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Current questions on space and time encoding

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Abstract

The Nobel Prize in Physiology or Medicine 2014 celebrated the groundbreaking findings on place cells and grid cells by John O'Keefe and May-Britt Moser and Edvard Moser. These findings provided an essential foothold for understanding the cognitive encoding of space and time in episodic memory function. This foothold provides a closer view of a broad new world of important research questions raised by the phenomena of place cells and grid cells. These questions concern the mechanisms of generation of place and grid cell firing, including sensory influences, circuit dynamics and intrinsic properties. Similar questions concern the generation of time cells. In addition, questions concern the functional role of place cells, grid cells and time cells in mediating goal-directed behavior and episodic memory function.

Keywords

place cells; grid cells; entorhinal cortex; rat

The importance of place cells and grid cells

The discoveries of place cells by John O'Keefe (O'Keefe, 1976) and grid cells by May-Britt and Edvard Moser (Moser and Moser, 2008) were celebrated by the Nobel prize committee because they provided an essential quantitative foothold for understanding the cognitive representation of space. As described in the classic book by O'Keefe and Nadel (O'Keefe and Nadel, 1978), the representation of space has been considered by philosophers for millennia. The discovery of place cells provided a quantifiable and highly replicable phenomena indicating the physiological representation of space (O'Keefe, 1976). The discovery of grid cells provided a further experimental breakthrough in our understanding of spatial representations (Moser and Moser, 2008), providing quantifiable data on spatial representation that includes the orientation, spatial phase and spatial scale of grid cell firing fields. The transformative nature of these discoveries can be seen in the wide range of subsequent experiments and models published on these phenomena. The discovery and description of other phenomena such as head direction cells (Ranck, 1984; Taube et al., 1990b; Taube et al., 1990a), boundary cells (Solstad et al., 2008; Savelli et al., 2008; Lever et al., 2009) and time cells (Pastalkova et al., 2008; MacDonald et al., 2011; Kraus et al.,

2013; MacDonald et al., 2013; Wang et al., 2015) provide additional bodies of quantifiable data that further contribute to elucidating our understanding of the mechanisms of spatial coding.

The dramatic advances of Physics over the past few centuries depended crucially on bodies of quantifiable data. For example, Newtonian mechanics required detailed and accurate measurements of the dynamics of falling bodies and planetary motion, and quantum mechanics required the precise measurements of absorption and emission spectra. Systems neuroscience has relatively few examples of highly quantitative phenomena at the network level, in contrast to the quantitative properties of membrane potential dynamics that have led to influential theoretical work (Hodgkin and Huxley, 1952; Izhikevich, 2007). The bodies of quantifiable data concerning place cells, grid cells, head direction cells, boundary cells and time cells have the potential to drive significant theoretical breakthroughs in systems neuroscience. Like many groundbreaking discoveries, the importance of the discovery of place cells and grid cells lies partly in the new broad range of new questions raised by these discoveries. I will review some of these important questions, and current and future research addressing these questions.

What is the mechanism of generation of place cells?

Right from the start the discovery of place cells raised the important question about the mechanism of their generation. This question remains unresolved, though numerous studies have analyzed both the nature of the sensory input influencing place cell firing as well as the circuit mechanisms contributing to their activity. A full review is beyond the scope of this article, but this has proved to be one of the most fruitful areas for theoretical modelling that guides experimental research. For example, research analyzed the systematic response of place cells to manipulations of environmental barriers (O'Keefe and Burgess, 1996). This work prompted development of the influential theory of boundary vector cells (Burgess et al., 2000; Hartley et al., 2000) that explicitly predicted the existence of boundary cells that were subsequently demonstrated experimentally (Barry et al., 2006; Savelli et al., 2008; Solstad et al., 2008; Lever et al., 2009). This prediction of boundary cells was an important achievement of theoretical modelling of place cells. The continued modelling and recording of boundary cells will help resolve questions of the sensory inputs guiding the firing of place cells and grid cells.

Another major breakthrough was the discovery of theta phase precession of place cells, in which spiking starts out at late phases of theta rhythm when a rat enters a firing field, and shifts to earlier phases as the rat moves through the firing field (O'Keefe and Recce, 1993). This provided essential evidence for temporal coding by spike times (O'Keefe and Recce, 1993; Skaggs et al., 1996), and has prompted numerous computational models of the generation of place cells. The testing and validation of individual models of theta phase precession remains an important open question, but the wealth of different models provides important opportunities for experiments to select between explicit experimental implications of sophisticated theoretical models.

Extensive work on head direction cells has traced the subcortical pathways and sensory influences on head direction cells (Taube et al., 1996; Taube and Bassett, 2003). This work provides inspiration for approaches to answering questions about the mechanism of generation of place cells and grid cells.

What is the mechanism of grid cells?

Questions about the mechanism of generation of place cells prompted the discovery of grid cells. In particular, the Mosers recorded in the dorsal parts of medial entorhinal cortex on the advice of Menno Witter to specifically explore the area sending input to the dorsal hippocampus where most place cells were recorded (Fyhn et al., 2007). The appearance of grid cell firing patterns suggests the possibility of an elegant theoretical account of their firing pattern. Grid cells generate spikes as an animal visits an array of locations in the environment that fall on the vertices of equilateral triangles tessellating the environment (Fyhn et al., 2004; Hafting et al., 2005; Moser and Moser, 2008). After the discovery of this regular geometric pattern of activity, researchers rapidly proposed a number of models addressing the mechanism of this characteristic geometric pattern.

