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Grid Cells and Place Cells: An Integrated View of their Navigational and Memory Function

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Abstract

Much has been learned about the hippocampal/entorhinal system, but an overview of how its parts work in an integrated way is lacking. One question regards the function of entorhinal grid cells.

We propose here that their fundamental function is to provide a coordinate system for producing mind-travel in the hippocampus, a process that accesses associations with upcoming positions. We further propose that mind-travel occurs during the second half of each theta cycle. By contrast, the first half of each theta cycle is devoted to computing current position using sensory information from the lateral entorhinal cortex (LEC) and path integration information from the medial entorhinal cortex (MEC). This model explains why lesions can abolish hippocampal phase precession but not place fields.

Much has been learned about the cell types in the hippocampal region that underlie the sense of place, culminating in the 2014 Nobel Prize. The first cell type discovered was the place cells of the hippocampus [1]. These fire when an animal is in a particular location of a given environment (Figure 1A). More recently, investigation of the medial entorhinal cortex (MEC), a cortical region that provides input to the hippocampus, led to the discovery of cells with various response properties. Of these, the best known are grid cells. These fire when the animal is in any of multiple locations that form a triangular grid [2] (Figure 1B). Other cell types include conjunctive grid cells (these fire only when the animal is on a vertex of the grid and when the animal moves in a particular direction) [3], head-direction cells [4–6], speed cells [7], and boundary vector cells [8] (Figure 1C). The lateral entorhinal cortex (LEC) also provides input to the hippocampus and contains cells that carry sensory information about the current position [9]. These cell types are pieces of the puzzle, but a framework for understanding how these cell types work together to produce the sense of place and access memory information is still needed.

A core question is the function of grid cells. It had generally been assumed that grid cells are an obligatory precursor of place cells [10–13]. However, such models have been called into question by results showing that place cells exist after elimination of grid cells [14–18].

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Recent reviews have suggested why place cells do not require grid cells; namely, place cells also receive sensory information about position from the LEC, information that is sufficient to define the place field [19,20]. This leaves unresolved the question of what the special role of grid cells might be and, more generally, how the identified pieces of the puzzle fit into a functional framework. Before suggesting such a framework, we first review what is known about **path integration** and **theta sequences (phase precession)**; see Glossary), two phenomena central to the framework that we will develop.

Path Integration (Dead-Reckoning)

As noted above, both the LEC and MEC provide information about position. However, this information is derived in different ways. The process of spatial localization can use sensory information about landmarks in the environment, information that is thought to come from the LEC [21]. However, these landmarks may be few and far between; information about intermediate positions is provided by a process termed ‘path integration’ that is thought to come via the MEC [22]. This computation takes a past estimate of the position of the animal and adds to it the change in position during the intervening time, thereby forming an estimate of current position. The change in position can be computed by integrating a velocity vector (direction and speed of the animal) that is based on vestibular information, sensorimotor information about self-motion, and optic flow [23]. Experiments demonstrate that information about path integration is present in place cells [24,25] and grid cells [26]. A major advance in theoretical neuroscience has been the understanding that a network of grid cells is capable of performing path integration. If activity bumps are moved in proportion to a velocity vector, bump position is determined by the integration of velocity and therefore provides an estimate of current position [22,27–30] (Box 1 for further explanation). Several influential models have thus assumed that grid cells perform path integration and that the results are then passed on to place cells [13,28,31–33]. However, we will argue below that the primary function of grid cells is integration of a different type of information: an **artificial velocity vector** (AAV) that represents the direction of imagined motion.

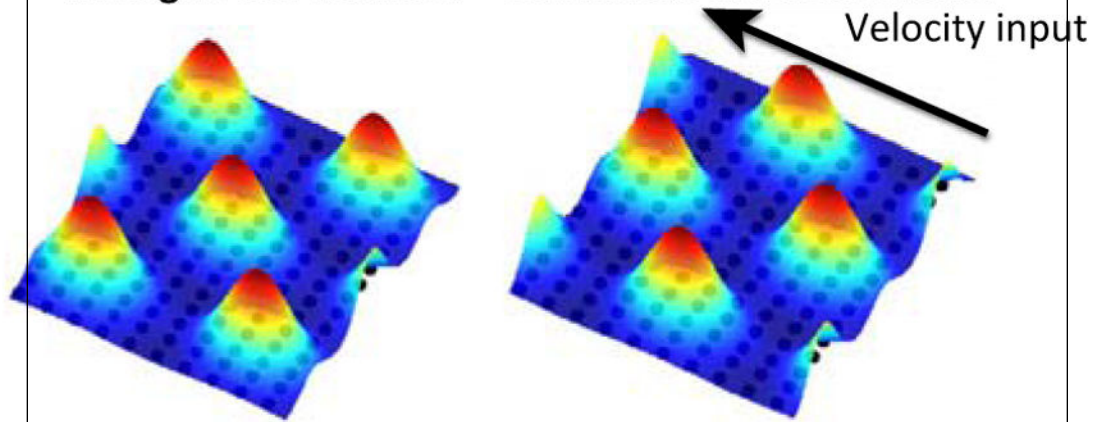
Box 1

Network Mechanisms of Integration by Grid Cells

This proposal builds on concepts about how neural networks having properties of the grid cell system could perform integration in two dimensions, leading to an analog representation of the position of the animal in an environment [13,28,31–33]. To understand how such networks work, it is useful to first consider a simpler integration network that works in one dimension, termed a ring attractor. A key feature of such networks is that a variable (e.g., position along a line) can be stably represented by the position of a ‘bump’ of activity in a group of cells at a given position in a ring of neurons. This bump can arise if cells that are close to each other in the ring excite each other but inhibit more-distant cells. There are also special cells that can move the bump. If these cells are inactive, the position of the bumps will be nearly stable. On the other hand, if these special cells are active, the bump will move. Moreover, if these cells have the property that they move the bump in proportion to the velocity of the animal, the bump will effectively integrate this signal, thereby making the position of the bump represent

