al., 2004). In these pioneering days of hippocampal research, a new generation of neuroscientists was seeking to understand behavior at the level of neurons and synapses. Donald Hebb's seminal work, 'The Organization of Behavior' (Hebb,

1949), had argued that the most complex functions of the brain could be understood by studying the activity of neuronal populations, and Hebb hypothesized that memories might be formed by strengthening synapses between neurons. As all of these various developments came together in the 1960s and 1970s, researchers became increasingly confident that the emerging knowledge of hippocampal function might reveal some of the contents of the 'black box' containing the biological circuits for memory and behavior in the mammalian brain.

In spite of these advances, the problems of linking synaptic physiology and behavior must have appeared overwhelming at this early time, considering that there was no experimental paradigm for studying hippocampal neuronal processes and behavior simultaneously in awake animals. This situation was radically changed with the discovery of place cells in the early 1970s (O'Keefe and Dostrovsky, 1971; O'Keefe, 1976). Place cells are neurons that fire only when an animal moves through a particular location in space (the 'place field' of the neuron). The location-specific activation of these cells is extremely reliable and observable during almost any behavior in a moving rat. The fact that nearly all pyramidal cells in the CA areas of the hippocampus are place cells led to a reinterpretation of a hippocampal experimental literature that was based largely on behavioral assessment of animals with relatively unspecific brain lesions, and it was proposed that the hippocampus is the center of a neural map of the animal's local environment (O'Keefe and Nadel, 1978). This suggestion, in its strictest form, was challenged by human clinical studies showing that patients with hippocampal damage had both spatial and nonspatial impairments (Squire et al., 2004) as well as observations in animals suggesting that some hippocampal cells express nonspatial information (Ranck, 1973; Young et al., 1994; Hampson et al., 1993; Wood et al., 1999; Ferbinteanu and Shapiro, 2003). However, it is now commonly believed that, in many or most hippocampal cells, this information is expressed on top of the spatial signal rather than instead of it (Leutgeb et al., 2005), and position is generally acknowledged as a major component of the signal carried by hippocampal neurons (Moser et al., 2008). This manifestation of a spatial code in hippocampal neurons has enabled researchers to take up

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Hebb's challenge and relate the discharge patterns of neuronal ensembles to a specific behavior, namely the ability to represent and recall the spatial environment and to use the neural representations to locate targets within that environment.

During the decades that followed the discovery of place cells, these cells began to attract attention not only from those who wanted to understand spatial mapping but also from a large community of researchers who saw these cells as a potential tool to understand computation in the brain more broadly. A major reason for this development was the invention of technology for large-scale recordings in neuronal ensembles (Georgopoulos et al., 1986; Wilson and McNaughton, 1993; Harris et al., 2003), which made it possible to observe hippocampal population dynamics in a manner unprecedented at this time. Some of the key questions in these analyses were about the origin of the place signal. Where was it produced and what were the underlying neural mechanisms? At the beginning of the twenty-first century, studies of place cells were still largely confined to the region where they were discovered—the CA1 field of the hippocampus. Place cells had also been observed in CA3 (Muller et al., 1987; Barnes et al., 1990), and neurons were known to exhibit spatial modulation, of a different kind, in the dentate gyrus (DG) (Jung and McNaughton, 1993) and in the medial entorhinal cortex (Quirk et al., 1992; Frank et al., 2000), but in spite of these scattered explorations, researchers had few clues at the turn of the century about how the place signal was generated and how it interacted with the various components of the hippocampal–parahippocampal network. The present issue of Hippocampus will hopefully show how the discovery of entorhinal grid cells in the year 2005 may shed new light on the computational processes underlying spatial representation and navigation in the hippocampus and surrounding regions.

FROM HIPPOCAMPUS TO ENTORHINAL CORTEX—THE DISCOVERY OF GRID CELLS

One of the most significant observations in the study of place cells during the past two decades is the discovery that place cells participate in multiple independent spatial representations. Under certain experimental conditions, place cells were found to totally alter their firing patterns in response to apparently minor changes in the sensory or motivational inputs to the hippocampus, a phenomenon now referred to as 'remapping' (Muller and Kubie, 1987; Bostock et al., 1991; Muller et al., 1991; Markus et al., 1995; Colgin et al., 2008). After small changes in the color or shape of the environment or in the reward contingencies, new place fields were seen to appear and old ones disappeared or moved to unpredictable locations. The multiplicity of the hippocampal representation implied by these observations raised the possibility that position is not computed in the hippocampus. If the computation were local, it might have to be performed separately for each of the hundreds or thousands of representations stored in the system (Sharp, 1999a; Touretzky and

Redish, 1996). Instead, it was proposed that the metrics of the spatial map were computed outside the hippocampus, in agreement with early suggestions (O'Keefe, 1976).

The entorhinal cortex is an obvious candidate for the neural network that computes the animal's current location, given that this area is only one synapse upstream or downstream of the place cells in the hippocampus (Touretzky and Redish, 1996). However, the first studies of spatial activity in this area found only weakly place-modulated signals (Quirk et al., 1992). It was commonly accepted, based on these early findings, that much of the position computation occurred within the hippocampus, between the weakly modulated entorhinal cells and the sharply modulated hippocampal cells. The fact that place cells existed in rats with large lesions of the DG (McNaughton et al., 1989) argued against a role for the earliest stage of the circuit, but these lesions did not disrupt the very strong connections of the entorhinal cortex with the CA3 field, and it could be argued that CA3, with its strong associational fibers, might be able to integrate cortical information from a number of places and sensory modalities to form an integrated representation of the spatial environment. Motivated by these somewhat conflicting observations, we decided at the turn of the century to test whether place signals persist in CA1 when the CA3 is also disconnected (Fig. 1; Brun et al., 2002). CA1 place cells were recorded after removal of both dentate gyrus and CA3, leaving intact only the direct connections from entorhinal cortex to CA1. Pyramidal cells in the isolated CA1 preparation continued to show sharp and stable spatial firing fields in familiar environments, suggesting either that the CA1 had sufficient intrinsic circuitry to compute the place signal, or that significant spatial information was received directly from the entorhinal cortex. Because of the relative lack of associational circuitry within CA1 itself, we considered the latter option—that spatial signals originate outside the hippocampus—and we decided to revisit the entorhinal cortex.