Questions to be addressed by models include different aspects of the spatial firing properties. For example, models must address questions about the mechanism for differences in the spacing of grid cells at different dorsal to ventral positions within medial entorhinal cortex (Hafting et al., 2005; Sargolini et al., 2006; Stensola et al., 2012). In addition, models must address the quantal spacing of firing fields in different grid cells and systematic shifts of spacing based on boundary location (Barry et al., 2007). Models must also address how modules of grid cells share properties of spacing with properties of orientation and ellipsoid distortion as well as properties of compression in response to movement of boundaries (Stensola et al., 2012).

Attractor models (Fuhs and Touretzky, 2006; McNaughton et al., 2006; Guanella et al., 2007; Burak and Fiete, 2009) drive grid cell firing based on circularly symmetric excitatory or inhibitory feedback. These models effectively generate the shared orientation and spacing of grid cell firing fields (Sargolini et al., 2006), the quantal nature of grid cell spacing in different modules (Barry et al., 2007; Stensola et al., 2012) and the clustering of orientation, spacing and elliptic stretching into modules (Stensola et al., 2012). The dynamics of grid cell firing are obtained with a velocity input proposed to arise from structured connectivity of conjunctive grid-by-head-direction cells (McNaughton et al., 2006; Burak and Fiete, 2009). In contrast with attractor models, other models use feedforward self-organization (Kropff and Treves, 2008; Mhatre et al., 2010; Si et al., 2012). Models using input to entorhinal cortex from place cells in hippocampus can account for the loss of grid cell firing with inactivation of the hippocampus (Bonnievie et al., 2013) and the retention of place cells during loss of grid cell firing (Brandon et al., 2014).

Oscillatory interference models (Burgess et al., 2005; Burgess et al., 2007; Blair et al., 2008; Burgess, 2008; Hasselmo, 2008; Welday et al., 2011) effectively address the theta rhythmic firing of grid cells (Hafting et al., 2008; Jeewajee et al., 2008; Brandon et al., 2011; Koenig et al., 2011; Stensola et al., 2012), including the frequently observed relationship between

the intrinsic theta rhythmicity of a neuron (measured by its autocorrelogram) and the spacing between grid cell firing fields ((Jeewajee et al., 2008; Stensola et al., 2012). Oscillatory interference models also account for the theta phase precession of grid cells (Hafting et al., 2008; Climer et al., 2013; Eggink et al., 2014) and the prominent theta in the local field potential of entorhinal cortex (Mitchell and Ranck, 1980; Mitchell et al., 1982; Alonso and Garcia-Austt, 1987; Jeffery et al., 1995). These models are consistent with phase precession of subthreshold oscillations relative to network theta. Researchers often contrast models using oscillatory interference with those using attractor dynamics or self-organization, but many features of these models are compatible and could coexist within a single network model of grid cells. Oscillatory interference can be merged with attractor dynamics (Bush and Burgess, 2014) to account for data showing depolarizations in grid cell firing fields without changes in envelopes of theta oscillations (Domnisoru et al., 2013; Schmidt-Hieber and Hausser, 2013). Questions remain about how grid cells could appear in bats (Yartsev et al., 2011) when theta rhythm oscillations are only intermittent, preventing constant coding of position by phase.

Is path integration alone sufficient?

Most initial models of grid cells focused on path integration of a self-motion signal. This is because grid cells continue to show regular firing fields in darkness (Hafting et al., 2005), suggesting that they do not require sensory input. However, studies have not analyzed the dependence of grid cells on other sensory input such as somatosensory input available in darkness from whisking or auditory localization input. The question remains whether path integration can generate grid cells in isolation from other sensory influences. Studies in absolute darkness should be combined with sound attenuation and clipping of whiskers to remove these components of sensory input so that the animal must rely entirely on proprioceptive and vestibular self-motion signals.

What is the role of movement direction versus head direction?

Models that rely on integration of a self-motion signal to obtain stable locations of firing fields assume that the grid cells in medial entorhinal cortex have access to a clear velocity signal. That is, they must have access to both translational speed and movement direction. This use of velocity input is present in all published attractor models (Fuhs and Touretzky, 2006; McNaughton et al., 2006; Guanella et al., 2007; Burak and Fiete, 2009; Bonnevie et al., 2013; Couey et al., 2013) as well as oscillatory interference models (Burgess et al., 2007; Burgess, 2008; Hasselmo, 2008; Blair et al., 2008; Zilli and Hasselmo, 2010). The requirement of a speed signal is supported by data showing a linear or logarithmic relationship of firing rate to running speed in recordings from hippocampus and medial entorhinal cortex (O'Keefe et al., 1998; Wills et al., 2012; Kemere et al., 2013)(Hinman et al., in review), but the requirement for movement direction is more problematic.

Many papers cite head direction responses of medial entorhinal cortex as the evidence for a movement direction signal. In particular, attractor dynamic models propose the use of grid-by-head-direction cells as the means of ensuring that grid cell firing shifts appropriately with movement (McNaughton et al., 2006; Burak and Fiete, 2009; Couey et al., 2013). However,

an analysis of behavioural data shows that the head direction signal does not match movement direction in a manner reliable enough for accurate grid cell firing (Raudies et al., 2014). In addition, analysis of the firing properties of medial entorhinal neurons during periods when head direction does not match movement direction shows little evidence of neurons coding movement direction. In the data, numerous neurons clearly code head direction alone, only a few neurons code head direction and movement direction and no neurons respond on the basis of movement direction alone (Raudies et al., 2014). This stronger coding of head direction suggests the importance of maintaining a representation of the head direction for evaluating the angle of input stimuli from sensory input that may include vision, audition and somatosensory input.

What is the role of moving visual features (optic flow) versus static visual features (landmarks)?

