Place Cells, Grid Cells, and the Brain's Spatial Representation System

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Key Words

Abstract

More than three decades of research have demonstrated a role for
hippocampal place cells in representation of the spatial environment in
the brain. New studies have shown that place cells are part of a broader
circuit for dynamic representation of self-location. A key component of
this network is the entorhinal grid cells, which, by virtue of their tessel-
lating firing fields, may provide the elements of a path integration–based
neural map. Here we review how place cells and grid cells may form the
basis for quantitative spatiotemporal representation of places, routes,
and associated experiences during behavior and in memory. Because
these cell types have some of the most conspicuous behavioral correlates
among neurons in nonsensory cortical systems, and because their spatial
firing structure reflects computations internally in the system, studies
of entorhinal-hippocampal representations may offer considerable
insight into general principles of cortical network dynamics.

Contents

INTRODUCTION

Questions about how we perceive space and our place in that space have engaged epistemologists for centuries. Although the British empiricists of the seventeenth and eighteenth centuries thought that all knowledge about the world was ultimately derived from sensory impressions, Kant argued that some ideas exist as a priori intuitions, independent of specific experience. One of these ideas is the concept of space, which he considered an innate organizing principle of the mind, through which the world is, and must be, perceived. With the birth of experimental psychology and neuroscience a century later, the organization and development of spatial behavior and cognition could be analyzed experimentally. We review evidence from the past three decades that indicates the presence of a preconfigured or semipreconfigured brain system for representation and storage of self-location relative to the external environment. In agreement with the general ideas of Kant, place cells and grid cells in the hippocampal and entorhinal cortices may determine how we perceive and remember our position in the environment as well as the events we experience in that environment.

PLACE CELLS AND THE HIPPOCAMPAL MAP

The experimental study of spatial representations in the brain began with the discovery of place cells. More than 35 years ago, O'Keefe & Dostrovsky (1971) reported spatial receptive fields in complex-spiking neurons in the rat hippocampus, which are likely to be pyramidal cells (Henze et al. 2000). These place cells fired whenever the rat was in a certain place in the local environment (the place field of the cell; **Figure 1a**). Neighboring place cells fired at different locations such that, throughout the hippocampus, the entire environment was represented in the activity of the local cell population (O'Keefe 1976, Wilson & McNaughton 1993). The same place cells participated in representations for different environments, but the relationship of the firing fields differed from one setting to the next (O'Keefe & Conway 1978). Inspired by Tolman (1948), who suggested that local navigation is guided by internal "cognitive maps" that flexibly represent the overall spatial relationships between landmarks in the environment, O'Keefe & Nadel (1978) proposed that place cells are the basic elements of a distributed noncentered map-like representation. Place cells were suggested to provide the animal with a dynamic, continuously updated representation of allocentric space and the animal's own position in that space. We now have abundant evidence from a number of mammalian species demonstrating that the hippocampus plays a key role in spatial representation and spatial memory (Nadel 1991, Rolls 1999, Ekstrom et al. 2003, Ulanovsky & Moss 2007),

although new evidence suggests that position is only one of several facets of experience stored in the hippocampal network (Eichenbaum et al. 1999, Leutgeb et al. 2005b).

GRID CELLS AND THE ENTORHINAL MAP

All subfields of the hippocampal region contain place-modulated neurons, but the most distinct firing fields are found in the CA areas (Barnes et al. 1990). On the basis of the apparent amplification of spatial signals from the entorhinal cortex to the CA fields (Quirk et al. 1992), many investigators thought, until recently, that place signals depended primarily on computations within the hippocampal network. This view was challenged by the observation that spatial firing persisted in CA1 neurons after removal of intrahippocampal inputs from the dentate gyrus (McNaughton et al. 1989) and CA3 (Brun et al. 2002). This raised the possibility that spatial signals were conveyed to CA1 by the direct perforant-path projections from layer III of the entorhinal cortex. Projection neurons in layers II and III of the medial entorhinal cortex (MEC) were subsequently shown to exhibit sharply tuned spatial firing, much like place cells in the hippocampus, except that each cell had multiple firing fields (Fyhn et al. 2004). The many fields of each neuron formed a periodic triangular array, or grid, that tiled the entire environment explored by the animal (Hafting et al. 2005) (**Figure 1b**). Such grid cells collectively signaled the rat's changing position with a precision similar to that of place cells in the hippocampus (Fyhn et al. 2004). The graphics paper–like shape of the grid immediately indicated grid cells as possible elements of a metric system for spatial navigation (Hafting et al. 2005), with properties similar to that of the allocentric map proposed for the hippocampus more than 25 years earlier (O'Keefe & Nadel 1978).