the position of the animal. Although different in details, current models of the grid cell network are similar, with the main difference being that the network is a 2D sheet. This allows the bump (or a grid of bumps in the case of the figure) to be moved in any direction, possibly under the control of conjunctive grid cells [28]. If the signal that stimulates movement of the bump is a velocity vector, the system will perform path integration (the bump will represent the calculated position in a 2D environment [22,28,30,88]) (Figure I).

MEC grid cell network – continuous attractor model



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Figure I. MEC Grid Cell Network

Grid cells in the network are indicated by the small dots; color represents level of activation. Actual position in the environment can be constructed from combining the representations from several such networks (modules) having different spatial scales and rotation. Laterally-connecting cells (not shown) move the position of all bumps (left, before movement; right, after) at a rate and direction proportional to the velocity vector (arrow).

Theta Sequences and Phase Precession

Population activity in the rodent hippocampal system exhibits theta-frequency oscillations (5–10 Hz), particularly during movement [34]. Recordings reveal ‘theta sequences,’ in which place cells fire during a theta cycle in order of the position of their place fields (Figure 2A–C) [35,36]. Thus, if cell 1 represents position 1, cell 2 represents position 2, and so on (these numbers define the ‘**true place field**’: see Figure 2D,E and next paragraph), then a segment of an actual path could be represented in a time-compressed way during a theta cycle by the firing sequence 1,2,3,4, with each cell firing at a progressively later theta phase. The sequence of place cell activations occurs during a single theta cycle despite the fact that the animal moves very little during a single ~100 ms theta cycle, implying that they are internally generated. Such theta sequences often relate to positions immediately ahead of the current position and thus have been termed ‘look-ahead’ [37–39]. For reasons noted

later, we now favor the term ‘**mind-travel**’. Such mind-travel may be of enormous functional importance in allowing information associated with upcoming positions [40] to be recalled (was there ever a cat at position 4 on the other side of this hole?).

The network process of mind-travel can be observed in single cells during a phenomenon termed ‘phase precession’ [41]. This phenomenon is illustrated in Figure 2E: as the animal moves through the place field of a cell, the spiking of a cell occurs at a systematically earlier theta phase on each successive theta cycle. It is important to understand that, because mind-travel is a process of predicting the sequence of upcoming places, cells fire over a broad region (the **rate place field**) before reaching the true place field. Consider cell 3 of Figure 2D–F. When the animal first enters the rate place field at position 1, the true place field of cell 3 (i.e., position 3) is far ahead of the animal, and the cell will therefore fire at the end of the theta sequence 1,2,3, in other words with late theta phase (upper part of y-axis of Figure 2E). On the next theta cycle, the animal will have moved to position 2, closer to the true place field (rightwards on x-axis of Figure 2E), such that the cell will fire during the sequence 2,3,4 and thus will have earlier theta phase. Finally, the animal reaches the true place field at position 3, and therefore the cell will fire first during the sequence 3,4,5 (lower part of y-axis of Figure 2E). This explanation of phase precession applies to data taken while the animal traverses a linear track; for related arguments about data taken in the open field, see [42]).

Closer analysis of phase precession has shown that it is not uniform as the rat traverses the rate place field, but instead has a bimodal property [43]. Immediately after entering the rate place field, firing occurs in a narrow phase range at late theta phase. As the animal progresses through the field, firing continues to occur in a narrow phase range at each position, a range that occurs with earlier phase on each successive theta cycle. This phase precession is restricted to the second half of the theta cycle (Figure 2E, top half of plot). When the rat reaches the far side of the rate place field (i.e., the true place field), the theta phase of firing does not vary with the position of the animal, and firing occurs over a relatively broad phase range confined to the first half of the theta cycle (bottom half of plot). Below we provide the first functional explanation for this bimodal property of phase coding.

Proposal: The Two Halves of the Theta Cycle Are for Computation of Current Position and Mind-Travel, Respectively

As a framework for understanding the bimodal nature of phase precession, we suggest that the system performs different functions during the two halves of each theta cycle (Figure 3). The first half is devoted to processing the current position (only the cells whose true place fields correspond to current position are active, and there is no place cell sequence). The second half of each theta cycle is devoted to mind-travel to a sequence of positions away from the current position. This explains why the phase precession plot only shows position-dependence of phase during the second half of the theta cycle (Figure 2E). For a specific experimental test of this framework, see Prediction (i) of Box 3. It should be noted that we are using the convention that 0° is the peak of theta as measured at the CA1 pyramidal cell layer. A rule of thumb is that the ‘first half of theta’ (when CA1 place cells fire in their ‘true

place field') occurs on the descending phase (0–180°) and the 'second half of theta' (when the mind-travel in CA1 occurs) occurs on the ascending phase (180–360°) [44,45].