In addition to the stronger representation of head direction versus movement direction in medial entorhinal cortex, other evidence indicates the influence of distal sensory input on grid cells. The rotation of a cue card on the wall of a cylinder causes rotation of the spatial location of grid cell firing fields (Hafting et al., 2005). In addition, movement of the walls of the environment will cause compression or expansion of the firing fields along the relevant dimension of the environment (Barry et al., 2007). This compression or expansion occurs selectively for individual modules of grid cells, such that modules with larger spacing may show compression of firing fields while a simultaneously recorded module with smaller spacing may show no compression of firing fields (Stensola et al., 2012). The firing accuracy of grid cells depends upon the recency of interaction with boundaries in the environment (Hardcastle et al., 2015).

The influence of sensory input on grid cells has not been modelled as extensively as path integration of self-motion. However, an early study showed how optic flow could be used to compute a velocity signal to drive an oscillatory interference model of grid cells (Raudies et al., 2012), or could be used to drive boundary cells (Raudies and Hasselmo, 2012). A different model showed that the influence of boundary cells could alter the positioning of grid cell firing fields based on different shapes of environments (Krupic et al., 2014), correctly predicting that an environment with trapezoid walls would have distorted firing field location as supported by recent data from grid cells (Krupic et al., 2015). More recent work has shown that differential sensitivity to boundary movement could arise from differences in the nature of location computation by different modules. Modules sensitive to static visual features on the walls of the environment should be particularly sensitive to the shift of these visual features with wall movement. In contrast, modules responding to visual features on the ground plane near the rat would be less sensitive to wall movement, particularly if the firing location is driven by integration of a moving feature signal from the ground plane near the rat (Raudies and Hasselmo, in review). The retinotopic position of ground plane versus wall features could result in processing at different anatomical positions in visual regions and along the dorsal to ventral axis of entorhinal cortex.

How do local circuits support grid cell firing?

The different types of models make very different demands on the local circuit connectivity of medial entorhinal cortex. Initial attractor models proposed both excitatory and inhibitory feedback with a Mexican hat profile in the dimensions of space being coded by the neurons (Fuhs and Touretzky, 2006; McNaughton et al., 2006). However, physiological data from slices suggests that entorhinal stellate cells primarily communicate via inhibitory feedback (Dhillon and Jones, 2000; Couey et al., 2013). Attractor models effectively account for this by using an annulus of circularly symmetric feedback inhibition coupled with strong external driving input (Burak and Fiete, 2009; Couey et al., 2013; Bonnevie et al., 2013).

The requirement of circularly symmetric connections in the space being coded by the neurons is difficult to test explicitly. However, recent physiological data suggests that neurons might have the necessary patterns of connectivity in anatomical space (Heys et al., 2014). Calcium imaging of the activity of large populations of grid cells in medial entorhinal cortex show a Mexican hat profile of correlations based on anatomical distance. Neurons that are close neighbors or distant neighbors in medial entorhinal cortex show correlated firing, whereas neurons at an intermediate distances show anti-correlated firing consistent with an annulus of inhibition (Heys et al., 2014).

In attractor models, the difference in spacing could arise either from a difference in the radius of the annulus of inhibition, or a difference in the speed of updating based on path integration. A difference in the radius of inhibition is supported by data showing systematic changes in the magnitude and radius of inhibitory interactions in slices from the dorsal versus the ventral medial entorhinal cortex (Beed et al., 2013). Different attractor models have different connectivity properties (Fuhs and Touretzky, 2006; McNaughton et al., 2006; Guanella et al., 2007; Burak and Fiete, 2009). Numerous questions remain about how the anatomical connectivity of entorhinal cortex could provide the necessary attractor dynamics. Oscillatory interference models provide a potential framework for replacing some of the requirements for spatially periodic connectivity with the periodic properties of oscillations or waves. In particular, models have addressed this question by generating grid cells by using input from ring attractors (Blair et al., 2008; Weldon et al., 2011; Blair et al., 2014) or using wave inputs (Hasselmo and Brandon, 2012; Hasselmo, 2014; Hasselmo and Shay, 2014).

How do intrinsic cellular membrane potential properties contribute to grid cell firing?

Another question concerns the relationship of grid cell firing to the intrinsic properties of medial entorhinal neurons. This could involve numerous properties of membrane channels or circuit connections. The simplified structure of most existing grid cell models does not address the full range of physiological data, such as the intrinsic membrane potential dynamics of entorhinal neurons. A link between grid cell firing properties and intrinsic properties is supported by the fact that unit recording data shows grid cells in medial entorhinal cortex (Hafting et al., 2005) but not lateral entorhinal cortex (Hargreaves et al., 2005). This is consistent with the appearance of intrinsic resonance in layer II stellate cells

in medial entorhinal cortex (Haas and White, 2002; Erchova et al., 2004; Canto and Witter, 2012b; Shay et al., 2012) but not in layer II neurons in lateral entorhinal cortex (Canto and Witter, 2012a; Shay et al., 2012).

In addition, a link to intrinsic properties is further supported by the frequently replicated data showing a difference in resonance frequency along the dorsal to ventral axis of medial entorhinal cortex (Giocomo et al., 2007; Giocomo and Hasselmo, 2008; Boehlen et al., 2010; Pastoll et al., 2012; Shay et al., 2012) that correlates with differences in the size and spacing of grid cell firing fields along the dorsal to ventral axis of medial entorhinal cortex (Hafting et al., 2005; Sargolini et al., 2006; Barry et al., 2007; Stensola et al., 2012). The differences in resonance properties are related to the difference in magnitude of the hyperpolarization activated cation current (h current) (Alonso and Llinas, 1989; Alonso and Klink, 1993; Dickson et al., 2000; Shay et al., 2012). Knockout of the HCN1 subunit of this current causes a loss of the dorso-ventral gradient of resonance frequency (Giocomo and Hasselmo, 2009) and causes an expansion of spacing between grid cell firing fields (Giocomo et al., 2011).