A key turning point was the recognition that the entorhinal cortex was severely undersampled in the earlier studies. Many of those studies did not show the position of the recording electrodes but where the recording sites were shown (Quirk et al., 1992; Frank et al., 2000), we realized, with the help of our close collaborator Menno Witter, that the studies were performed largely in the intermediate band of the medial entorhinal cortex. This region projects primarily to the intermediate part of the hippocampus, midway between the dorsal and ventral poles (Witter et al., 1989; Dolorfo et al., 1998; Naber et al., 2001). Place cells in this region have broad firing fields with little spatial modulation in conventionally sized laboratory environments (Jung et al., 1994; Kjelstrup et al., 2008). Place cells with more confined fields, similar to those commonly reported in the literature, exist only in the dorsal one-third of the hippocampus. The entorhinal inputs to this region come essentially from the dorsolateral band of the entorhinal cortex (Witter et al., 1989; Dolorfo et al., 1998; Naber et al., 2001). The firing properties of cells in this band were not known at the time when the Brun et al. (2002) study was published. Thus, to better match the entorhinal and hippocampal re-
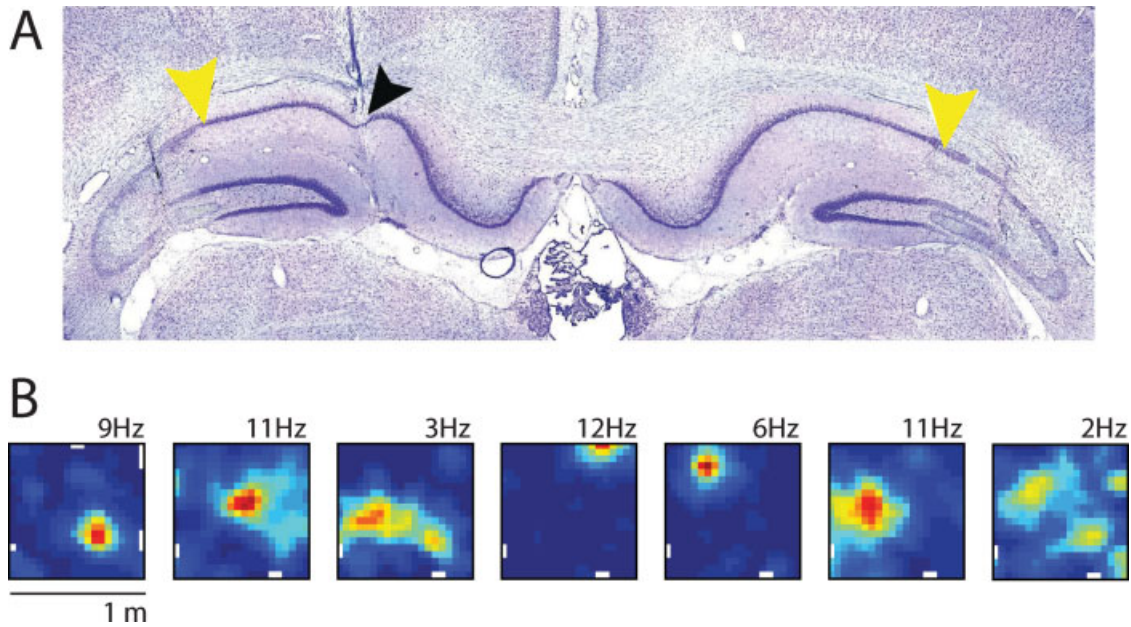
FIGURE 1. Place fields in the CA1 of the hippocampus after removal of dorsal CA3 by ibotenic acid. (A) Coronal section showing Nissl stain of neuronal cell bodies in the dorsal hippocampus of a lesioned rat. Yellow arrowheads indicate the border between lesioned and intact tissue; the black arrowhead indicates the trace of the tetrodes. (B) Color-coded firing rate maps for seven well-isolated pyramidal cells recorded at the hippocampal position in A while the CA3-lesioned rat was running in a 1×1 m^2 square open field. Dark red indicates maximum rate; dark blue is 0 Hz. Peak rates are indicated for each cell. Regions not visited by the rat are white. Modified from Brun et al. (2002).

cording locations, we implanted recording electrodes in the dorsolateral band (Fig. 2A,B). Not unexpectedly, clear spatial signals could now be recorded from the medial entorhinal cortex in every single rat (Fyhn et al., 2004). Neurons in the superficial cell layers had discrete firing fields with a diameter of ~20 cm in the most dorsal parts of the structure. The signal-to-noise (S/N) ratio was large, with rates of 10–20 Hz in the fields and no spikes at all outside. Different neurons fired in different locations, just like place cells in the hippocampus, and based on the collective activity of less than 10 entorhinal cells,

it was possible to reconstruct the trajectory of a moving animal (Movie S1 in Fyhn et al., 2004), implying that the animal's position might be represented as accurately in the medial entorhinal cortex as in the place cells one synapse downstream in the hippocampus. The results pointed to the medial entorhinal cortex as an essential part of the brain's system for spatial representation and navigation, a conjecture that was confirmed by studies showing striking impairments in spatial navigation and

FIGURE 2. Grid cells in medial entorhinal cortex. (A) Three-dimensional surface reconstruction showing range of recording locations in the dorsal quarter of the medial entorhinal cortex. For each of 17 animals, the position and dorsoventral extent of the tetrode tract is indicated as a colored ellipsoid. (B) Sagittal Nissl-stained section indicating a typical recording location in layer II of the dorsal medial entorhinal cortex. The red line indicates the dorsal border of medial entorhinal cortex. The red circle indicates the recording location in C. (C) Firing fields of a grid cell recorded at the location indicated in B during 30 min of running in a large circular enclosure (2 m diameter). Left: Trajectory of the rat (black) with superimposed spike locations (red). Middle: Corresponding color-coded rate map (as in Fig. 1B). Right: Spatial autocorrelation for the rate map in the middle panel. The color scale is from blue ($r = -1$) through green ($r = 0$) to red ($r = 1$). The distance scale is half of that of the rate map in B. A is modified from Sargolini et al. (2006); B and C are modified from Hafting et al. (2005).
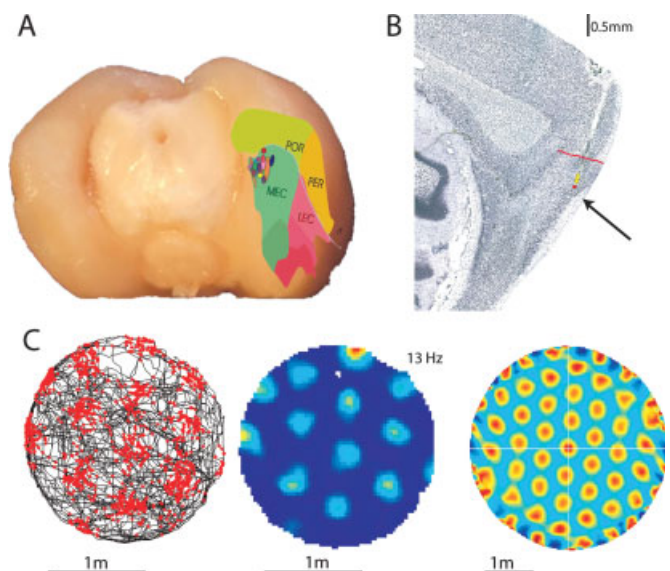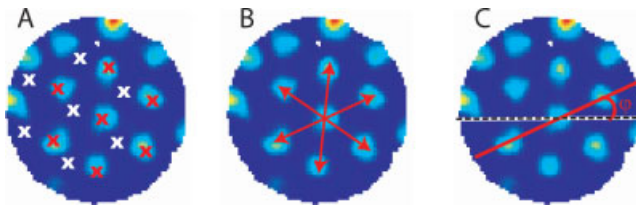
FIGURE 3. Parameters of the grid. (A) Spatial phase is the position of the grid vertices in the *xy* plane. Two possible phases are indicated with crosses, one set in red and one in white. (B) The spacing of the grid is the distance between any vertex of the grid and the six adjacent vertices in the rate map or in the autocorrelogram. Spatial frequency is the inverse of spacing. (C) The orientation of the grid is defined by the lines that intersect the grid vertices. Each grid has three such axes. The grid orientation is the angle between a horizontal reference line (black) and the axis with the smallest angle relative to this reference line (red).

memory after lesions of the dorsolateral band of this brain region (Steffenach et al., 2005).