Box 3

Predictions

- i. As shown in Figure 2, the firing during the first half on the theta cycle occurs when the rat enters the 'true place field.' If the animal heads toward this location, the predictive part of the phase precession that occurs during the second part of theta cycles should be present; however, if the animal eventually veers to the side of the true place field, the extensive firing that occurs during the first part of the theta cycle should be absent because the rat never reaches the true place field. Visual analysis of such veering trials [98,99] suggests this to be the case, but more rigorous analysis will be required.
- ii. In our model, the remaining place fields after grid cell disruption are due to LEC input and should thus depend on sensory information. It follows that the place fields under these conditions should not depend on path integration.
- iii. LEC lesions should not affect the generation of theta phase sequences.
- iv. MEC lesions should specifically affect navigational behaviors that require mind-travel. Consistent with this prediction, MEC lesions cause deficits in the Morris water maze, but not in the object/place associations that do not require mind-travel [18].
- v. The AVV that drives mind-travel should have several distinctive properties. Their firing rate should be proportional to the distance of mind-travel, which can be affected by goal location [38]. Furthermore, when mind-travel is behind the animal [61], the AVV system should point opposite to the head direction. Finally, the magnitude of the AVV should correspond with the distance of mind-travel.
- vi. Sequences driven by grid cells are promptly available in a new environment and must be linear (but see [39]), whereas sequence recall dependent on the hippocampus can follow non-linear experienced paths. Thus, the first sequences in a new environment should be linear and should be truncated at turns, whereas the sequence can become nonlinear with experience.

According to the framework presented above, when cells represent current position, they fire over the entire first half of the theta cycle. Devoting such a large fraction of the theta cycle to the current position allows time for several processes. First, the system can bring together the LEC (sensory) and MEC (path integration) information in the hippocampus, resulting in an improved estimate of current position (see arrows 1 and 2 in Figure 3A; Box 1 for how CA3 could contribute to this compromise). This estimate is then imposed on the grid cell system (Figure 3A, arrow 3), providing a good starting point for the mind-travel process driven by grid cells (see below) that occurs during the second half of the theta cycle. A second process occurring during the first half of the theta cycle is the synaptic association of

current position with the sensory events at that position (e.g., a cat or a landmark). The required synaptic modifications may be effectively driven because of the long-duration firing that occurs over the first half of the theta cycle ([46,47] for a related proposal). By contrast, place cells are active for much shorter periods during the second half of each theta cycle because this half-cycle must be divided among cells representing the many sequential positions involved in mind-travel.

Proposal: Grid Cells Drive Mind-Travel during the Second Half of the Theta Cycle

We now come to the heart of our proposal: that a major function of the grid cell network is to produce the mind-travel that occurs during the second half of each theta cycle. This mind-travel is driven by integration of an AVV input to the grid cell network. The AVV describes an imagined movement in a particular direction and with a particular velocity, neither of which are necessarily tied to the current motion of the animal. We emphasize that the resulting mind-travel is a gradual process: during the second half of each theta cycle, mind-travel occurs to successive positions at increasing distance from the animal. As described earlier, expression of theta sequences during animal movement followed by reset to current position results in phase precession. Thus, integration of the AVV by grid cells is sufficient to generate phase precession.

The most straightforward implication of our model is that interfering with grid cell function should interfere with mind-travel (but not place fields). Consistent with this expectation, disabling grid cells or ablating the MEC strongly reduces phase precession and theta sequences without destroying place fields [48,49]. A complementary expectation is that there should be conditions that abolish place fields but preserve mind-travel. Recent work in which animals are placed in a 2D virtual reality under conditions with no vestibular information demonstrates this result [50]: place fields are not consistent over long timescales, but on short timescales phase precession is expressed normally.

In the simplest case, mind-travel would be generated in the grid cell network and then imposed on downstream hippocampal networks (dentate gyrus, CA3, CA1) with little delay. To a first approximation, this appears to be the case (Figure 2G), supporting an inheritance model [51] of phase precession, in which phase precession originates in the grid cell network and is then imposed on downstream networks. This way of understanding phase precession as the network phenomenon of mind-travel generated by grid cells [39,51–53] contrasts with models of single cell generation of phase precession [33,54].

The function of mind-travel is presumably to determine whether good or bad events have been previously associated with potential upcoming positions. This raises the question of how far ahead the system can mind-travel. Given the larger spatial scales of grid cells and place cells in the ventral as compared to the dorsal parts of the system [55,56], we envisage that the dorsal and ventral entorhinal/hippocampal regions work in parallel to perform mind-travel over small and large scales, respectively (see [57] for computational benefits of such a system).

Implementation of Control Processes

The above model raises the question of what mechanisms could provide the control signals outlined in Figure 3. Below we discuss possible candidates.

Generation of the AVV under Cognitive Control

Which cells generate the AVV must be under flexible cognitive control, allowing both the direction and magnitude of the AVV to be specified. Such flexibility is necessary to allow the distance of mind-travel to be increased with distance to goal [38] or speed [37], as experimentally observed.