The question is still open of how these cellular properties of the h current might contribute to the spacing of grid cell firing fields. This may involve regulation of the summation of synaptic input (Garden et al., 2008). Alternately, the h current might influence grid cell firing properties by causing different time courses of rebound spiking in response to hyperpolarizing inhibitory input (Hasselmo, 2014; Hasselmo and Shay, 2014). Rebound spiking does not necessarily have to depend upon h current, as it could be mediated by a calcium activated non-specific cation current (CAN current) (Egorov et al., 2002; Fransén et al., 2006) that causes a rebound spike after a preceding spike (Navratilova et al., 2012) and can result in persistent spiking (Egorov et al., 2002; Fransén et al., 2006; Jochems et al., 2013; Knauer et al., 2013). The CAN current is enhanced by muscarinic cholinergic receptor activation due to cholinergic input from medial septum to hippocampus and entorhinal cortex. Loss of this current could underlie loss of grid cells after systemic injections of the muscarinic blocker scopolamine (Newman et al., 2014). Another potential relationship to intrinsic properties concerns the modulatory reductions in cellular resonance frequency caused by acetylcholine (Heys et al., 2010). This could underlie the difference in spacing observed in novel environments (Barry et al., 2012a; Barry et al., 2012b) due to an increase in acetylcholine release in novel environments (Acquas et al., 1996)

What is the role of medial septal input?

The discovery of place cells and grid cells helped drive interest in the role of medial septal input to the hippocampus. Questions include whether the impairments of spatial memory caused by inactivation of the medial septum (Chrobak et al., 1989) are due to the loss of spatial periodicity of grid cells when network theta rhythm oscillations are reduced by inactivation of the medial septum (Brandon et al., 2011; Koenig et al., 2011). The role of medial septum in place cell or grid cell firing activity may be linked to the changes in the frequency of neuronal firing or theta oscillations observed in the medial septum or hippocampus during changes in running speed (King et al., 1998; Hinman et al., 2011). Unanswered questions also concern the mechanism and functional role of theta cycle

skipping observed in neurons of the medial entorhinal cortex (Jeffery et al., 1995; Deshmukh et al., 2010; Brandon et al., 2013), and medial septum (King et al., 1998; Varga et al., 2008) and data showing different populations active on opposite phases of theta (Mizuseki et al., 2009; Newman and Hasselmo, 2014).

What is the mechanism of time cells?

Episodic memory involves the memory of both the location and time of an event. The discovery of spatial coding in structures involved in episodic memory function raised the question of how the time of an event could be coded. The discovery of time cells has provided a potential mechanism for the coding of the time of events in episodic memory. Time cells are neurons that fire at a specific time intervals when rats remain in a single spatial location (McDonald et al., 2011). Time cells are particularly prominent in tasks that put demands on maintenance of memory during a waiting period as in a delayed spatial alternation task, and are particularly prominent if the rats are running on a running wheel (Pastalkova et al., 2008) or a treadmill (Kraus et al., 2013).

The discovery of time cells raises important questions about their mechanism. They can be modelled using oscillatory interference, in a manner analogous to models of grid cells. In oscillatory interference models, the frequency of oscillations is modulated by running velocity to allow relative phase to code space. In contrast, if two interacting oscillations maintain fixed frequency, their summed interaction will show peaks at specific time intervals ((Hasselmo, 2008; Hasselmo, 2012; Hasselmo and Stern, 2014). This resembles previous models of time interval coding (Miall, 1989). Similar to grid cell models, the generation of time cells in the hippocampus could involve interactions of oscillatory input from the medial septum (Hasselmo, 2008; Hasselmo and Stern, 2014) as supported by the data showing that inactivation of the medial septum causes loss of time cells in the hippocampus (Wang et al., 2015).

Time cells have also been proposed to arise from spiking interactions of cells showing persistent spiking. This could involve interactions of the firing frequency of different sets of persistent spiking neurons (Hasselmo and Stern, 2014). Because muscarinic cholinergic receptors enhance persistent spiking (Klink and Alonso, 1997; Egorov et al., 2002; Fransen et al., 2006; Hasselmo and Stern, 2006) the medial septum could block time cells due to removal of cholinergic modulation. Alternately, generation of time cells could depend on the interaction of the exponential decay of firing rate in different neurons (Shankar and Howard, 2012; Howard et al., 2014; Tiganj et al., 2015)

What is the function of place cells and grid cells?

Behavioral data indicates that humans and animals do not need the hippocampus and entorhinal cortex to navigate in a familiar environment. The bilateral surgical removal of all of the entorhinal cortex and most of the hippocampus in Henry Molaison (Patient HM) caused a profound impairment of episodic memory for newly learned verbal stimuli (Scoville and Milner, 1957) and learning new pathways in a peg maze task (Milner et al., 1968) but did not prevent him from being able to find his way back to his original home

location before the surgery (Scoville and Milner, 1957) or being able to draw a plan of the house that he lived in after his surgery after he had lived there for eight years (Milner et al., 1968). Similarly, rats with hippocampal lesions are not impaired in the use of reference memory to avoid unrewarded arms in an 8-arm radial maze (Olton et al., 1979; Olton et al., 1986). Thus, the spatial representations in hippocampus and entorhinal cortex are uniquely important to conditions in which new information must be encoded in episodic memory to guide subsequent behavior. Rather than requiring the hippocampus, the mechanisms of navigation in highly familiar environments appears to depend upon neocortical regions such as the parietal cortex (Byrne et al., 2007). Computational models have demonstrated how grid cells and other functional neurons in medial entorhinal cortex may allow the formation of spatial associations with sensory input in novel environments (Milford et al., 2010; Erdem et al., 2015), to allow behaviors such as forward planning of trajectories to goal locations (Erdem and Hasselmo, 2012; Erdem and Hasselmo, 2014).