The spatial firing properties of the entorhinal neurons differed from place cells in that all cells had multiple nonoverlapping fields. Moreover, the many fields of each cell were not randomly distributed. The interfield distance was much larger than in a shuffled distribution and a striking regularity was apparent (Fyhn et al., 2004). The regularity generated quite some discussion when we presented them to colleagues. We particularly appreciate a breakfast meeting with Bill Skaggs at the Society for Neuroscience in 2004, where Bill drew our attention to the apparent hexagonal structure of the grids in the Fyhn paper. Whether a periodic pattern was present could not be determined from the existing data; larger environments were needed. Together with Torkel Hafting, Marianne Fyhn and Sturla Molden in our lab, we thus constructed a 2-m wide circular arena and,
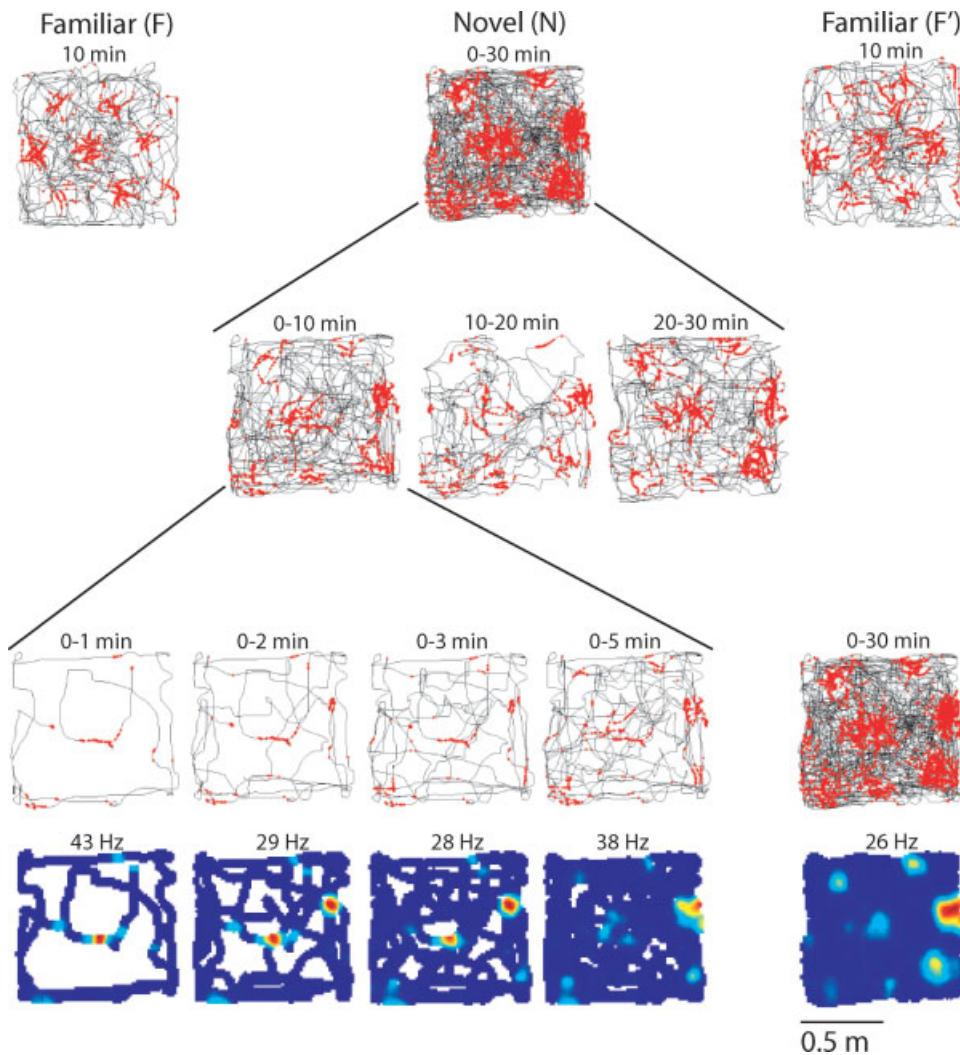

FIGURE 4. Grid structure is expressed instantly in a novel environment. The figure shows trajectories with superimposed spike locations in a rat that was running in a familiar room for 10 min, in a novel room for 30 min, and a second time in the familiar room for 10 min (top row). The middle row shows the trial in the novel room broken down into 10 min segments. In the bottom row, the trial is broken down further to the first 1, 2, 3, 5 and 30 min. Corresponding color maps are shown beneath each trajectory. Modified from Hafting et al. (2005).
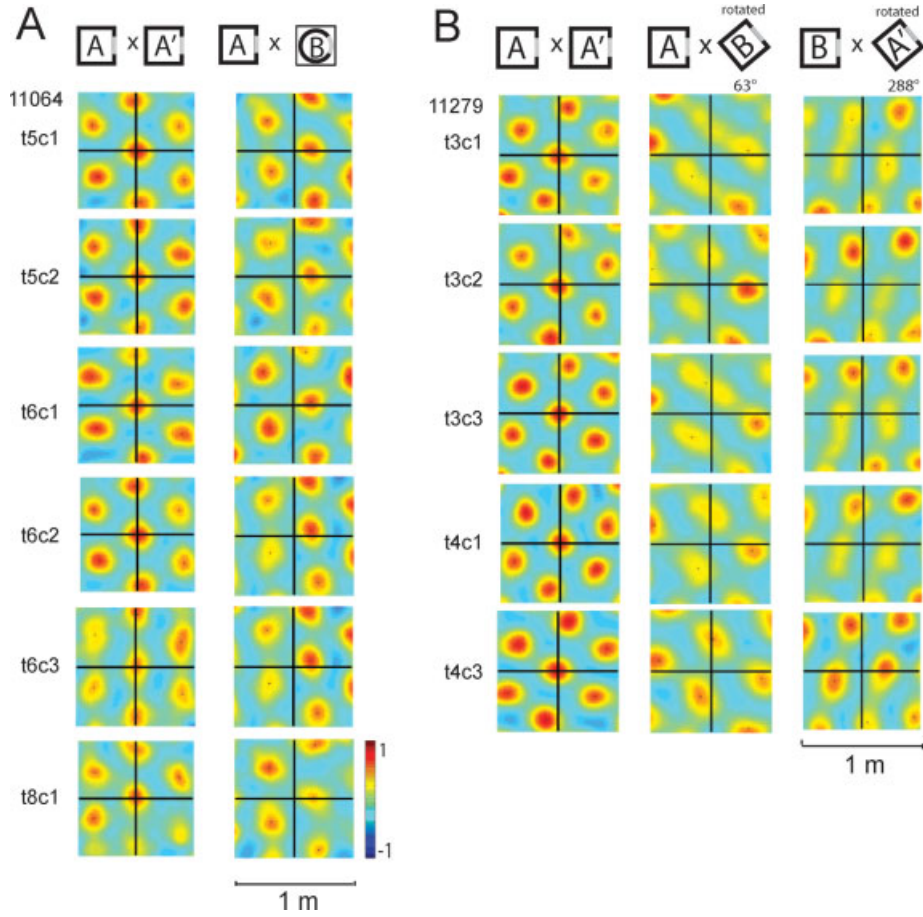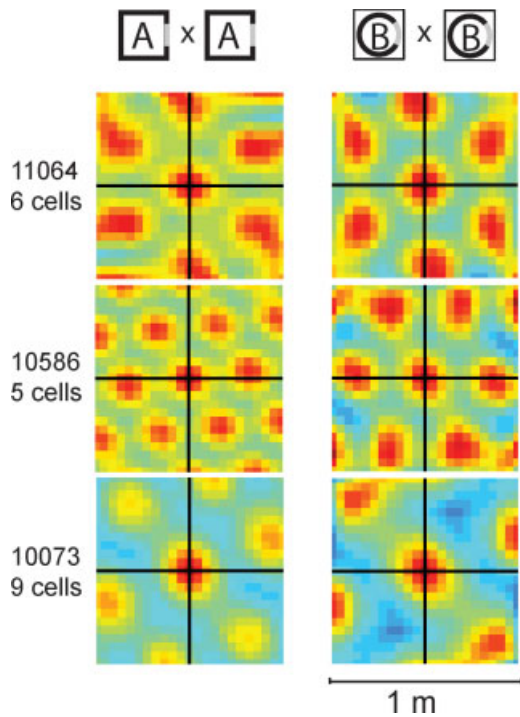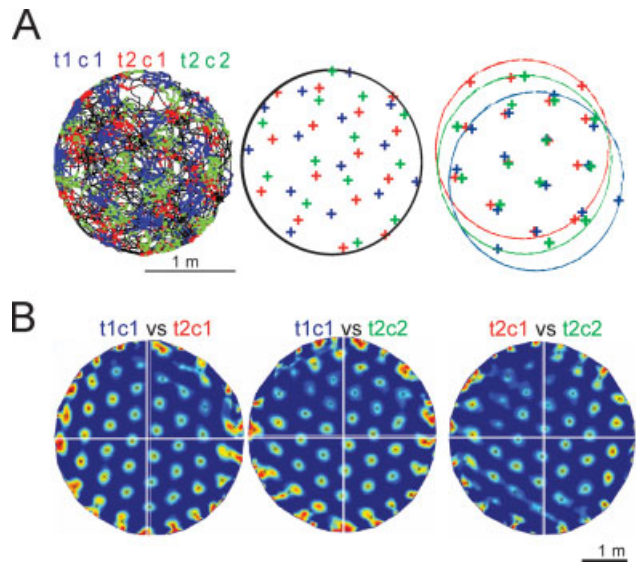
FIGURE 5