What would a signal appropriate to act as the AVV look like? As a velocity vector, it must have both direction and speed components, which may be provided by separate cell types. Given the need for a directional component of the AVV, cells currently classified as head-direction cells are possible candidates. Head-direction cells have been found in the thalamus, subiculum, and MEC [3,4,58], but these have diverse properties and are therefore not a single population. For example, head-direction cells in the MEC are more tuned to head direction itself [59], whereas thalamic head-direction cells seem to be more responsive to movement [58]. We have doubts that the head-direction cells in the MEC are in fact the AVV because of the following observation. If an animal is forced to move backwards, mind-travel looks behind the animal [60,61] (it is for this reason that ‘look-ahead’ is a misleading term and that we prefer the term ‘mind-travel’). We would thus expect that the AVV should point backwards under these circumstances, but MEC head-direction cells do not [61]. It is important to explore whether other types of ‘head-direction’ cells have directional preferences corresponding to the direction of mind-travel, as would be needed for the AVV.

The speed component of the AVV may be provided by the recently discovered speed cells of the entorhinal cortex [7]. Notably, there are two major populations of speed cells. One is not theta-modulated, and thus would be appropriate for use in the integration of true velocity. The other is highly theta-modulated, such that it is specifically active during the part of the theta cycle in which mind-travel occurs. Such theta-modulated speed cells may combine with a direction signal to form the AVV.

Transition from Self-Localization to Mind-Travel

Based on functional considerations, we have posited that different pathways are modulated on or off during different halves of the theta cycle (Figure 3). For instance, during the mind-travel that occurs in the second half of the theta cycle, it makes sense to stop the flow of information from the LEC about current position. Each control signal could be mediated by a class of interneurons, given that a wide range of theta phase-specific and input-specific interneurons have been described [62].

Where is Path Integration Calculated?

We now turn to the question of where path integration occurs. Settling this issue will require further experimentation, but we favor the possibility that path integration is not performed by grid cells but is provided to grid cells by an upstream area (Figure 3A, arrow 1). We

favor this view because the contrary view, that grid cells perform both path integration and mind-travel, poses difficult computational problems. During a theta cycle, the network would need to integrate both the true velocity and the AVV. The difficulty comes at the beginning of the next theta cycle, when, to determine current position, the integration due to the AVV must be subtracted out without affecting the integration due to real velocity. While this could potentially be accomplished [31], it seems simpler to suppose that path integration is maintained in a separate network and that the computed current position is imposed on grid cells at the beginning of each theta cycle. In such a system, mind-travel would not interfere with path integration.

There are several possible candidates for upstream sites where path integration might occur. One candidate is a class of spatially modulated non-grid cells (boundary vector cells, Figure 1, or spatially periodic cells) found in the parasubiculum, subiculum, and EC [17,63,64]. Boundary vector cells form a stripe of activity with the stripe at a particular distance from a boundary. Although it has been proposed that these cells depend on visual computations that determine the distance from the boundary [19], it seems equally plausible that these cells arise as a result of one-dimensional path integration of the perpendicular distance from the boundary (and could thus be computed by a ring attractor, with the starting point of integration being set by boundary cells). Indeed, much recent work points to the importance of boundaries as fixing the path integrator to an environment [26,65,66]. Given different boundary vector cells that have perpendicular stripes of activity, a common target of these cells would have a place field at the intersection of the two input stripes. Another possibility [20] is that entorhinal pyramidal grid cells are the true path integrator, whereas the entorhinal stellate grid cells generate mind-travel. A final possible site for path integration is a type of grid cell in layer III of MEC. Intriguingly, this type does not show phase precession [45,67], and it is noteworthy that our model would predict that the true path integrator would not show phase precession because phase precession is the signature of mind-travel, which would not occur in the true path integrator. Several methods provide assays for path integration [24,25,68] and may be helpful in determining where it actually originates.

Role of Grid Cells versus Place Cells in Memory Processes

The hippocampal and entorhinal systems have different roles in the computation of place, roles that ultimately serve memory functions. Notably, the hippocampal network represents the current environment, allowing associations with particular places to be formed and recalled. By contrast, the grid cell network represents universal spatial structure [52], providing a coordinate system that can be used to organize mind-travel (even over non-experienced paths). Evidence for this difference between the hippocampal and grid cells systems comes from the study of how representation properties change when the animal is placed in different environments [69]. It was found that hippocampal place representations are uncorrelated from environment to environment [40,70]; in particular, two cells that have adjacent place fields in one environment may have place fields on opposite sides of the room in a second environment. This has been termed ‘global remapping.’ By contrast, grid cells within the same **grid cell module** shift coherently from environment to environment, preserving the relative spatial relations between the grid fields of different cells [71,72]. The

grid cells thus represent universal aspects of spatial structure that can be applied to any environment (see below). In the next sections we describe how these properties contribute to memory function.

Environment-Specific Memory Stored in the Hippocampus

The hippocampus is considered to be the main storage site for episodic memory, which can occur in two forms. In the hippocampus, sensory information about a location is associated with the neural representation of that position by a process termed ‘rate remapping’. This form of episodic memory can include information about sensory qualities, task demands, and actions [40,73,74]. Because the hippocampal representations of space differ from environment to environment (see above), non-spatial associates of each location are stored in an environment-specific way, thereby minimizing interference. The hippocampus can also learn and recall a second form of episodic memory: position sequences that describe experienced paths in a given environment [75,76] (Figure 4A). How these two forms of episodic memory are accessed is described in the next sections.