The hippocampus and entorhinal cortex may code spatial location not for general purpose navigation in familiar environments, but for the episodic memory of the spatial location of items and events. Computational models have addressed how place cells, grid cells, head direction cells and time cells might mediate the episodic memory for location and time, but these models have only covered a small portion of the space of possible models, and they are seriously underconstrained by the experimental data. Typical of an early stage of research field, it is not even clear what form an effective mathematical theory might take. However, a possible form of an effective theory would be a wave-based model representing propagation of rhythmic neural activity within multiple dimensions of cortical representation. During encoding, the activity in hippocampus and entorhinal cortex would code the complex spatiotemporal trajectory of self-location and time during behavior, and encode associations between different elements of the trajectory (Hasselmo, 2009; Hasselmo, 2012). The segments of this complex spatiotemporal trajectory would also be associated with a vector representing the spherical angle and information content of sensory input encountered at specific locations and head directions along the trajectory, via modifications of synaptic connections or intrinsic properties. During replay or recollection, a retrieval cue activating a specific segment of the trajectory would trigger retrieval of other segments and the associated multidimensional information content and spherical angle of sensory input.

Models of this type could address the physiological data on replay of previously encoded sequences of place cells observed in behaving rats (Johnson and Redish, 2007; Davidson et al., 2009; Jadhav et al., 2012). These dynamics can be used to address the neural activity correlated with recollection of episodic memory in humans (Kirchhoff et al., 2000; Brown et al., 2010; Brown et al., 2014; Brown and Stern, 2014) and the network of interacting regions involved in spatial navigation (Doeller et al., 2010; Sherrill et al., 2013), demonstrating potential frameworks for linking from cellular to circuit to behavioural function based on dynamical properties of place cells and grid cells. This article addresses only a few questions and models, but these examples illustrate the broad scope of theoretical and experimental questions raised by the discovery of place cells and grid cells.

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References

- Acquas E, Wilson C, Fibiger HC. 1996 Conditioned and unconditioned stimuli increase frontal cortical and hippocampal acetylcholine release: effects of novelty, habituation, and fear. *J Neurosci* 16(9):3089–96. [PubMed: 8622138]
- Alonso A, Garcia-Austt E. 1987 Neuronal sources of theta rhythm in the entorhinal cortex of the rat. I. Laminar distribution of theta field potentials. *Experimental Brain Research* 67(3):493–501. [PubMed: 3653311]
- Alonso A, Klink R. 1993 Differential electroresponsiveness of stellate and pyramidal-like cells of medial entorhinal cortex layer II. *J Neurophysiol* 70(1):128–43. [PubMed: 8395571]
- Alonso A, Llinas RR. 1989 Subthreshold Na-dependent theta-like rhythmicity in stellate cells of entorhinal cortex layer II. *Nature* 342:175–177. [PubMed: 2812013]
- Barry C, Ginzberg LL, O’Keefe J, Burgess N. 2012a Grid cell firing patterns signal environmental novelty by expansion. *Proc. Natl. Acad. Sci. USA* 109(43):17687–17692. [PubMed: 23045662]
- Barry C, Hayman R, Burgess N, Jeffery KJ. 2007 Experience-dependent rescaling of entorhinal grids. *Nat Neurosci* 10(6):682–4. [PubMed: 17486102]
- Barry C, Heys JG, Hasselmo ME. 2012b Possible role of acetylcholine in regulating spatial novelty effects on theta rhythm and grid cells. *Front Neural Circuits* 6:5. [PubMed: 22363266]
- Barry C, Lever C, Hayman R, Hartley T, Burton S, O’Keefe J, Jeffery K, Burgess N. 2006 The boundary vector cell model of place cell firing and spatial memory. *Rev Neurosci* 17(1-2):71–97. [PubMed: 16703944]
- Beed P, Gundlfinger A, Schneiderbauer S, Song J, Bohm C, Burgalossi A, Brecht M, Vida I, Schmitz D. 2013 Inhibitory Gradient along the Dorsoventral Axis in the Medial Entorhinal Cortex. *Neuron* 79(6):1197–207. [PubMed: 24050405]
- Blair HT, Gupta K, Zhang K. 2008 Conversion of a phase- to a rate-coded position signal by a three-stage model of theta cells, grid cells, and place cells. *Hippocampus* 18(12):1239–55. [PubMed: 19021259]
- Blair HT, Wu A, Cong J. 2014 Oscillatory neurocomputing with ring attractors: a network architecture for mapping locations in space onto patterns of neural synchrony. *Philos Trans R Soc Lond B Biol Sci* 369(1635):20120526. [PubMed: 24366137]
- Boehlen A, Heinemann U, Erchova I. 2010 The range of intrinsic frequencies represented by medial entorhinal cortex stellate cells extends with age. *J Neurosci* 30(13):4585–9. [PubMed: 20357109]
- Bonnevie T, Dunn B, Fyhn M, Hafting T, Derdikman D, Kubie JL, Roudi Y, Moser EI, Moser MB. 2013 Grid cells require excitatory drive from the hippocampus. *Nat Neurosci* 16(3):309–17. [PubMed: 23334581]
- Brandon MP, Bogaard AR, Libby CP, Connerney MA, Gupta K, Hasselmo ME. 2011 Reduction of theta rhythm dissociates grid cell spatial periodicity from directional tuning. *Science* 332(6029):595–9. [PubMed: 21527714]
- Brandon MP, Bogaard AR, Schultheiss NW, Hasselmo ME. 2013 Segregation of cortical head direction cell assemblies on alternating theta cycles. *Nat Neurosci* 16(6):739–48. [PubMed: 23603709]
- Brandon MP, Koenig J, Leutgeb JK, Leutgeb S. 2014 New and distinct hippocampal place codes are generated in a new environment during septal inactivation. *Neuron* 82(4):789–96. [PubMed: 24853939]
- Brown TI, Hasselmo ME, Stern CE. 2014 A high-resolution study of hippocampal and medial temporal lobe correlates of spatial context and prospective overlapping route memory. *Hippocampus* 24(7):819–39. [PubMed: 24659134]