FIGURE 6

FIGURE 7

indeed, in this environment the multiple firing fields of individual entorhinal neurons formed a striking triangular or hexagonal structure (Hafting et al., 2005). In most layer II cell, the firing fields created a regularly tessellating pattern—or a 'grid'—spanning the entire two-dimensional environment available to the animal. The repeating unit of the grid was an equilateral triangle or, more precisely, two triangles with an opposite orientation. Combining six of these triangles gave a regular hexagon (Fig. 2C). Each grid had a specific spacing (distance between fields), orientation (tilt relative to an external reference axis), and phase (*xy* displacement relative to an external reference point) (Fig. 3). There was usually considerable variation in the rate of firing at different grid vertices; at some vertices, the rate exceeded 30 Hz; at others, there were only a few scattered spikes. The grid cells were largely nondirectional, i.e., the firing rates did not depend on the direction of the animal as it passed the grid vertices.

A MECHANISM FOR PATH INTEGRATION?

The strict periodicity of the firing pattern pointed to grid cells as a possible element of a metric system for spatial navigation (Hafting et al., 2005; Fuhs and Touretzky, 2006; McNaughton et al., 2006). The fact that the periodic firing pattern is maintained in spite of constant changes in running speed and running direction suggests that the grid must rely on path integration, i.e., changes in velocity and heading must be integrated over time to enable a constant representation of the spatial relationship between positions. Because similar firing patterns have not yet been observed in any of the major inputs to the grid cell area (Fyhn et al., 2004), the integration is thought to take place locally, in the network of grid cells. The expression of path integration in this area is consistent with the observation that the grid fields appear independently of specific landmarks and environmental configu-

rations (Hafting et al., 2005). They can be seen immediately as an animal starts to explore a new environment (Fig. 4), and the grids persist when external sensory cues are removed, for example when all lights are turned off. The proposed role of the medial entorhinal cortex in path integration in rats is also supported by the fact that rats with lesions in this region cannot find their way back to a starting refuge based on self-motion information only (Parron and Save, 2004).

Unlike place cells, ensembles of grid cells maintain a rigid spatial relationship (Fig. 5). The spatial relationship between grids of cells in the same part of entorhinal cortex remains constant across environments, such that if the grid vertices of two cells are displaced by 10 cm in one room they will be displaced by 10 cm in the adjacent room too. The cells will also rotate by similar amounts between the two environments. The rigid spatial relationship of colocalized grid cells makes the network uninformative about environment or context, but enables it to provide accurate metric information about the animal's position relative to reference points in the environment. The rigid ensemble properties are analogous to those of the head direction system, where the cells retain differences in directional tuning from one environment to the next (Taube et al., 1990; Taube, 1998; Hargreaves et al., 2007). Collectively, these findings suggest that grid cells and head direction cells are part of a single coherent representation that operates uniformly across environments, irrespective of the content of those environments. This would only be possible if the key input were similar in all environments, as it would be if the firing patterns are driven primarily by vestibular-kinesthetic feedback from the animal's own movement.

While the configuration of the environment may not be essential for producing the grid pattern, the spatial phase and orientation of the grid are likely determined by landmarks and geometrical boundaries. Several observations suggest that these properties depend on such associations with the environment. First, on repeated tests in the same environment, the vertices of

FIGURE 5. Crosscorrelations between grid fields in different environments. Each crosscorrelogram is for one individual cell (t, tetrode; c, cell number). The crosscorrelograms are color-coded, with blue indicating $r = -1$ and red indicating $r = +1$. (A) Tests in different boxes in the same place. Box A was a square; box B was a circle. The rat was tested twice in box A (A and A'). (B) Tests in similar boxes in different rooms. The rat was tested twice in room A and once in room B. Grid fields in different rooms were compared by rotating one field relative to the other in steps of 3 degrees and computing the crosscorrelation for each rotation. The rotation that gave the maximal crosscorrelation is shown. Note that all grid cells at the recording location showed similar displacements and rotations. Modified from Fyhn et al. (2007).

FIGURE 6. Expansion of the grid. Each diagram shows an autocorrelation for ensembles of grid cells recorded in different boxes in the same room (a square box A and a circular box B). The grid fields of all simultaneously recorded cells were stacked on top of each other and autocorrelation matrices were determined for the entire ensemble by computing correlations between two identical copies of the stack at all possible displacements in the *xy* plane. Grid structure in the ensemble autocorrelation map indicates that the grid cells had similar spacing and orientation (see Fig. 8). Note that the grid scales up in the circle in two of the animals (10,586 and 10,073) whereas one animal shows no change (11,064). Modified from Fyhn et al. (2007).

FIGURE 7. Spatial phase is distributed among neighboring grid cells. (A) Firing fields of the three grid cells, each with a separate color (t, tetrode number; c, cell number). Left: Trajectory maps. Middle: Peak locations. Right: Peaks are shifted to visualize similarity in spacing and orientation. (B) Spatial crosscorrelations for pairs of grid fields (same three cells). The offset from the origin indicates that the grids are shifted relative to each other. Modified from Hafting et al. (2005).

the grid are usually located at identical positions. Second, when prominent landmarks are rotated in an otherwise ambiguous circular environment, the grids rotate with the landmark (Hafting et al., 2005). Third, when a familiar square or rectangular enclosure is deformed by stretching the environment in one direction, the grid is extended parametrically in the same direction, whereas the spacing remains essentially unchanged in the orthogonal direction (Barry et al., 2007). Rescaling may perhaps also occur within environments, near the boundaries, as the spacing and orientation of the grid is sometimes less regular along the periphery than in the rest of the box (Hafting et al., 2005). Taken together, these observations suggest that the vertices of the grid are firmly anchored to geometrical boundaries and beacons of the environment.

The mechanisms of the anchoring process have not been identified. However, the contextual specificity of the hippocampal representations (Muller et al., 1991; Colgin et al., 2008) and the enormous storage capacity of its intrinsic networks (Battaglia and Treves, 1998) point to the hippocampus as a possible storage site for associations between the path integrator and the specific features of the individual environment (Hafting et al., 2005; O'Keefe and Burgess, 2005). Through backprojections to the deep and superficial layers of the entorhinal cortex (Iijima et al., 1996; van Haeften et al., 2003; Kloosterman et al., 2003; Witter and Amaral, 2004), outputs from place cells in the hippocampus may reset the entorhinal path integrator as errors accumulate during movement. Associations with landmarks, stored in the hippocampus, may also enable alignment of grid maps from one trial to the next, even when the animal's point of departure is different. In agreement with these suggestions, grids have been shown to destabilize after inactivation of the hippocampus (Bonnevie et al., 2006; Hafting et al., 2008a). The grid pattern persists for some minutes after the entire assembly of place cells is turned off, but with continued inactivation, the grid fields become less coherent and finally no spatial structure is apparent. How grid cells are reset by place cells, if they are, remains to be determined. For example, is the calibration between landmark and self-motion information a continuous process, or are the updates intermittent? If so, how often is the path integrator calibrated and what factors trigger the calibration? Preliminary analyses suggest that grid patterns reset, along with place cells, at the turning points in a multisegmented maze (Derdikman et al., 2008), suggesting that, in complex environments, the grid is broken into smaller units, which each are initialized as the rat passes a prominent landmark or boundary in the environment.