The AVV Probes Association with Positions: Funding Shortcuts

The integrator properties of the grid cell network allow the network to play out the result of any linear AVV and thereby access associations with upcoming positions. Consider a rat that moves from $(0,0)$ to $(+x,+y)$, followed by movement of $(-x,0)$ before experiencing reward at the final location $(0,y)$. As suggested previously [39,53], a simple process could be used to find a shortcut to the reward sites. In this process, AVVs of different direction are generated sequentially. The grid cell network performs integration of each AVV and activates the place cells corresponding to those sequential locations. If a place cell associated with reward is activated, as would be the case for the AVV pointing due north, which intersects $(0,y)$, then the AVV used points out the correct direction for a shortcut (Figure 4B). This strategy can be utilized even if the animal has never before moved along this northward path because it utilizes the universal coordinate system of the grid cells, not the particular representation of the place cells. Thus, the grid cell coordinate system can be used in conjunction with the hippocampus to find shortcuts, even over never-experienced paths [39,53].

Possibility of Episodic Sequence Memory Cued by Mind-Travel

More complex memories involve sequences such as those that would define an entire route to a reward site. Such routes may involve several turns and thus be nonlinear; they can be replayed during non-theta states (e.g., during sharp waves; Figure 4A). The recall of such sequences can be observed as intrahippocampally generated replay during sharp-wave ripples [77,78].

An interesting possibility is that, in theta states, mind-travel might act as a cue for hippocampal sequence recall (Figure 4C). This might be initiated in grid cells by mind-travel in a particular direction of interest. As mind-travel progresses to a position in the hippocampus that is on a previously experienced route, the strength of the intrahippocampal synaptic connections that store route information may be so strong that they dominate the next steps in sequencing, thereby producing recall of the non-linear route (Figure 4C). In

this case, grid cell mind-travel serves as a cue for the recall of an episodic memory from the hippocampus.

Significance of Theta

In our proposal we suggest that one function of theta frequency oscillations is to temporally organize two complementary computations. Such differential function of different phases of theta is also suggested by other findings [see Outstanding Question (ii)]. The essential aspect of rhythmic activity as a framework is that different network states alternate with each other. This alternation need not occur at a fixed frequency. Work in bats demonstrating lack of a theta-frequency peak in the hippocampal power spectrum has called into question emphasis on theta oscillations [79]. However, recent work in humans [80] and bats [81], both of which lack a clear theta-band peak in the power spectrum, demonstrates that theta oscillations in the hippocampus are fairly prominent, but that their frequency varies over a much wider range than in rodents. We emphasize that the frequency of the oscillation is not essential; instead, it is the alternation of state between representation of current position and mind-travel.

Outstanding Questions

- i. The true path integrator must have a start location for integration. This location must be determined by sensory information about landmarks, but how this information gets to the path integrator is not known. What is known is that, when learning an environment, animals start from a 'home base' [82] and make gradually incrementing excursions from the base. We imagine that sensory information about new landmarks might reach the path integrator through CA1 or through grid cells (Figure 3B, see dashed lines), but virtually nothing is known about this. In particular, it would be important to know the conditions under which the path integrator is updated using landmarks.
- ii. Several other lines of evidence point towards the existence of functionally different parts of the theta cycle. (a) Excitatory cells in entorhinal cortex layer II (EC2) and layer III (EC3), two of the input streams into the hippocampus, fire preferentially on opposite phases of theta [67]. (b) The CA1 region of the hippocampus receives inputs from the CA3 region as well as EC3. These two inputs have greatest strength on opposite phases of theta, as measured by power in their signature frequency bands [83] and by power in their spatially segregated input layers [84]. (c) Other evidence suggests that synaptic plasticity can switch from long-term potentiation to long-term depression depending on the theta phase of stimulation [85]. (d) Theoretical work has assigned the two halves of theta the functions of encoding and recall [46]. This idea fits with our proposal because mind-travel (driven in CA1 by EC2 via CA3) is fundamentally a recall process. Furthermore, representing current position during the first half of theta could result in the encoding of these events. A general model that explains all of these phase-dependent processes remains to be developed.
- iii. In different environments, place cells change their relative position [86]. To achieve this global remapping, the grid cell system must be anchored to the

arbitrary place cell representation specific to each environment. Possibilities for this process include boundary cells [64,66], using multiple modules of different spatial frequencies [12,13,87]. This must involve the flow of sensory information to the grid cell system. Exactly how this works is not known.

Summary

In this article we have presented an integrated view of how various cell types found in the entorhinal/hippocampal system might work together to produce navigational and memory functions. Our proposal builds on previous ideas [19,22,46,53,82], but also introduces new insights about the differential function of the two halves of theta. During the first half of theta, place cells represent current position. During the second half of theta, grid cells drive mind-travel, which is then expressed in the place cell network to retrieve associations of those locations. This allows the linkage between the navigational and memory processes to be understood in a simple way. Experimental tests of this framework are suggested in Boxes 2

Box 2

CA3 Network Mechanisms for Producing Compromise of LEC and MEC Information

The position estimates provided by the MEC and LEC are thought to have different bases (path integration and sensory landmark information, respectively). The CA3 hippocampal region may contribute to this process by calculating a compromise position [92]. The CA3 region has the properties of an attractor network [93–95]. If such a network is briefly exposed to a pattern, its activity is subsequently ‘attracted’ to the closest stored pattern (i.e., no compromise). However, experiments [96] and simulations [94,97] show that, if an input pattern is maintained, the network state is a compromise between the input patterns. Thus, CA3 could represent a position that is a compromise between the MEC and LEC estimates. This estimate would then be passed from CA3 to CA1, and from there back to the MEC (Figure 3A, arrow 3). This overall process would provide the MEC (and grid cells) with an improved estimate of the start position for the mind-travel process that occurs during the second half of the theta cycle.