How do grid representations map onto the surface of the entorhinal cortex? Each grid is characterized by spacing (distance between fields), orientation (tilt relative to an exter-
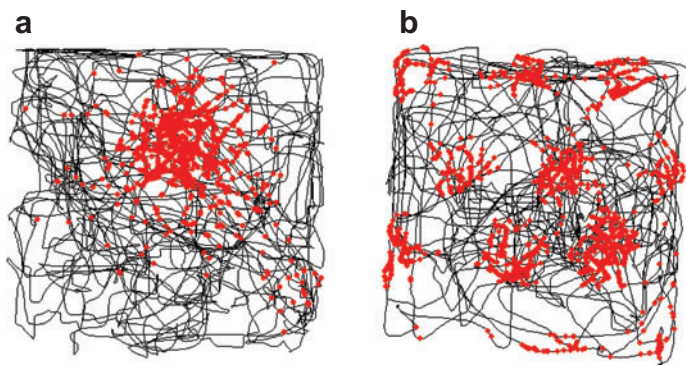

Figure 1

Place cell in the hippocampus (*a*) and grid cell in the medial entorhinal cortex (MEC) (*b*). Spike locations (*red*) are superimposed on the animal's trajectory in the recording enclosure (*black*). Whereas most place cells have a single firing location, the firing fields of a grid cell form a periodic triangular matrix tiling the entire environment available to the animal.

nal reference axis), and phase (*xy* displacement relative to an external reference point). Although cells in the same part of the MEC have similar grid spacing and grid orientation, the phase of the grid is nontopographic, i.e., the firing vertices of colocalized grid cells appear to be shifted randomly, just like the fields of neighboring place cells in the hippocampus. The spacing increases monotonically from dorsomedial to ventrolateral locations in MEC (Hafting et al. 2005, Solstad et al. 2007), mirroring the increase in size of place fields along the dorsoventral axis of the hippocampus (Jung et al. 1994, Maurer et al. 2005, Kjelstrup et al. 2007). Cells in different parts of the MEC may also have different grid orientations (Hafting et al. 2005), but the underlying topography, if there is one, has not been established. Thus, we do not know whether the entorhinal map has discrete subdivisions. The entorhinal cortex has several architectonic features suggestive of a modular arrangement, such as periodic bundling of pyramidal cell dendrites and axons and cyclic variations in the density of immunocytochemical markers (Witter & Moser 2006), but whether the anatomical cell clusters correspond to functionally segregated grid maps, each with their own spacing and orientation, remains to be determined.

MEC: medial entorhinal cortex

SENSORY CUES AND PATH INTEGRATION

Which factors control the spatial discharge pattern of place cells and grid cells? Early on, it became apparent that place fields are strongly influenced by distal sensory cues. When rats walked in a circle, rotation of the circumferential cues caused rotation of the place fields, whereas rotation of the proximal environment itself, in the presence of fixed distal cues, failed to change the firing locations (O'Keefe & Conway 1978, O'Keefe & Speakman 1987, Muller & Kubie 1987). Extending the sides of a rectangular recording box stretched or split the fields in the extended direction (O'Keefe & Burgess 1996). These observations indicate a primary role for extrinsic cues, and especially geometric boundaries, in defining the firing location of a place cell, although individual proximal landmarks do exert some influence under certain conditions (Muller & Kubie 1987, Gothard et al. 1996b, Cressant et al. 1997, Shapiro et al. 1997, Zinyuk et al. 2000, Fyhn et al. 2002). A similar dependence on distal landmarks and boundaries has since been demonstrated for entorhinal grid cells (Hafting et al. 2005, Barry et al. 2007). However, place cells and grid cells do not merely mirror sensory stimuli. When salient landmarks are removed while the animal is running in a familiar environment, both cell types continue to fire in the original location (Muller & Kubie 1987, Hafting et al. 2005). Moreover, representations in the hippocampus are often maintained when the recording box is transformed smoothly into another familiar box (J.K. Leutgeb et al. 2005), suggesting that the history of testing may sometimes exert stronger control on place cell activity than would the actual sensory stimuli.

Discrete representations of individual places would not be sufficient to support navigation from one place to another. The brain needs algorithms for linking the places in metric terms. When animals move away from a start position, they can keep track of their changing positions by integrating linear and angular self-motion (Barlow 1964, Mittelstaedt & Mittelstaedt 1980, Etienne & Jeffery 2004).

This process, referred to as path integration, is a primary determinant of firing in place cells. When rats are released from a movable start box on a linear track with a fixed goal at the end, the firing is initially determined by the distance from the start box (Gothard et al. 1996a, Redish et al. 2000). Although the activity is soon corrected against the external landmarks, this initial firing pattern suggests that place-selective firing can be driven by self-motion information alone.

Where is the path integrator? The hippocampus itself is not a good candidate. Without invoking a separate hippocampal circuit for this process, it would be hard to imagine how the algorithm could be adapted for each of the many overlapping spatial maps stored in the very same population of place cells. Place cells may instead receive inputs from a general metric navigational system outside the hippocampus (O'Keefe 1976). Grid cells may be part of this system. The persistence of grid fields after removal or replacement of major landmarks points to self-motion information as the primary source for maintaining and updating grid representations (Hafting et al. 2005, Fyhn et al. 2007). The system has access to direction and speed information required to transform the representation during movement (Sargolini et al. 2006b). However, whereas path integration may determine the basic structure of the firing matrix, the grid map is anchored to geometric boundaries and landmarks unique to each environment. These associations may, under some circumstances, override concurrent path integration–driven processes, such as when the sides of a familiar rectangular recording environment are extended moderately (Barry et al. 2007). The origin of the self-motion signals and the mechanisms for integration of self-motion signals with extrinsic sensory inputs have not been determined.

THEORETICAL MODELS OF GRID FORMATION

Most current models of grid field formation suggest that MEC neurons path-integrate

speed and direction signals provided by specialized cells, whereas sensory information related to the environment is used for setting the initial parameters of the grid or adjusting it to correct the cumulative error intrinsically associated with the integration of velocity.