The proposed role of the grid cells as an intrinsic metric for space is challenged by observations suggesting that the scale of the grid map may vary over time. While grid patterns may have a similar scale in environments with distinct physical differences (Hafting et al., 2005), Barry et al. (2007) showed that grid patterns are deformable when rats are first trained in a square enclosure and then introduced to a rectangular version of the same environment, or vice versa. In their study, the grid rescaled in the stretched dimension, although to a lesser amount than the environmental deformation. The rescaling fac-

tor was between 10 and 20% (Fig. 2A,B in Barry et al., 2007). Some rescaling has also been observed when animals are transferred between identically shaped recording enclosures in rooms with different cue configurations (Fig. 6; Fyhn et al., 2007). Under such conditions, when scaling occurs, the grid expands equally in the x and y dimension. The factors controlling rescaling have not been determined, but they appear to correlate with experience. The deformation in the rectangle-shaped environments was most pronounced when the box was extended or compressed for the first time; no significant rescaling was observed if the animal was already familiar with the alternative shape (Barry et al., 2007). The fact that grids may revert to an unstretched pattern with prolonged training (Hafting et al., 2005; Barry et al., 2007) implies that the system has a default intrinsic grid scale. Yet, such reversals are slow, occurring over many days and possibly not fast enough to recalibrate position estimates at the behavioral level. How the animal compensates for rescaling, when it happens, is not known, but it is possible that the absolute or relative change in scale is similar across the entire grid map and that the read-out mechanisms, wherever they are, are able to adjust for such a global change.

A MAP OF GRID CELLS

The possible existence of a path-integration mechanism in the entorhinal cortex raises the possibility that significant parts of the spatial map proposed for the hippocampus by O'Keefe and Nadel in 1978 (O'Keefe and Nadel, 1978) are actually located in the entorhinal cortex. The map-like nature of the entorhinal grid representation is supported by its strict anatomical organization, which in some respects is reminiscent of the modular organization of cell types in sensory systems (Hubel and Wiesel, 1977). Grid cells in the same part of medial entorhinal cortex have similar grid spacing and grid orientation (Fig. 7; Hafting et al., 2005), but the phase of the grid is nontopographic, i.e., the firing fields of colocalized cells appear to be shifted randomly relative to each other (Fig. 8; Hafting et al., 2005), just like the fields of neighboring place cells in the hippocampus (O'Keefe, 1976; Hirase et al., 2001; Redish et al., 2001). The colocalization of cells with identical grid spacing and grid orientation is suggestive of a topographical arrangement.

Recordings from grid cells at different locations in the entorhinal cortex have provided some clues to the organization of the spatial map. There is a striking and approximately linear increase in the spacing of the grid from dorsal to ventral positions in the medial entorhinal cortex (Fyhn et al., 2004; Hafting et al., 2005; Brun et al., 2008). The increase in scale mirrors the increase in the size of place fields observed along the dorsoventral axis of the hippocampus (Jung et al., 1994; Maurer et al., 2005; Kjelstrup et al., 2008). The orientation of the grid may also be subject to some topographical organization, but how this variable is mapped onto the entorhinal
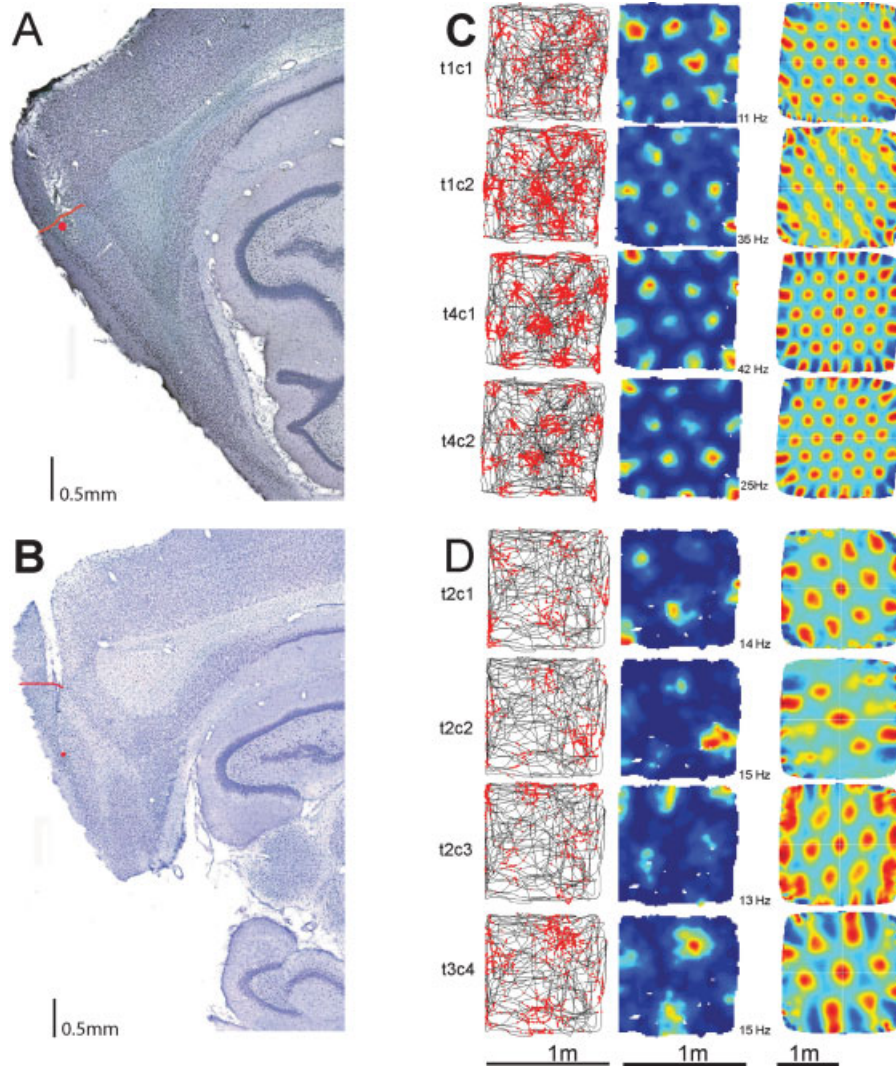
FIGURE 8. Grid spacing increases topographically along the dorso-ventral axis of the medial entorhinal cortex. Grid cells were recorded while the rat was running in a 1 × 1 m² square open field. (AB) Sagittal Nissl-stained sections showing recording locations at the dorsal end of the medial entorhinal cortex (A) and at a more ventral position, ~25% along the dorsoventral axis of the region (B). (CD) Color-coded firing rate maps show denser grid spacing for cells recorded at the dorsal position (A) than at the ventral position (B). Note that the spacing and orientation are similar for cells recorded at the same brain position. Modified from Hafting et al. (2005).
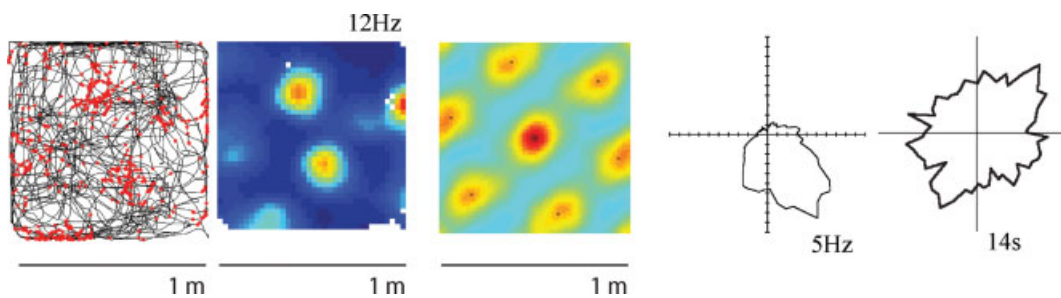