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Glossary

Artificial velocity vector (AAV)	consists of a direction of interest and a distance of interest. This vector is integrated by the grid cell network to generate mind-travel in the appropriate direction
Grid cell modules	the grid cell network consists of several discrete modules. The grid cells in each module have a consistent spatial scale, a scale that differs between modules. The grid cells in each module move coherently when introduced into a new environment. Mind-travel, the process of internally generating a sequence of place cell activations without corresponding motion
Path integration	also known as ‘dead-reckoning.’ Starting with an identified position, adding the change in position derived from self-motion cues provides a new estimate of position
Phase precession	single-cell manifestation of theta sequences observed as a negative correlation between position and the theta phase of spiking
Rate place field	the area in which a place cell fires. This is the standard method for defining a place field in the literature
Theta sequence	within a theta cycle, an internally generated sequence of place cells fire corresponding to a sequence of locations. This sequence is time-compressed compared to the length of time it would take to traverse this path in space. See mind-travel
True place field	small part of the place field corresponding to region that cell actually represents. Firing outside that small region can be understood as predictive firing during mind-travel

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Trends

Previous models of place cell generation by summing of grid cell inputs have been called into question by recent results.

The phase precession aspect of place cell firing does depend on grid cells.

Phase precession is an expression of theta sequences, in which place cells fire in order during a single theta cycle.

The theta cycle can be broken into two parts: during the first half of the theta cycle, current position is represented; during the second half of the theta cycle, the system performs mind-travel to upcoming locations.

Mind-travel during the second half of theta is hypothesized to be driven by grid cells given their universal representation of spatial adjacency.

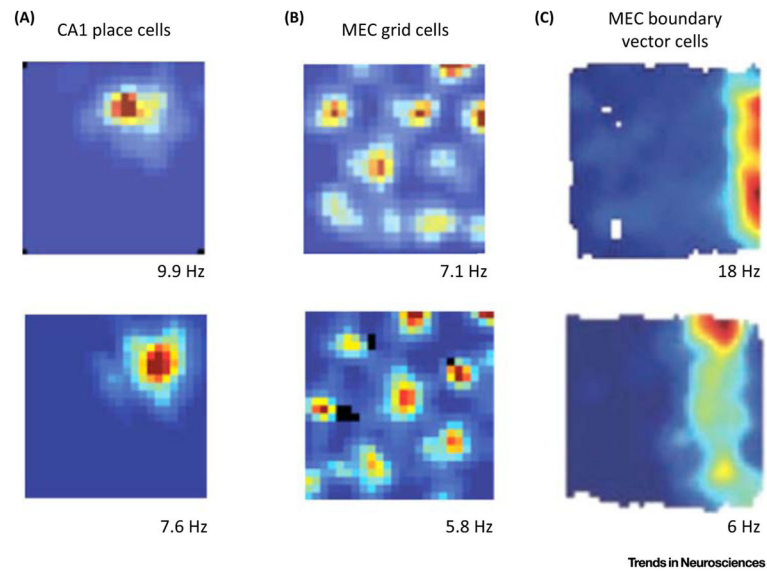


Figure 1. Firing properties of cell types

Rats forage for food in a square-shaped environment. Whenever a spike occurs, the location of the animal is recorded. The heat map shows the spike rate of a given cell as a function of location. The color scale ranges from no activity in dark blue to the maximum rate in red (shown below maps). (A) CA1 place cells [17]. (B) MEC layer II grid cells, adapted from [17]. (C) MEC boundary vector, cells adapted from [8].