One class of models suggests that grid formation is a result of local network activity. In these models, a single position is represented by an attractor, a stable firing state sustained by recurrent connections with robust performance in the presence of noise (Hopfield 1982, Amit 1989, Rolls & Treves 1998). A network can store several attractor states associated with different locations and retrieve any of them in response to sensory or path integration cues. When a large number of very close positions are represented, a continuous attractor emerges, which permits a smooth variation of the representation in accordance with the rat's trajectory (Tsodyks & Sejnowski 1995, Samsonovich & McNaughton 1997, Battaglia & Treves 1998). We review two of the models in this class.

Fuhs & Touretzky (2006) proposed that MEC is roughly topographically organized; neighboring grid cells display similar activity, and the representation of a single place forms a grid pattern on the neuron layer. Such a pattern emerges naturally at a population level in a network with Mexican hat connectivity, where every neuron is excited by its neighbors, inhibited by neurons at an intermediate distance, and unaffected by those far away. The authors include several alternating excitation and inhibition ranges and an overall decay of the synaptic strength with distance. With this connectivity rule, a grid of activity appears spontaneously in the MEC layer, except at the borders of the layer, where the lack of balance overexcites neurons and additional attenuation is required. To transform the grid pattern in the MEC layer into a grid firing field in each neuron, the representation of a single place must be rigidly displaced along the topographically organized network following the movements of the rat (**Figure 2a**). This happens if any given neuron receives an input proportional to the running speed only when the rat runs in a preferred direction, which is different for each neuron. Increased speed produces increased excitation and a faster displacement of the grid pattern across the neural layer. The proposed mechanism may fail to displace the initial representation accurately for realistic trajectories of the rat, resulting in neurons that do not express grid fields (Burak & Fiete 2006; see authors' response at **http://www. jneurosci.org/cgi/data/26/37/9352/DC1/1**).

The above model is challenged by the apparent lack of topography in grid phases of neighboring MEC neurons (Hafting et al. 2005). Motivated by this experimental observation, McNaughton et al. (2006) proposed, in an alternative model, that a topographically arranged network is present in the cortex during early postnatal development and serves as a tutor to train MEC cell modules with randomly distributed Hebbian connections and no topographical organization (**Figure 2b**). Attractor representations of space are formed in each of these modules during training. Because the inputs from the tutor are scrambled, neurons in a similar phase are not necessarily neighbors, but they are associated through synaptic plasticity. If after the training period neurons in a module were rearranged according to their firing phase or connection strength, a single bump of activity would be observed at any time. Because the tutor has the periodicity of a grid, the rearranged network has no borders and resembles the surface of a torus (**Figure 2b**). To displace representations along the abstract space of the continuous attractor, the model introduces an additional layer of cells whose firing is modulated by place, head direction, and speed. Sargolini et al. (2006b) have identified neurons with such properties. Neurons in this hidden layer may receive input from currently firing grid cells and project back selectively to grid cells that fire next along the trajectory; the activation of target cells depends on the current head direction and velocity of the rat (Samsonovich & McNaughton 1997, McNaughton et al. 2006; **Figure 2b**).

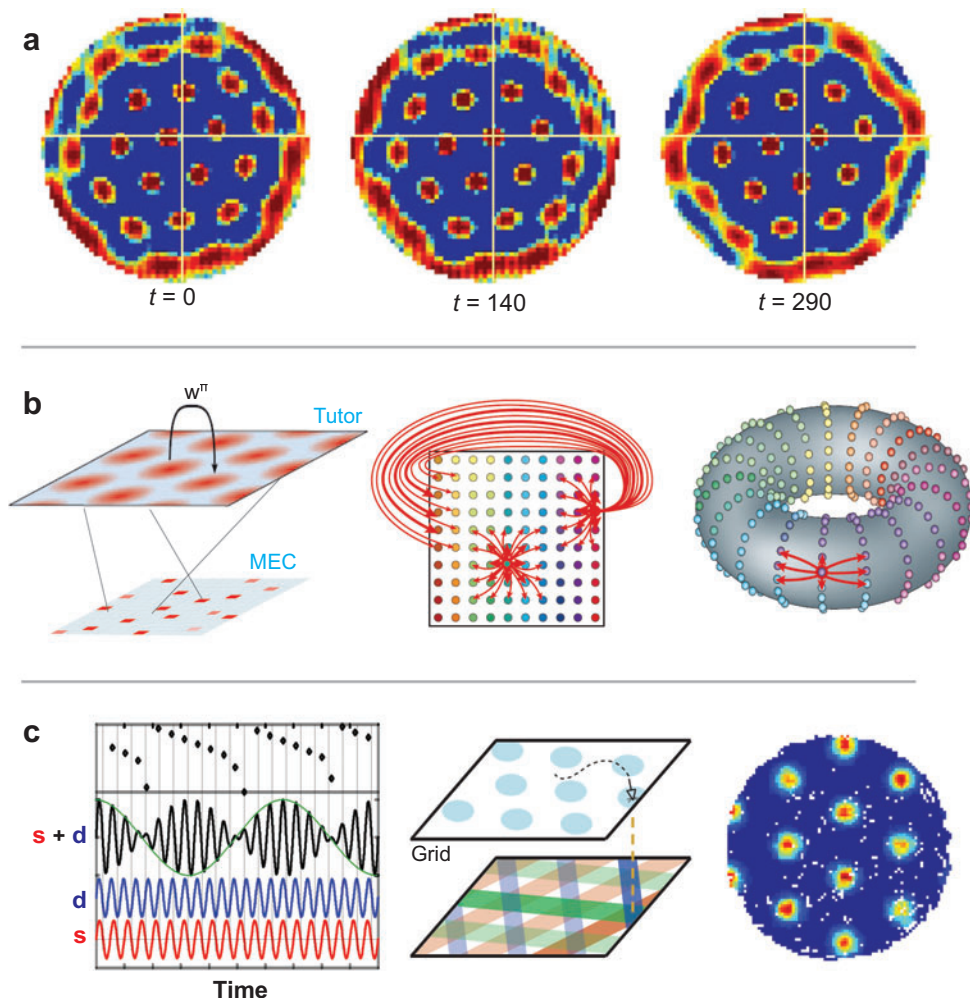In a second class of models, path integration occurs at the single cell level and is intimately