- Brown TI, Ross RS, Keller JB, Hasselmo ME, Stern CE. 2010 Which way was I going? Contextual retrieval supports the disambiguation of well learned overlapping navigational routes. *J Neurosci* 30(21):7414–22. [PubMed: 20505108]
- Brown TI, Stern CE. 2014 Contributions of medial temporal lobe and striatal memory systems to learning and retrieving overlapping spatial memories. *Cereb Cortex* 24(7):1906–22. [PubMed: 23448868]
- Burak Y, Fiete IR. 2009 Accurate path integration in continuous attractor network models of grid cells. *PLoS Comput Biol* 5(2):e1000291. [PubMed: 19229307]
- Burgess N. 2008 Grid cells and theta as oscillatory interference: theory and predictions. *Hippocampus* 18(12):1157–74. [PubMed: 19021256]
- Burgess N, Barry C, Jeffery KJ, O'Keefe J. 2005 A grid and place cell model of path integration utilizing phase precession versus theta. *Computational Cognitive Neuroscience Meeting*.
- Burgess N, Barry C, O'Keefe J. 2007 An oscillatory interference model of grid cell firing. *Hippocampus* 17(9):801–12. [PubMed: 17598147]
- Burgess N, Jackson A, Hartley T, O'Keefe J. 2000 Predictions derived from modelling the hippocampal role in navigation. *Biol Cybern* 83(3):301–12. [PubMed: 11007303]
- Bush D, Burgess N. 2014 A hybrid oscillatory interference/continuous attractor network model of grid cell firing. *J Neurosci* 34(14):5065–79. [PubMed: 24695724]
- Byrne P, Becker S, Burgess N. 2007 Remembering the past and imagining the future: a neural model of spatial memory and imagery. *Psychol Rev* 114(2):340–75. [PubMed: 17500630]
- Canto CB, Witter MP. 2012a Cellular properties of principal neurons in the rat entorhinal cortex. I. The lateral entorhinal cortex. *Hippocampus* 22(6):1256–76. [PubMed: 22162008]
- Canto CB, Witter MP. 2012b Cellular properties of principal neurons in the rat entorhinal cortex. II. The medial entorhinal cortex. *Hippocampus* 22(6):1277–99. [PubMed: 22161956]
- Chrobak JJ, Stackman RW, Walsh TJ. 1989 Intraseptal administration of muscimol produces dose-dependent memory impairments in the rat. *Behav. Neural Biol* 52(3):357–369. [PubMed: 2556105]
- Climer JR, Newman EL, Hasselmo ME. 2013 Phase coding by grid cells in unconstrained environments: two-dimensional phase precession. *Eur J Neurosci* 38(4):2526–41. [PubMed: 23718553]
- Couey JJ, Witoelar A, Zhang SJ, Zheng K, Ye J, Dunn B, Czajkowski R, Moser MB, Moser EI, Roudi Y, Witter MP. 2013 Recurrent inhibitory circuitry as a mechanism for grid formation. *Nat Neurosci* 16(3):318–24. [PubMed: 23334580]
- Davidson TJ, Kloosterman F, Wilson MA. 2009 Hippocampal replay of extended experience. *Neuron* 63(4):497–507. [PubMed: 19709631]
- Deshmukh SS, Yoganarasimha D, Voicu H, Knierim JJ. 2010 Theta modulation in the medial and the lateral entorhinal cortices. *J Neurophysiol* 104(2):994–1006. [PubMed: 20505130]
- Dhillon A, Jones RS. 2000 Laminar differences in recurrent excitatory transmission in the rat entorhinal cortex in vitro. *Neuroscience* 99(3):413–22. [PubMed: 11029534]
- Dickson CT, Magistretti J, Shalinsky MH, Fransen E, Hasselmo ME, Alonso A. 2000 Properties and role of I(h) in the pacing of subthreshold oscillations in entorhinal cortex layer II neurons. *J Neurophysiol* 83(5):2562–79. [PubMed: 10805658]
- Doeller CF, Barry C, Burgess N. 2010 Evidence for grid cells in a human memory network. *Nature* 463(7281):657–61. [PubMed: 20090680]
- Domnisoru C, Kinkhabwala AA, Tank DW. 2013 Membrane potential dynamics of grid cells. *Nature* 495(7440):199–204. [PubMed: 23395984]
- Eggink H, Mertens P, Storm E, Giocomo LM. 2014 Hyperpolarization-activated cyclic nucleotide-gated 1 independent grid cell-phase precession in mice. *Hippocampus* 24(3):249–56. [PubMed: 24638961]
- Egorov AV, Hamam BN, Fransen E, Hasselmo ME, Alonso AA. 2002 Graded persistent activity in entorhinal cortex neurons. *Nature* 420(6912):173–8. [PubMed: 12432392]