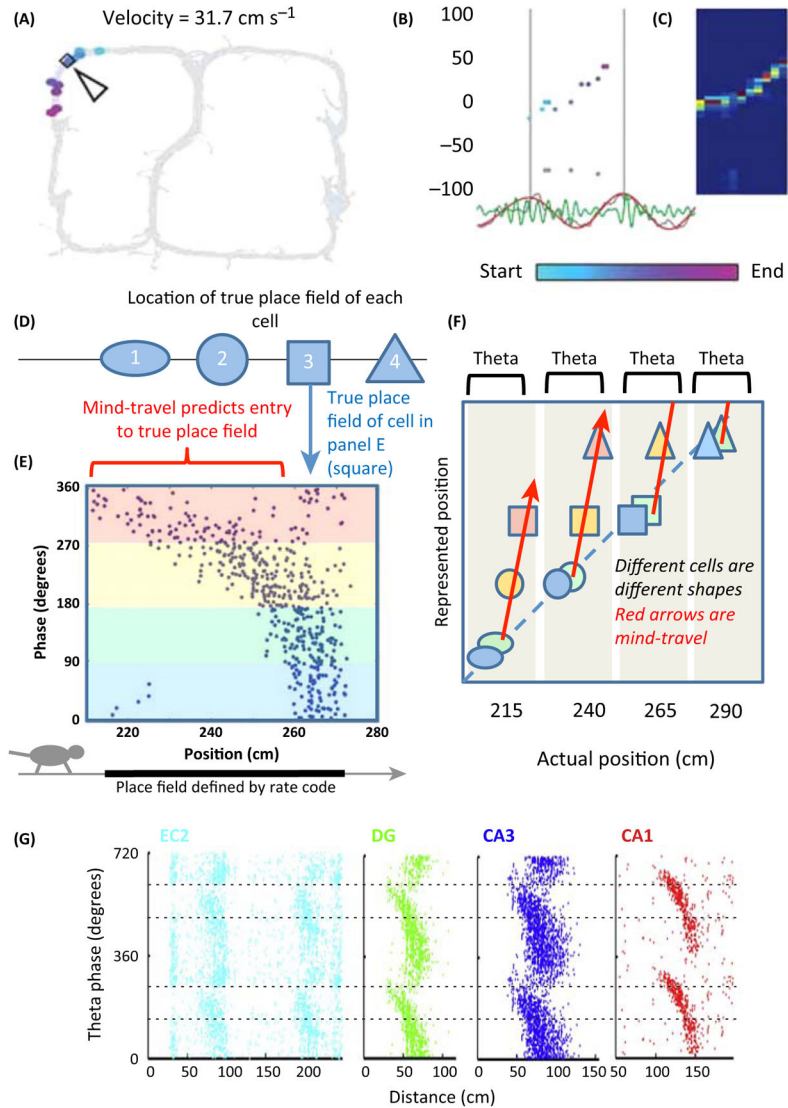
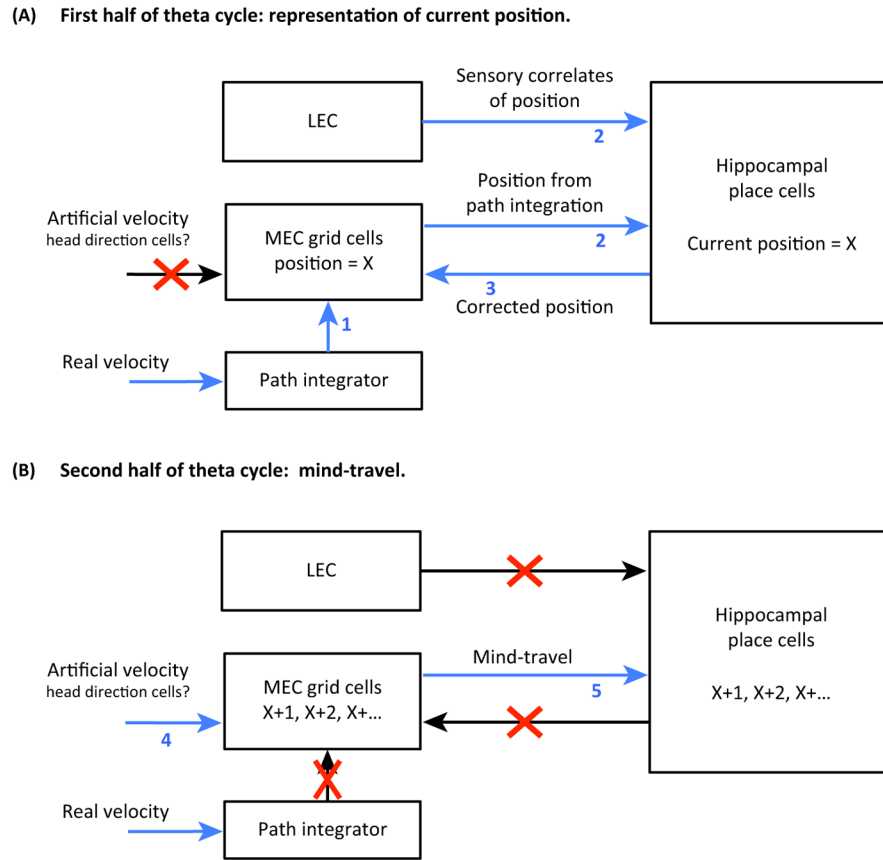


Figure 2. Theta Sequences, Phase Precession, and Mind-Travel

(A) A sequence of place cells representing locations ahead of the animal fire in sequential order during the second half of the theta cycle. Path of rat shown in grey. The arrow and diamond show the current location of the animal. The colored dots represent the place cells that fired during this theta cycle. The location of the dot corresponds to the center of the place field of that cell. The color corresponds to the theta phase of the spikes from that cell, light-blue meaning early theta phase and light-purple meaning late theta phase. (B) Same data as in A. The x-axis is time; one theta cycle is shown. The y-axis is the position of the center of the place field of each cell (cm). Dots correspond to spikes and are colored the same as in A; grey dots are spikes inconsistent with the sequence. The unfiltered local field potential (LFP) is plotted below (grey) together with theta-band (6–12 Hz) filtered (red) and gamma-band (40–100 Hz) filtered (green) traces. (C) Bayesian decoding of position from spike sequence shown on left. Red denotes high probability, blue low. Axes same as middle. (D) Location of true place field of each cell. Mind-travel predicts entry to true place field. True place field of cell in panel E (square). (E) Phase (degrees) vs. Position (cm) scatter plot. (F) Represented position vs. Actual position (cm) plot. Different cells are different shapes. Red arrows are mind-travel. (G) Theta phase (degrees) vs. Distance (cm) for EC2, DG, CA3, and CA1.