Figure 2

Different models of grid field formation. (*a*) Three consecutive snapshots of the activity in an MEC network adapted from Fuhs & Touretzky (2006). A stable grid pattern of activity emerges spontaneously, and following rightward movement of the rat, the activity is rigidly displaced in the corresponding direction across the network. In the origin of the white axes, a neuron is not firing at time $t = 0$, fires in the maximum of a grid node at $t = 140$, and is at rest again at $t = 290$. (*b*) Geometry of the connectivity inside a module of grid cells, adapted from McNaughton et al. (2006). A topographically arranged network similar to the one in *a* serves as a tutor to train an MEC module with no topographical arrangement (*left*). Owing to the periodicity of the tutor, if after training the module was rearranged so as to make strongly connected neurons neighbors (*center*), the effective geometry would be that of a toroidal surface (*right*). (*c*) Sum of three or more linear interference maps, adapted from Burgess et al. (2007). While the animal is running on a linear track, the sum of a somatic (s) and a dendritic (d) oscillation with slightly different frequencies results in an interference pattern exhibiting phase precession and slow periodic spatial modulation (*left*). Combining three or more linear interference maps, responding to different projections of the velocity, results in a grid map (*center*). Simulated grid map after 10 min of a rat's actual trajectory (*right*). All panels reprinted with permission (Fuhs & Touretzky 2006, McNaughton et al. 2006, Burgess et al. 2007).

related to phase precession, a progressive advance of spike times relative to the theta phase observed in hippocampal place cells (O'Keefe & Recce 1993) and entorhinal grid cells (Hafting et al. 2006) when rats run through a localized firing field. O'Keefe & Reece (1993) modeled phase precession on a linear track as the sum between two oscillatory signals with frequencies around the theta rhythm but slightly differing by an amount proportional to the rat's running speed. The resulting interference pattern can be decomposed into an oscillation at the mean of the two frequencies, which advances with respect to the slower (theta) rhythm, and a slow periodical modulation with a phase that integrates the rat's speed and thus reflects its position along the track (O'Keefe & Recce 1993, O'Keefe & Burgess 2005, Lengyel et al. 2003). Burgess et al. (2007) extended the interference model to two dimensions by considering the interaction of one somatic intrinsic oscillator of frequency w_s ($\sim$ theta rhythm) with several dendritic oscillators, each with a frequency equal to w_s plus a term proportional to the projection of the rat velocity in some characteristic preferred direction. The interference of the somatic signal with each of these dendritic oscillators has a slow modulation that integrates the preferred component of the velocity into a linear spatial interference pattern (a plane wave). When combining several of these linear patterns, a triangular grid map is obtained, provided that their directions differ in multiples of $60°$ and the phases are set in such a way that all maxima coincide, a choice of parameters that could result from a self-organization process maximizing the neuron's overall activity. In a variant of this idea, Blair et al. (2007) proposed that the interference sources could be two theta-grid cells (grid cells with a high spatial frequency associated with the theta rhythm), differing in either their relative size or their orientation, although evidence for such cells has not yet been reported.

The above models make different predictions about the organization of the entorhinal grid map. The network models explicitly or implicitly rely on a discontinuous module arrangement with different grid spacing and grid orientation. Fuhs & Touretzky (2006) propose large clusters of MEC cells each with fixed grid spacing and orientation but with continuous topographic variation of phase among neighbors. They estimate $\sim$17 such clusters in layer II, restricting the variability in grid parameter values in a given environment. Possibly smaller and larger in number, the attractor networks proposed by McNaughton and colleagues inherit in principle the orientation and spacing from their tutor, whereas the phase varies randomly inside each cluster. However, if two networks trained by the same tutor were fed with speed signals of different gain, the displacement of the representations in response to a rat movement would differ, resulting in grids with different spacing, as observed along the dorsoventral axis. Burgess et al. associate such a modulation in spacing with a gradient in the frequency of subthreshold membrane potential oscillations along this axis, a prediction that was recently verified (Giocomo et al. 2007), whereas their model is agnostic to neighboring cells' orientation and phase.

PLACE FIELDS MAY BE EXTRACTED FROM GRID FIELDS

Inspired by Fourier analysis, researchers have proposed that grid fields of different spacing, playing the role of periodic basis functions, combine linearly to generate place fields in the hippocampus (O'Keefe & Burgess 2005, Fuhs & Touretzky 2006, McNaughton et al. 2006). The resulting hippocampal representation would be periodic but because the period would be equal to the least common multiple of the grid spacings, and because it would be further enhanced by differences in grid orientation, only single fields would be observed in standard experimental settings. The peak of the representation would be at the location where most of the contributing grids are in phase. In a computational model, Solstad et al. (2006) showed that in small two-dimensional environments, single place fields can be formed by summing the activity of a modest number (10–50) of grid cells with relatively similar grid phases,

random orientations, and a biologically plausible range of spacings corresponding with convergence of inputs from ~25% of the dorsoventral axis of MEC (Dolorfo & Amaral 1998). Rolls et al. (2006) showed that the choice of grid cells contributing to a given place field need not be hardwired but can result from a competitive Hebbian learning process starting from random connectivity, provided that enough variability in orientation, phase, and spacing is available in the afferent population of grid cells. They also showed that if variability in the in-peak frequency of grid cells is considered, more place cells have a single field, whereas trace learning (a variant of Hebbian learning that uses short time averages of, for example, the postsynaptic firing rate) produces broader fields, more similar to the ones observed in hippocampus.