FIGURE 9. Conjunctive cell showing both grid structure and head direction modulation. From left to right: trajectory with spike locations, color-coded rate map, color-coded autocorrelation matrix, and a polar plot showing firing rate as a function of head direction (left) and amount of time that the rat faced each direction (right). The scale of the autocorrelation map is the same as for the rate map; only the central part of the autocorrelogram is shown. Maximum firing rates are indicated for the rate map (second from left) as well as the polar plot (second from right). Maximum occupancy (in the southwest and northeast directions) is indicated in the right panel. Modified from Sargolini et al. (2006).

cortex has not been determined. Although neighboring grid cells always have the same grid orientation, simultaneously recorded cells from noncorresponding locations in the left and right entorhinal cortices do sometimes have different grid orientations (Fig. 2e in Hafting et al., 2005; Hafting et al., 2008b), suggesting that more than one orientation is represented in each brain. We do not know if all or only a few grid orientations are represented.

Several architectonic features of the entorhinal cortex are suggestive of a modular arrangement of the grid map. These factors include the periodic bundling of pyramidal cell dendrites and axons and the periodic variation in the density of several immunocytochemical markers (Witter and Moser, 2006). If the map is modular, a challenge will be to determine the number and location of the modules and, after that, to establish when and how the modules are synchronized. Whether the anatomical clusters correspond to functionally segregated grid maps with different grid spacings or grid orientations also remains to be determined. Preliminary observations are consistent with a modular organization. The spacing has been reported to increase in quantal steps along the dorsoventral axis of the entorhinal cortex, with a step size ~1.7 times the grid scale of the shortest spacing (Barry et al., 2007). It is not clear from the data whether quantal jumps occur within cell layers, in the tangential plane, or if the steps reflect cell groups in different layers, which may not be aligned in terms of grid scale. Irrespective of whether the map is quantal or not, the map remains coherent over large distances, as grid cells at different dorsoventral levels in different hemispheres maintain a constant spatial relationship (Hafting et al., 2008b), much like dispersed cells in the head direction system (Taube et al., 1990; Hargreaves et al., 2007).

THE EXTENDED MAP

Not all entorhinal cells are grid cells. While most layer II cells have grid fields similar to those of the original reports, cells in the middle and deeper layers have somewhat different properties (Sargolini et al., 2006). First, these layers contain a substantial proportion of head direction cells, which fire if and only if the rat's head is facing in a certain direction relative to the surrounding landmarks. Such cells were originally reported in the dorsal presubiculum (Ranck, 1985; Taube et al., 1990) but have subsequently been identified in a number of cortical and subcortical brain regions (Taube, 1998). The middle and deeper layers also contain a large proportion of grid cells, but, unlike their counterparts in layer II, these cells are conjunctively modulated by the rat's head direction (Fig. 9; Sargolini et al., 2006). Both grid cells and conjunctive cells are modulated by the rat's running speed. The degree of directional modulation varies from cell to cell, with the weakest conjunctive cells fusing into the population of classical head-direction cells. Head direction cells and conjunctive cells are located in overlapping regions. Based on the strong projections from dorsal presubiculum to medial entorhinal cortex (van Haeften

et al., 1997), it is tempting to speculate that signals from presubicular head direction cells control the head direction preference of cells in the middle and deeper layers of the medial entorhinal cortex as well as the orientation of grid fields in all layers, but this has not been tested.

Preliminary evidence from our lab suggests that, intermingled between grid cells, head direction cells and conjunctive grid × head direction cells, there is another cell type, also confined primarily to the middle and deeper layers of the medial entorhinal cortex. This cell type fires exclusively along the geometrical borders of the available environment, often along a single border (Solstad et al., 2008; see also Savelli et al., 2008). The cells continue to fire when the height of the border is reduced to a minimum, allowing the rat to step over it, and these cells are also active at the boundaries of large elevated platforms, suggesting that it is the presence of a border—and not the physical features of the walls—that induce the edge-specific firing. Currently, it is not known how these cells interact with other cell types in the entorhinal cortex and hippocampus. Cells with boundary-related activity have previously been reported in the subiculum (Sharp, 1999b; Barry et al., 2006), one synapse downstream of the hippocampus and one synapse upstream of the entorhinal cortex, but the reports are still anecdotic and the number of border cells with high S/N ratios in this area is apparently extremely low ($n \approx 2$ in Barry et al., 2006; 0 in Henriksen et al., 2007).

These observations together imply that the entorhinal network contains information about position, speed, distance, direction, and boundaries—probably enough to construct an accurate metric representation of the animal's changing position in the environment. The ability of layer II cells to read out the signals from the middle and deep layers may be critical for translating activity between grid cells with a different spatial phase as the animal moves around at varying speed and direction (Sargolini et al., 2006; McNaughton et al., 2006). Border cells may be instrumental in anchoring the grid to the geometrical boundaries of the environment. Whether and how the various entorhinal cell types interact remains to be determined, however. With the rapidly growing toolbox for targeted genetic silencing, the function of specific entorhinal cell types and their mechanisms of interaction may be uncovered in the not too distant future.

The spatial representation network is certainly not confined to the medial entorhinal cortex. The function of the lateral entorhinal cortex is currently unsettled. Grid cells have not been observed in this region (Hargreaves et al., 2005). The apparently nonspatial firing properties of lateral entorhinal neurons is consistent with the absence of input to this region from head direction cells in the presubiculum (Witter and Moser, 2006), although position may still be represented in ways not detectable in time-averaged rate maps. In contrast, grid cells can readily be identified in some other parahippocampal regions, notably the parasubiculum and the presubiculum (Boccara et al., 2008). In the parasubiculum, a relatively large fraction of the cell population appears to have grid properties. Like in the medial entorhinal cortex, grid cells intermingle with head direction cells

and conjunctive cells, especially in the middle and deeper layers. These cells have broad waveforms, suggesting that they are not merely axons of projection neurons in the entorhinal cortex. A few grid cells may also be located in the presubiculum (Boccara et al., 2008). These may be identical to the θ-modulated place × direction cells observed in small recording environments in an earlier study (Cacucci et al., 2004). However, the majority of cells in the presubiculum are tuned primarily to head direction (Taube et al., 1990; Johnson et al., 2005; Boccara et al., 2008). The existence of grid cells in these parahippocampal regions, outside the classical boundaries of the medial entorhinal cortex, suggests that grid structure is tolerant to some variation in neural network architecture.

Finally, it is important to realize that the hippocampal–parahippocampal circuit only forms a representation. Representations can only influence navigation to the extent that information about the animal's location is transferred to brain regions involved in planning and initiating movement. There are a number of possible pathways to the motor control systems of the brain, including the outputs from the hippocampus and subiculum to the striatum and prefrontal cortex. An alternative set of routes includes the posterior parietal cortex, which in head-restrained primates has a pivotal role in preparing and guiding movement towards proximal targets (Andersen and Buneo, 2002). This region of cortex may be responsible for the translation of a world-centered spatial representation of self-location, possibly generated in the entorhinal cortex, to a set of body-centered reference frames needed for bringing the animal to a particular goal location (Whitlock et al., 2008b). Lesions of the rat homolog of the posterior parietal cortex cause severe impairment in the ability to navigate back to a refuge under conditions where the return pathway can only be computed on the basis of the animal's own movement (Save et al., 2001; Parron and Save, 2004). Studies of spatial representation in the rat parietal cortex are in their infancy, but the region is known to contain neurons that map navigational epochs when the animal follows a fixed route (Nitz, 2006; Whitlock et al., 2008a). A key objective for future studies of this region will be to determine if neurons in this area express information received from grid maps in the entorhinal cortex and, if they do, how this information is further converted to a movement plan in parietal cortex or elsewhere.