Adapted from [36]. (D) Different cells (designated by different shapes) have true place fields at different positions along path (see position axis in E). (E) At bottom, left-to-right path of rat is shown (arrow) with thick line designating the place field determined by the positions where firing occurs (rate code). During this period there are many theta cycles; each dot represents the theta phase and position of the animal at the time of a spike. Over most of the place field, firing is due to mind-travel and occurs during the second half of theta cycles (yellow and red). Starting at 260 cm, the rat is in the true place field and firing occurs over a broader phase range that is in the first half of theta cycles (blue and green). Adapted from [89]. (F) Position represented by different cells is shown. Cell in E is designated by a square, corresponding to cell 3 in D. Color fill represents theta phase, corresponding to colors in E. Dashed line signifies when represented position corresponds to actual position. During the first half of each theta cycle, cells represent current position; during the second half, they perform mind-travel to upcoming positions (red arrows) as a result of an artificial velocity vector (AAV) integrated by the grid cell network. Each theta cycle is marked by grey background. Only four theta cycles are shown, but there are generally seven to ten during traversal of a place field. (G) Phase precession in different regions analyzed with respect to a common phase reference of the local field potential in layer III of the entorhinal cortex (two cycles are shown). Region between pairs of dashed lines marks phase range where precession is strong. Adapted from [67]. Note that the phase reference used here is different from that in the rest of Figure 2. This panel shows that phase precession occurs nearly concurrently in entorhinal cortex layer II (EC2), dentate gyrus (DG), CA3, and CA1 (albeit with ~30 ms offset in CA1). The order in which the areas are shown corresponds to the order of information flow through the trisynaptic pathway (EC2 onto DG, DG onto CA3, CA3 onto CA1).



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Figure 3. Tentative Assignment of Roles to Different Cell Types

Operations during the first and second halves of the theta cycle, respectively. Numbering corresponds to sequences of operations during a theta cycle. Place cells can be driven by the lateral entorhinal cortex (LEC) or the medial entorhinal cortex (MEC). Path integrator is assumed to provide input to layer II grid cells. (A) During the first half of the theta cycle, information from LEC and MEC is combined in CA3 to determine the improved estimate of current position, which is then imposed onto grid cells. (B) In the second half of the theta cycle, integration of an artificial velocity vector (AVV) by the grid cell network produces mind-travel, which in turn drives mind-travel in the hippocampus. Red Xs show pathways that are inactivated, perhaps by a signal from interneurons that fire at the appropriate theta phase (phase-locked interneuron firing has been observed [90]).

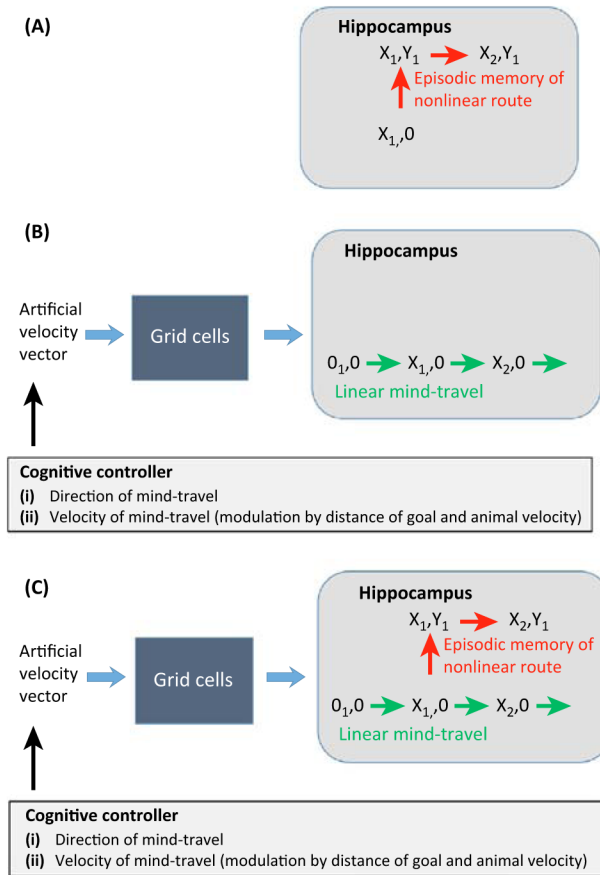


Figure 4. Forms of Mind-Travel Generated by Grid Cells and Place Cells

(A) Intra-hippocampal sequence generation is based on associations that have been experienced in that environment. This allows non-linear paths but limits mind-travel to transitions that have actually been experienced [75,76]. Such replay occurs during sharp-wave ripples [91]. (B) Because grid cells have a universal understanding of spatial structure, they are able to integrate an artificial velocity vector (AAV) and impose the corresponding path on the place cells, even if sections of that path have never been experienced. Because the grid cells do not store information about the specific environment and can only integrate the result of a single AVV, they are restricted to linear mind-travel. (C) It is possible that mixed hippocampal/entorhinal mind-travel could occur, in which the integration of an AVV by grid cells starts the mind-travel, but that intra-hippocampal connections could take over once mind-travel intersects a position in a known path.