The idea that place fields emerge through LTP-like competitive learning mechanisms receives only partial support from studies of place field formation in the presence of NMDA receptor blockers. When animals explore new environments, it takes several minutes for the firing fields to reach a stable state (Hill 1978, Wilson & McNaughton 1993, Frank et al. 2004). During this period, place fields may fade in or out, or their fields may expand toward earlier parts of the trajectory (Mehta et al. 1997, 2000). The stabilization is slower in CA3 than in CA1 (Leutgeb et al. 2004). Although synaptic plasticity is necessary for experience-dependent field expansions (Ekstrom et al. 2001), synaptic modifications may not be required for manifestation of place-specific firing as such. In the absence of functional NMDA receptors, CA1 place cells continue to express spatially confined firing fields, although some selectivity and stability may be lost (McHugh et al. 1996, Kentros et al. 1998). Whether hardwired connections are sufficient for place cell formation in all parts of the circuit remains to be determined, however. Preliminary data suggest that during exploration of new environments, systemic blockade of NMDA receptors disrupts spatial selectivity in dentate granule cells while CA3 cells continue to exhibit localized activity (Leutgeb et al. 2007b), raising the possibility that on dentate granule cells, unlike hippocampal pyramidal cells, spatial selectivity may be established by competitive selection of active inputs.

PLACE CELLS AND HIPPOCAMPAL MEMORY

Following the discovery of place cells, several studies indicated a broader role for the hippocampus in representation and storage of experience, consistent with a long tradition of work on humans implying hippocampal involvement in declarative and episodic memory (Scoville & Milner 1957, Squire et al. 2004). Not only are hippocampal neurons triggered by location cues, but also they respond to salient events in a temporal sequence (Hampson et al. 1993) and nonspatial stimuli such as texture or odors (Young et al. 1994, Wood et al. 1999). However, nonspatial variables are not represented primarily by a dedicated subset of neurons or a nonspatial variant of the place cells. Fenton and colleagues observed that when a rat passed through a neuron's place field, the rate variation across traversals substantially exceeded that of a random model with Poission variance (Fenton & Muller 1998; Olypher et al. 2002). This excess variance, or overdispersion, raised the possibility that nonspatial signals are represented in place cells on top of the location signal by continuous rate modulation within the field. More direct support for this idea comes from the observation that, in hippocampal cell assemblies, spatial and nonspatial variables (place and color) are represented independently by variation in firing location and firing rate, respectively (Leutgeb et al. 2005a). Together these studies indicate a conjunctive spatial-nonspatial code for representation of experience in the hippocampus.

How could memories be stored in the place cell system? On the basis of the extensive intrinsic connectivity and modifiability of the CA3 network, theoretical work has indicated attractor dynamics (Hopfield 1982, Amit 1989) as a potential mechanism for low-interference storage of arbitrary input patterns

to the hippocampus (McNaughton & Morris 1987, Treves & Rolls 1992, Hasselmo et al. 1995, McClelland & Goddard 1996, Rolls & Treves 1998). In networks with discrete attractor states (a Hopfield network), associative connections would allow stored memories to be recalled from degraded versions of the original input (pattern completion) without mixing up the memory with other events stored in the network (pattern separation).

Many observations suggest that place cells perform both pattern completion and pattern separation. Pattern completion is apparent from the fact that place cells maintain their location specificity after removing many of the landmarks that originally defined the environment (O'Keefe & Conway 1978, Muller & Kubie 1987, O'Keefe & Speakman 1987, Quirk et al. 1990, Nakazawa et al. 2002). Representations are regenerated with greater strength in CA3 than in CA1 (Lee et al. 2004, Vazdarjanova & Guzowski 2004, J.K. Leutgeb et al. 2005), possibly because the relative lack of recurrent collaterals in CA1 makes firing patterns more sensitive to changes in external inputs. As predicted from the theoretical models, pattern completion is disrupted by blockade of NMDA receptor–dependent synaptic plasticity in CA3 (Nakazawa et al. 2002). Pattern separation can be inferred from the ability of place cells to undergo substantial remapping after only minor changes in the sensory input, such as a change in color or shape of the recording enclosure or a change in the overall motivational context (Muller & Kubie 1987, Bostock et al. 1991, Markus et al. 1995, Wood et al. 2000). Two forms of remapping have been reported (Leutgeb et al. 2005b): The cell population may undergo complete orthogonalization of both firing locations and firing rates (global remapping), or the rate distribution may be changed selectively in the presence of stable firing locations (rate remapping). In each instance, remapping tends to be instantaneous (Leutgeb et al. 2006, Fyhn et al. 2007), although delayed transitions occur under some training conditions (Lever et al. 2002). The disambiguation of the firing patterns is stronger in CA3 than in CA1

(Leutgeb et al. 2004, Vazdarjanova & Guzowski 2004). Pattern separation in the CA areas may be facilitated by prior orthogonalization of hippocampal input patterns in the dentate gyrus (Leutgeb et al. 2007a, McHugh et al. 2007, Leutgeb & Moser 2007). The sparse firing of the granule cells (Jung & McNaughton 1993, Chawla et al. 2005, Leutgeb et al. 2007a) and the formation of one-to-one detonator synapses between granule cells and pyramidal cells in CA3 (Claiborne et al. 1986, Treves & Rolls 1992) may jointly contribute to decorrelation of incoming cortical signals in the dentate gyrus (McNaughton & Morris 1987, Treves & Rolls 1992).