- Erchova I, Kreck G, Heinemann U, Herz AV. 2004 Dynamics of rat entorhinal cortex layer II and III cells: characteristics of membrane potential resonance at rest predict oscillation properties near threshold. *J Physiol* 560(Pt 1):89–110. [PubMed: 15272028]
- Erdem UM, Hasselmo M. 2012 A goal-directed spatial navigation model using forward trajectory planning based on grid cells. *Eur J Neurosci* 35(6):916–31. [PubMed: 22393918]
- Erdem UM, Hasselmo ME. 2014 A biologically inspired hierarchical goal directed navigation model. *J Physiol Paris* 108(1):28–37. [PubMed: 23891644]
- Erdem UM, Milford MJ, Hasselmo ME. 2015 A hierarchical model of goal directed navigation selects trajectories in a visual environment. *Neurobiol Learn Mem* 117:109–21. [PubMed: 25079451]
- Fransén E, Tahvildari B, Egorov AV, Hasselmo ME, Alonso AA. 2006 Mechanism of graded persistent cellular activity of entorhinal cortex layer v neurons. *Neuron* 49(5):735–46. [PubMed: 16504948]
- Fuhs MC, Touretzky DS. 2006 A spin glass model of path integration in rat medial entorhinal cortex. *J Neurosci* 26(16):4266–76. [PubMed: 16624947]
- Fyhn M, Hafting T, Treves A, Moser MB, Moser EI. 2007 Hippocampal remapping and grid realignment in entorhinal cortex. *Nature* 446(7132):190–4. [PubMed: 17322902]
- Fyhn M, Molden S, Witter MP, Moser EI, Moser MB. 2004 Spatial representation in the entorhinal cortex. *Science* 305(5688):1258–64. [PubMed: 15333832]
- Garden DL, Dodson PD, O'Donnell C, White MD, Nolan MF. 2008 Tuning of synaptic integration in the medial entorhinal cortex to the organization of grid cell firing fields. *Neuron* 60(5):875–89. [PubMed: 19081381]
- Giocomo LM, Hasselmo ME. 2008 Computation by oscillations: implications of experimental data for theoretical models of grid cells. *Hippocampus* 18(12):1186–99. [PubMed: 19021252]
- Giocomo LM, Hasselmo ME. 2009 Knock-out of HCN1 subunit flattens dorsal-ventral frequency gradient of medial entorhinal neurons in adult mice. *J Neurosci* 29(23):7625–30. [PubMed: 19515931]
- Giocomo LM, Hussaini SA, Zheng F, Kandel ER, Moser MB, Moser EI. 2011 Grid cells use HCN1 channels for spatial scaling. *Cell* 147(5):1159–70. [PubMed: 22100643]
- Giocomo LM, Zilli EA, Fransen E, Hasselmo ME. 2007 Temporal frequency of subthreshold oscillations scales with entorhinal grid cell field spacing. *Science* 315(5819):1719–22. [PubMed: 17379810]
- Guanella A, Kiper D, Verschure P. 2007 A model of grid cells based on a twisted torus topology. *Int J Neural Syst* 17(4):231–40. [PubMed: 17696288]
- Haas JS, White JA. 2002 Frequency selectivity of layer II stellate cells in the medial entorhinal cortex. *J Neurophysiol* 88(5):2422–9. [PubMed: 12424283]
- Hafting T, Fyhn M, Bonnevie T, Moser MB, Moser EI. 2008 Hippocampus-independent phase precession in entorhinal grid cells. *Nature* 453(7199):1248–52. [PubMed: 18480753]
- Hafting T, Fyhn M, Molden S, Moser MB, Moser EI. 2005 Microstructure of a spatial map in the entorhinal cortex. *Nature* 436(7052):801–6. [PubMed: 15965463]
- Hardcastle K, Ganguli S, Giocomo LM. 2015 Environmental boundaries as an error correction mechanism for grid cells. *Neuron* in press.
- Hargreaves EL, Rao G, Lee I, Knierim JJ. 2005 Major dissociation between medial and lateral entorhinal input to dorsal hippocampus. *Science* 308(5729):1792–4. [PubMed: 15961670]
- Hartley T, Burgess N, Lever C, Cacucci F, O'Keefe J. 2000 Modeling place fields in terms of the cortical inputs to the hippocampus. *Hippocampus* 10(4):369–79. [PubMed: 10985276]
- Hasselmo ME. 2008 Grid cell mechanisms and function: contributions of entorhinal persistent spiking and phase resetting. *Hippocampus* 18(12):1213–29. [PubMed: 19021258]
- Hasselmo ME. 2009 A model of episodic memory: mental time travel along encoded trajectories using grid cells. *Neurobiol Learn Mem* 92(4):559–73. [PubMed: 19615456]
- Hasselmo ME. 2012 *How we remember: Brain mechanisms of episodic memory*. Cambridge, MA: MIT Press.
- Hasselmo ME. 2014 Neuronal rebound spiking, resonance frequency and theta cycle skipping may contribute to grid cell firing in medial entorhinal cortex. *Philos Trans R Soc Lond B Biol Sci* 369(1635):20120523. [PubMed: 24366135]