FROM GRID CELLS TO PLACE CELLS, OR VICE VERSA

Place cells are likely to receive most of their cortical input from grid cells, considering that the majority of principal cells in layers II and III of medial entorhinal cortex project to the hippocampus (Witter and Amaral, 2004). Grid patterns can also be recorded from putative axons in the perforant path termination area of CA1 and dentate gyrus (Leutgeb et al., 2007). We do not presently know how place cells convert grid patterns to single place fields. There are at least two possible sets of mechanisms. First, place fields could be generated by linear combination of signals from grid cells with different grid spac-

ing (Fig. 10; O'Keefe and Burgess, 2005; Fuhs and Tourezky, 2006; McNaughton et al., 2006; Solstad et al., 2006). The combined signal will also be a periodic pattern, with a peak at the location where most of the contributing grids are in phase, but because the period would be large, equal to the least common multiple of the grid spacings, only one field would be observed in a standard experimental setting. Models have shown that individual fields can be generated by a combination of only 10–50 grid cells with variable grid spacing and grid orientation but overlapping spatial phase (Solstad et al., 2006). In a second type of mechanism, place cells receive inputs from grid cells with variable spacing, orientation, and spatial phase (Rolls et al., 2006). Single-peaked place fields are generated from the resulting distribution of activity peaks by competitive Hebbian learning processes. Experimental studies have not yet distinguished between these models. The idea that place fields are formed by long-term potentiation (LTP)-like learning mechanisms receives only partial support in that place fields develop also in the presence of NMDA receptor blockers (McHugh et al., 1996; Kentros et al., 1998; Ekstrom et al., 2001). NMDA receptor-dependent plasticity is necessary for experience-dependent changes in the shape and size of the place field (Ekstrom et al., 2001), but not for the manifestation of place-specific firing as such, implying that hardwired connections may be sufficient for place cell formation in at least some parts of the circuit. Competitive learning mechanisms may instead be necessary for formation of new cell assemblies when rats acquire information about unfamiliar environments (Leutgeb et al., 2004, 2006).

Although place cells are downstream of grid cells, they are also upstream in the sense that CA1 neurons project back to the entorhinal cortex, both directly and via the subiculum. These bakprojections mainly terminate in layer V, but layer V neurons have extensive connections with neurons in the superficial layers (van Haeften et al., 2003; Kloosterman et al., 2003), where most of the cells have grid properties (Sargolini et al., 2006). Because the connections are bidirectional, it is conceivable that grid cells are driven by place cells, just as much as place cells are driven by grid cells. The maintenance of grid patterns during the first minutes after inactivation of the hippocampus (Hafting et al., 2008a) speaks against a direct role for place cells in maintaining firing, but place cells may nonetheless be instrumental in forming the grids initially (Kropff and Treves, 2008).

Similar arguments can, in principle, be made about the direction of influence when hippocampal and entorhinal neurons undergo changes in reference frames. When animals move from one environment to another, the distribution of activity across the population of place cells is nearly orthogonalized, with many cells turning off, others turning on, and the rest firing in different positions relative to each other (Bostock et al., 1991, Muller et al., 1991; Colgin et al., 2008). Such remapping is accompanied by a simultaneous realignment of the grid patterns of cells in the medial entorhinal cortex (Fyhn et al., 2007). As an animal is moved from one room to the other, the grid fields shift and rotate, although the intrinsic relationship between grids of different colocalized cells remains the same.
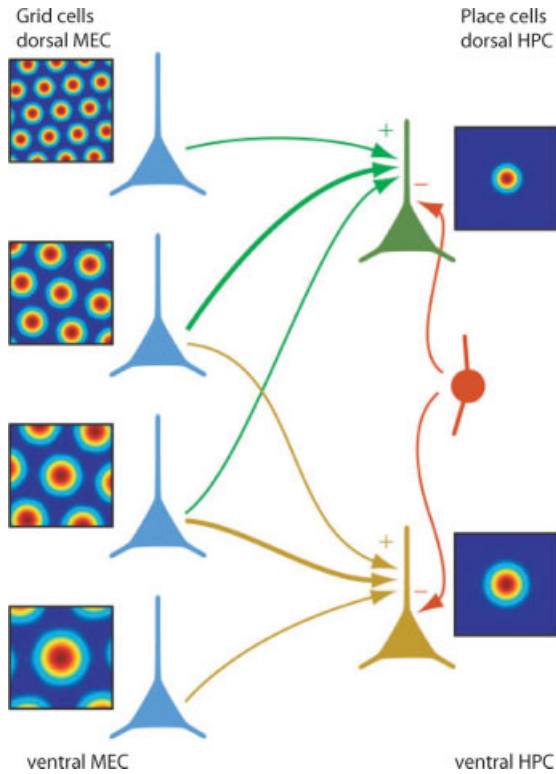
FIGURE 10. Model showing how periodic grid cells could be transformed to nonperiodic place cells by linear summation. Place cells receive input from grid cells with overlapping spatial phase but different grid spacing and grid orientation. Reproduced from Solstad et al. (2006), with permission.

We do not know if remapping in the hippocampus is caused by grid realignments in the entorhinal cortex, or vice versa. Most likely, grid cells and place cells interact as an integrated circularly connected system.

THE ORIGIN OF THE GRID PATTERN

Of all questions raised by the discovery of grid cells, the greatest and most interesting challenge is perhaps to understand the origin of the periodic pattern. How do grids develop during the ontogenesis of the nervous system and how is the pattern maintained in the adult brain? Models of grid formation appeared already in 2006 and 2007. In these first-generation models, the triangular distribution of neural activity is a consequence of a process where entorhinal neurons path-integrate speed and direction inputs from other cells. The models cluster into two groups, those that ascribe grid formation to intracellular processes and those suggesting that the pattern is a result of local network activity.