Although place cells exhibit both pattern completion and pattern separation, we cannot discount that firing is maintained by unidentified stimuli that are present both during encoding with the full set of landmarks and during retrieval with a smaller subset of landmarks. A more direct way to test the attractor properties of the network is to measure the response of the place cell population to continuous or step-wise transformations of the recording environment. Wills et al. (2005) trained rats, on alternating trials, in a square and a circular version of a morph box with flexible walls. Different place cell maps were formed for the two environments. On the test day, rats were exposed to multiple intermediate shapes. A sharp transition from square-like representations to circle-like representations was observed near the middle in the geometric sequence, as predicted if the network had discrete attractor states corresponding to each of the familiar square and circular shapes. Whether the implied attractor dynamics occurs in the hippocampus itself or in upstream areas such as the MEC, or both, remains to be determined. Because the changes in firing patterns indicate global remapping and global remapping is invariably accompanied by realignment and rotation of the entorhinal grid map (Fyhn et al. 2007), it may well be that some of the underlying attractor dynamics lies in the MEC (S. Leutgeb et al. 2007).

Hippocampal representations cannot always be discontinuous as in a Hopfield network.

Hippocampal memories are characterized by events that are tied together in sequences (Tulving & Markowitsch 1998, Shapiro et al. 2006), just like positions are tied together in two dimensions as spatial maps. A continuous attractor network (Tsodyks & Sejnowski 1995) may be needed to preserve the continuity of both types of representations. Recent observations support this possibility. When two recording environments are morphed in the presence of salient distal landmarks, the firing locations remain constant across the sequence of intermediate shapes, but the rate distribution changes smoothly between the preestablished states (J.K. Leutgeb et al. 2005). Stable states can thus be attained along the entire continuum between two preexisting representations (Blumenfeld et al. 2006). This ability to represent continua may provide hippocampal networks with a capacity for encoding and retrieving consecutive inputs as uninterrupted, distinguishable episodes.

SEQUENCE CODING IN PLACE CELLS AND GRID CELLS

The idea that neuronal representations have a temporal dimension can be traced back to Hebb (1949), who suggested that cell assemblies are activated in sequences, and that such phase sequences may provide the neural basis of thought. More recent theoretical studies have proposed a number of mechanisms by which temporal sequences could be formed and stored as distinct entities. Such mechanisms include potentiation of asymmetric connections between serially activated neurons (Blum & Abbott 1996) and orthogonalization of the individual sequence elements (McNaughton & Morris 1987). However, although these and related ideas have nourished important experiments, the mechanisms of sequence coding are still not well understood.

The most intriguing example of a temporal code in the rodent hippocampus is probably the expression of theta phase precession in place cells when animals follow a fixed path in a linear environment (O'Keefe & Recce

1993, Skaggs et al. 1996). The reliable tendency of place cells to fire at progressively earlier phases of the theta rhythm during traversal of the place field increases the information about the animal's location in the environment, both in one-dimensional (Jensen & Lisman 2000, Harris et al. 2003, Huxter et al. 2003) and two-dimensional (Huxter et al. 2007) environments. Moreover, when the rat runs through a sequence of overlapping place fields from different cells, the firing sequence of the cells will be partially replicated in compressed form within individual theta periods (Jensen & Lisman 1996, Skaggs et al. 1996, Tsodyks et al. 1996, Dragoi & Buzsaki 2006). The repeated compression of discharges within windows of some tens of milliseconds provides a mechanism for associating temporally extended path segments on the basis of the rules of spike-dependent plasticity (Dan & Poo 2004). Such associations may be necessary for storage of route and event representations in the network.

We do not know the neuronal mechanisms of phase precession or their locations in the brain. O'Keefe & Recce (1993) suggested that phase precession is caused by interference between intrinsic and extrinsic neuronal membrane potential oscillations with slightly different frequencies (**Figure 2c**). Spike times are determined, in this view, by the high-frequency wave of the interference pattern, which advances progressively with reference to the field theta activity. An alternative set of models suggests that phase precession occurs when theta-modulated inhibition interacts with progressively increasing excitation of the place cell over the extent of the firing field (Harris et al. 2002, Mehta et al. 2002). Because of the ramp-up of the excitation, cells would discharge at successively earlier points in the theta cycle. A third type of models puts the mechanism at the network level (Jensen & Lisman 1996, Tsodyks et al. 1996, Wallenstein & Hasselmo 1998). By intrinsic connections between place cells, cells that are strongly activated by external excitation may initiate, at each location, a wave of activity that spreads toward the cells with place fields that are further along the animal's path.