In the intracellular models, grid formation is a consequence of interference between membrane potential oscillations at two frequencies in the theta range differing by an amount that is proportional to the running speed of the rat. The interference pattern can be decomposed into a fast oscillation at the mean of the two primary frequencies and a slow modulation with a phase that integrates the speed of the rat and thus reflects its linear position (O'Keefe and Recce, 1993; Lengyel et al., 2003). In this way, the slow modulation is expressed as a linear spatial oscillation. The
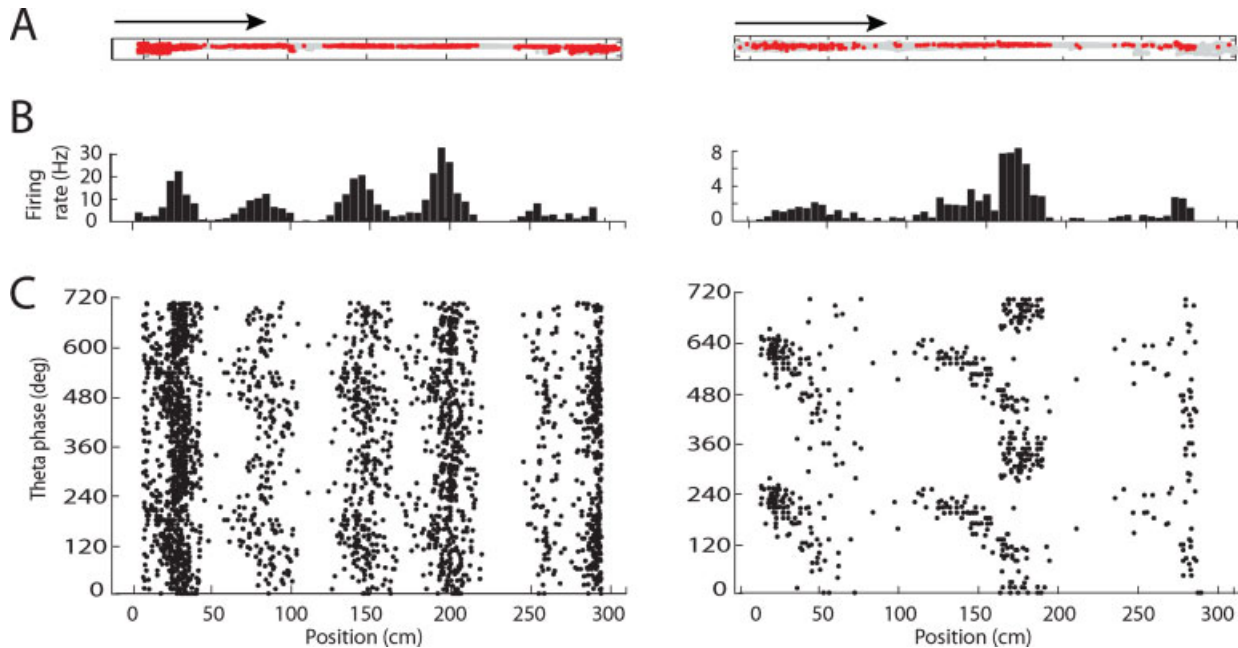

FIGURE 11. Phase precession in grid cells in layer II of medial entorhinal cortex. Spikes were recorded from two cells while a rat ran back and forth on a 320 cm long linear track. The cell to the left was at a dorsal recording location where the grid spacing is small; the cell to the right was recorded at a more ventral location where the grid spacing is larger. Only left-to-right runs are shown. (A) Trajectory (gray) with locations of individual spikes (red). (B) Linearized spatial firing rate map (bins of 5 cm). (C) Theta phase as a function of position. Two theta cycles are displayed to illustrate that phase precession is restricted to a single theta cycle. Note gradual advance of firing phase as the rat passes through each field. Modified from Hafting et al. (2008a).

model was extended to two dimensions after the discovery of grid cells (Burgess et al., 2007; Hasselmo et al., 2007). It was suggested that an interference wave is generated from a somatic oscillator reflecting the theta rhythm in the neural population and each of several dendritic oscillators, whose frequencies are equal to the somatic oscillator plus a term proportional to the projection of the rat velocity in a characteristic preferred direction. As in the original model, the slow modulation of each interference wave was suggested to integrate the projected component of the velocity into a linear periodic spatial pattern. By combining several linear patterns, a triangular grid map could be obtained, provided that the directions differed in multiples of 60° and the phases were set to overlap maximally. There are essentially two variants of this type of model, one in which interference occurs as a result of integration of signals from separate dendrites, as above, and one in which the interference pattern emerges from separate cells with different linear firing fields (Burgess et al., 2007, 2008), or separate microgrid cells with a different spacing or orientation (Blair et al., 2007). Both of these fundamental cell classes are hypothetical.

In the network models, grid patterns are generated from continuous attractor dynamics. A continuous attractor is a manifold of stable states, which, given a certain amount of global inhibition in the network, permits smooth variation of a spontaneously generated representation across a surface of interconnected cells (Tsodyks and Sejnowski, 1995). The 'bump' of activity is centered on mutually connected cells, which, in the case of the grid cells, may have a common set of firing vertices (Fuhs and Touretzky, 2006; McNaughton et al., 2006). The bump is thought to move between grid cells with different vertices, as the animal runs from one place to the other in its environment, with distance and direction of bump movement matching the animal's running trajectory. In the first model that was published, Fuhs and Touretzky (2006) proposed that grid cells are part of a topographically organized network where adjacent cells have adjacent grid phases, such that each place in the environment is represented as a grid pattern on the cell layer. When the animal moves, this 'grid skeleton' is rigidly translated across the entorhinal cell surface in accordance with direction and speed-dependent inputs to the cells. This model showed how attractor dynamics could generate periodic structure, but it conflicted with data suggesting that neighboring grid cells do not have similar grid phases (Hafting et al., 2005). In response to this challenge, a second model was proposed by McNaughton et al. (2006). As in the Fuhs and Touretzky model, the bump of activity is translated across the cell surface based on direction and speed signals from other cells, but the model is different in that a topographical network is present only during development of the nervous system, when the network serves as a tutor to train smaller clusters of grid cells with randomly distributed Hebbian connections. The inputs from the tutor are scrambled, such that neurons with similar phase are distributed but yet can be associated by synaptic plasticity. Because the tutor has the periodicity of a grid, the synaptic matrix of the developing entorhinal network becomes toroidal. This toroidal connectivity is thought to account for the spatial periodicity of the grid pattern in moving animals. Whether such toroidal matrices exist is of course not known.

Experimental data confirm some broad predictions of both classes of models but certainly do not prove anyone of them. Preliminary observations suggest that grid scale increases in a step-like manner along the dorsoventral axis of the medial entorhinal cortex (Barry et al., 2007), much as predicted by the neural network models, which explicitly or implicitly rely on a discontinuous arrangement of modules with different grid spacing and grid orientation (Fuhs and Touretzky, 2006; McNaughton et al., 2006). The wave interference model, on the other hand, is consistent with the existence of intrinsic membrane potential oscillations in the theta frequency range in medial entorhinal layer II neurons (Alonso and Llinas, 1989; Klink and Alonso, 1993), and the fact that the frequency of these intrinsic oscillations decreases from dorsal to ventral levels of the medial entorhinal cortex (Giocomo et al., 2007; Giocomo and Hasselmo, 2008), just like the spatial frequency of grid fields decreases along this same axis (Fyhn et al., 2004; Hafting et al., 2005; Brun et al., 2008). The wave interference models also predict the existence of phase precession in grid cells, as, according to the model, the discharge times are determined also by the faster component of the interference wave, whose frequency exceeds that of the theta rhythm in the field. Phase precession was originally observed in hippocampal place cells when the animal passed through the place field (O'Keefe and Recce, 1993) but has recently been observed in individual fields of entorhinal grid cells too (Fig. 11; Hafting et al., 2008a). The wave interference models are also consistent with the observation that grid cells fire at increased theta frequency during increases of running speed, and that such increases correlate with a decrease in grid spacing (Jeewajee et al., 2008). Other attributes of the grid pattern, however, cannot readily be explained by wave interference, such as the nonlinear shape of the phase-by-position curve and the somewhat asymmetric shape of the grid fields (Fig. 11; Hafting et al., 2008a), suggesting that the mechanism is more complex. At present, attempts to test the models are suffering from a lack of tools for direct measurement of the postulated interactions; no one has observed whether wave interference actually occurs in entorhinal neurons, and no one has ever seen attractor dynamics in the entorhinal network.

CONCLUSION

The discoveries of place cells and grid cells have opened paths for understanding how the brain forms representations of the animal's position in the environment. With increasing insights into how features of the spatial environment are represented in numerous interacting cell types in the hippocampal–parahippocampal circuit, the sense of self-location may be one of the first cognitive functions to be understood in some mechanistic detail. Key tasks for the future will be to understand the function of individual cell types in the entorhinal circuit, how

they interact with each other as well as outside brain regions, and to what extent the individual contributions are shaped by experience or determined by genetic programs. Some of the most important questions are perhaps related to the origin of the grid pattern. Because the crystal-like structure of the grid pattern is generated within the nervous system itself, grid cells provide scientists with an experimental model to access on a broad basis the neuronal interactions responsible for pattern formation in the brain.

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