Experimental data do not rule out any of these models. To understand the underlying mechanisms, it may be necessary to identify the neural circuits that support phase precession and then determine which of those are able to generate phase precession on their own. Recent observations imply that phase precession is not exclusively hippocampal. Phase precession in CA1 is not frozen by brief inhibition of hippocampal activity (Zugaro et al. 2005), which suggests that the precession may, at least under some circumstances, be imposed on hippocampal place cells by cells from other areas. One such area could be the MEC. Grid cells in this region exhibit phase precession (Hafting et al. 2006). Of particular interest is the stellate cell in layer II of MEC. Because stellate cells exhibit voltage-dependent intrinsic oscillations that may be faster than the field theta rhythm (Alonso & Llinas 1989, Klink & Alonso 1993, Giocomo et al. 2007), these cells may express interference patterns of the type proposed by O'Keefe and colleagues (O'Keefe & Recce 1993, Burgess et al. 2007). Additional assumptions must be invoked, however, to explain the stronger correlation of phase with position, and the presence of intrinsic oscillations does not rule out other potential mechanisms including rampant excitation or neural network properties.

REPLAY AND PREPLAY IN PLACE CELL ENSEMBLES

After a memory trace is encoded during an experience, the memory is thought to undergo further consolidation off-line when the subject is sleeping or is engaged in consummatory activities. Although the cascade of events leading to consolidation of hippocampal memory is not well understood, ensemble recordings in sleeping rats have provided some clues. Cells that are coactivated in the hippocampus during awake behavior continue to exhibit correlated activity during sleep episodes subsequent to behavioral testing (Wilson & McNaughton 1994). The order of firing is generally preserved but the rate may be faster (Skaggs & McNaughton

1996, Lee & Wilson 2002). Such replay or reactivation is associated with hippocampal sharp waves, which are bursts of synchronous pyramidal-cell activity during slow-wave sleep and awake rest (Buzsáki et al. 1983). Sharp-wave bursts can induce plasticity in downstream areas and may therefore be involved in information transfer from the hippocampus to the neocortex during the consolidation time window (Buzsáki 1989). Direct evidence for this hypothesis is still lacking. The correlation of sharp waves in CA1 and upstates in the neocortex suggests interaction between these brain areas during sleep, but the slight delay of membrane potential changes in CA1 compared with neocortex suggests that signals are transferred from neocortex to CA1 and not vice versa (Isomura et al. 2006, Hahn et al. 2007, Ji & Wilson 2007). Much work is still needed to establish the potential significance of sleep-associated reactivation in memory consolidation.

Reactivation of place cell discharges is observed not just during sleep. Recent studies have reported reactivation during sharp waves that are "interleaved" in waking activities (Foster & Wilson 2006, O'Neill et al. 2006), which indicates possible mechanisms for maintaining recent memories on shorter time scales when rest is not possible. When the animal stops at the turning points of a linear track, the hippocampus enters sharp-wave mode, and the preceding sequence of place-cell activity on the track is replayed, but now in a time-reversed order (Foster & Wilson 2006). Reverse replay may facilitate the storage of goal-directed behavioral sequences by allowing reinforcement signals that coincide with reward induction (e.g., dopamine release) to strengthen primarily the later parts of the behavioral sequence. The point at which sharp wave-associated reactivation is forward or backward has not been determined, and further work is needed to establish how the two forms of reactivation contribute to memory, if at all.

Not all nonlocal activity is retrospective. During theta-associated behaviors, place-cell discharges may sometimes correlate with future locations. Training rats to choose the correct

goal location on discrete trials in a plus maze, Ferbinteanu & Shapiro (2003) found that firing on the start arm was in some cells determined by the subsequent choice of goal arm. Johnson & Redish (2007) showed that when rats reach the choice point of a modified T maze, representations sweep ahead of the animal in the direction of the reward location. The forward-looking activity was experience dependent. Together, these observations suggest that before animals choose between alternative trajectories, future locations are preplayed in the hippocampal place-cell ensembles, probably by retrieving stored representations. This interpretation implies a direct involvement of hippocampal networks in active problem solving and evaluation of possible futures, consistent with the recently reported failure to imagine new experiences in patients with hippocampal amnesia (Hassabis et al. 2007).

SPATIAL MAPS INCLUDE MORE THAN HIPPOCAMPUS AND ENTORHINAL CORTEX

Spatial representation engages a wide brain circuit. A key component is the network of head direction–modulated cells in presubiculum (Ranck 1985, Taube et al. 1990) and upstream areas such as the anterior thalamus (see Taube 1998 for review). Axons from the presubiculum terminate in layers III and V of MEC (Witter & Amaral 2004), where grid cells are modulated by head direction (Sargolini et al. 2006b), possibly as a consequence of the presubicular input. Head-direction cells may also control grid field orientation. The MEC has strong connections with the parasubiculum and the retrosplenial cortex (Witter & Amaral 2004), which contain cells that are tuned to position or head direction (Chen et al. 1994, Taube 1995, Sargolini et al. 2006a). Lesion studies suggest that the retrosplenial cortex is necessary for path integration–based navigation and topographic memory (Sutherland et al. 1988, Takahashi et al. 1997, Cooper & Mizumori 1999), although little is known about the specific role of this area in these processes. The MEC also interacts closely with the lateral entorhinal cortex, where cells apparently do not show spatial modulation (Hargreaves et al. 2005). Although the lateral entorhinal cortex provides a major component of the cortical input to the hippocampus, its function is not known.

The parietal cortex may be an important element of the spatial representation and navigation system. Similar to rats with lesions in the entorhinal cortex, rats with parietal cortex lesions fail to navigate back to a refuge under conditions where the return pathway can be computed only on the basis of the animal's own movement (Save et al. 2001, Parron & Save 2004). Rats and humans with parietal cortex lesions also fail to acquire spatial tasks and remember positional relationships (Kolb et al. 1983, DiMattia & Kesner 1988, Takahashi et al. 1997). The parietal cortex of the rat contains neurons that map navigational epochs when the animal follows a fixed route (Nitz 2006). These cells fire in a reliable order at specific stages of the route, but the firing is not determined by landmarks or movement direction. Much additional work is required to determine whether these discharge patterns are path integration based and contribute to a representation of self-location, and whether they are dependent on grid cells (Hafting et al. 2005) and path-associated firing (Frank et al. 2000) in the MEC. Finally, it is possible that navigation can be aided also by action-based neural computations in the striatum, where key positions along the trajectory are reflected in the local activity (Jog et al. 1999; see also Packard & McGaugh 1996, Hartley et al. 2003).

DEVELOPMENT OF THE SPATIAL REPRESENTATION SYSTEM

Is space an organizing principle of the mind, imposed on experience according to brain preconfiguration, as Kant suggested? Some properties of the spatial representation system certainly indicate a preconfigured network. Grid fields appear from the very first moment of exploration in a new environment and persist following major landmark removal (Hafting et al.

2005), and the spatial phase relationship of different grid cells remains constant across environments (Fyhn et al. 2007). This suggests a rigidly structured map, but whether animals are born with it remains to be determined. Grid structure may appear from genetically specified properties of the entorhinal circuit, but specific maturational programs and experiences may also be necessary for the development of an adult map-like organization (Hubel et al. 1977, McNaughton et al. 2006). Unfortunately, we do not know much about the ontogeny of the spatial representation system. Apparently, only one study has systematically explored the development of spatial representations. Martin & Berthoz (2002) found that sharp and confined place fields were not expressed in CA1 until ~P50 in the rat. The lack of functional studies is matched by a similarly fragmented understanding of how intrinsic and extrinsic connections of the entorhinal and hippocampal cortices develop relative to each other. The few existing studies suggest that, in the rat, some connections of the system, such as the cholinergic innervation of the entorhinal cortex, appear only at ~35 days of age (Ritter et al. 1972, Matthews et al. 1974). Although most other connections are apparently present a few days after birth, functional entorhinal-hippocampal circuits may not emerge until all connections are in place. The slow development of the entorhinal-hippocampal system leaves considerable possibilities for postnatal shaping of the spatial map. A major challenge, if we want to address the Kantian question about the a priori nature of space perception, will be to identify the factors that control map formation in young animals.

CONCLUSION

The past few years have witnessed radical advances in our understanding of the brain's spatial representation system. We are beginning to see the contours of a modularly organized network with grid cells, place cells, and head-direction cells as key computational units. Interactions between grid cells and place cells may underlie the unique ability of the hippocampus to store large amounts of orthogonalized information. The mechanisms of this interaction, their significance for memory storage, and their interactions with representations in other cortical regions remain to be determined. More work is also required to establish the computational principles by which grid maps are formed and by which self-location is mapped dynamically as animals move through spatial environments. Perhaps the largest knowledge gap is concerned with how grid structure emerges during ontogenesis of the nervous system. With the emerging arsenal of genetic tools for time-limited selective activation and inactivation of specific neuronal cell types and circuits and with new possibilities for in utero application of these techniques (Callaway 2005, Tervo & Karpova 2007, Zhang et al. 2007), we should be able to address these issues in the near future. If so, spatial navigation may become one of the first nonsensory cognitive functions to be understood in reasonable mechanistic detail at the microcircuit level.

SUMMARY POINTS

1. The hippocampal-entorhinal spatial representation system contains place cells, grid cells, and head-direction cells.

2. Grid cells have periodic firing fields that form a regular triangular grid across the environment. Grid fields are likely generated by path integration to serve as part of a neural map of self-location.

3. The integration of speed and direction signals may take place at the population level by virtue of recurrent connectivity or at the single neuron level as a consequence of interference among temporal oscillators with frequencies that depend on speed.

4. Hippocampal place fields may be formed by summing convergent input from grid cells with a range of different spacings, similar to a Fourier transform.

5. Unlike ensembles of grid cells, place cells participate in a number of highly orthogonalized environment-specific representations. Attractor dynamics may play a role in storing and reactivating representations during memory retrieval.

6. Theta-phase precession provides a possible mechanism for sequence representation in place cells.

FUTURE ISSUES

1. How is the grid pattern generated during nervous system development? Are specific maturational events required, and does grid formation depend on specific experience? Which elements of the map, if any, remain plastic in the adult brain?

2. What are the cellular and neural network mechanisms of path integration, and how is the grid representation updated in accordance with the rat's own movement? Which mechanism corrects cumulative error, and on what information does it rely?

3. How is the entorhinal map organized? Is the map modular or continuous? How are modularity and continuity generated during development, and how do modules interact in the mature nervous system?

4. What is the mechanism of phase precession, where does precession originate, and what is its relationship with spatial periodicity?

5. What is the function of the lateral entorhinal cortex, and how does it contribute to representation in the hippocampus?

6. How do hippocampal memories influence neocortical memory formation, and what is the function of grid cells or other entorhinal neurons in this process?

7. How does the entorhinal-hippocampal spatial map interact with other cortical systems required for spatial navigation, such as the parietal cortex or the striatum?

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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