- Hasselmo ME, Brandon MP. 2012 A model combining oscillations and attractor dynamics for generation of grid cell firing. *Front Neural Circuits* 6:30. [PubMed: 22654735]
- Hasselmo ME, Shay CF. 2014 Grid cell firing patterns may arise from feedback interaction between intrinsic rebound spiking and transverse traveling waves with multiple heading angles. *Front Syst Neurosci* 8:201. [PubMed: 25400555]
- Hasselmo ME, Stern CE. 2014 Theta rhythm and the encoding and retrieval of space and time. *Neuroimage* 85 Pt 2:656–66. [PubMed: 23774394]
- Heys JG, Giocomo LM, Hasselmo ME. 2010 Cholinergic modulation of the resonance properties of stellate cells in layer II of medial entorhinal cortex. *J Neurophysiol* 104(1):258–70. [PubMed: 20445030]
- Heys JG, Rangarajan KV, Dombeck DA. 2014 The functional micro-organization of grid cells revealed by cellular-resolution imaging. *Neuron* 84(5):1079–90. [PubMed: 25467986]
- Hinman JR, Penley SC, Long LL, Escabi MA, Chrobak JJ. 2011 Septotemporal variation in dynamics of theta: speed and habituation. *J Neurophysiol* 105(6):2675–86. [PubMed: 21411562]
- Hodgkin AL, Huxley AF. 1952 A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol. (London)* 117:500–544. [PubMed: 12991237]
- Howard MW, MacDonald CJ, Tiganj Z, Shankar KH, Du Q, Hasselmo ME, Eichenbaum H. 2014 A unified mathematical framework for coding time, space, and sequences in the hippocampal region. *J Neurosci* 34(13):4692–707. [PubMed: 24672015]
- Izhikevich EM. 2007 *Dynamical systems in neuroscience: The geometry of excitability and bursting*. Cambridge, MA: MIT Press, p. 315.
- Jadhav SP, Kemere C, German PW, Frank LM. 2012 Awake hippocampal sharp-wave ripples support spatial memory. *Science* 336(6087):1454–8. [PubMed: 22555434]
- Jeewajee A, Barry C, O’Keefe J, Burgess N. 2008 Grid cells and theta as oscillatory interference: electrophysiological data from freely moving rats. *Hippocampus* 18(12):1175–85. [PubMed: 19021251]
- Jeffery KJ, Donnett JG, O’Keefe J. 1995 Medial septal control of theta-correlated unit firing in the entorhinal cortex of awake rats. *Neuroreport* 6(16):2166–70. [PubMed: 8595195]
- Jochems A, Reboreda A, Hasselmo ME, Yoshida M. 2013 Cholinergic receptor activation supports persistent firing in layer III neurons in the medial entorhinal cortex. *Behav Brain Res* 254:108–15. [PubMed: 23810207]
- Johnson A, Redish AD. 2007 Neural ensembles in CA3 transiently encode paths forward of the animal at a decision point. *J Neurosci* 27(45):12176–89. [PubMed: 17989284]
- Kemere C, Carr MF, Karlsson MP, Frank LM. 2013 Rapid and continuous modulation of hippocampal network state during exploration of new places. *PLoS One* 8(9):e73114. [PubMed: 24023818]
- King C, Reece M, O’Keefe J. 1998 The rhythmicity of cells of the medial septum/diagonal band of Broca in the awake freely moving rat: relationships with behaviour and hippocampal theta. *European Journal of Neuroscience* 10(2):464–477.
- Kirchhoff BA, Wagner AD, Maril A, Stern CE. 2000 Prefrontal-temporal circuitry for episodic encoding and subsequent memory. *J Neurosci* 20(16):6173–80. [PubMed: 10934267]
- Knauer B, Jochems A, Valero-Aracama MJ, Yoshida M. 2013 Long-lasting intrinsic persistent firing in rat CA1 pyramidal cells: A possible mechanism for active maintenance of memory. *Hippocampus*.
- Koenig J, Linder AN, Leutgeb JK, Leutgeb S. 2011 The spatial periodicity of grid cells is not sustained during reduced theta oscillations. *Science* 332(6029):592–5. [PubMed: 21527713]
- Kraus BJ, Robinson RJ 2nd, White JA, Eichenbaum H, Hasselmo ME. 2013 Hippocampal “Time Cells”: Time versus Path Integration. *Neuron* 78(6):1090–101. [PubMed: 23707613]
- Kropff E, Treves A. 2008 The emergence of grid cells: Intelligent design or just adaptation? *Hippocampus* 18(12):1256–69. [PubMed: 19021261]
- Krupic J, Bauza M, Burton S, Barry C, O’Keefe J. 2015 Grid cell symmetry is shaped by environmental geometry. *Nature* 518(7538):232–5. [PubMed: 25673417]
- Krupic J, Bauza M, Burton S, Lever C, O’Keefe J. 2014 How environment geometry affects grid cell symmetry and what we can learn from it. *Philos Trans R Soc Lond B Biol Sci* 369(1635):20130188. [PubMed: 24366142]

- Lever C, Burton S, Jeewajee A, O'Keefe J, Burgess N. 2009 Boundary vector cells in the subiculum of the hippocampal formation. *J Neurosci* 29(31):9771–7. [PubMed: 19657030]
- MacDonald CJ, Carrow S, Place R, Eichenbaum H. 2013 Distinct hippocampal time cell sequences represent odor memories in immobilized rats. *J Neurosci* 33(36):14607–16. [PubMed: 24005311]
- MacDonald CJ, Lepage KQ, Eden UT, Eichenbaum H. 2011 Hippocampal “time cells” bridge the gap in memory for discontinuous events. *Neuron* 71(4):737–49. [PubMed: 21867888]
- McNaughton BL, Battaglia FP, Jensen O, Moser EI, Moser MB. 2006 Path integration and the neural basis of the ‘cognitive map’. *Nat Rev Neurosci* 7(8):663–78. [PubMed: 16858394]
- Mhatre H, Gorchetchnikov A, Grossberg S. 2010 Grid cell hexagonal patterns formed by fast self-organized learning within entorhinal cortex. *Hippocampus* 22(2):320–34. [PubMed: 21136517]
- Miall R. 1989 The storage of time intervals using oscillating neurons. *Neural Comput* 1:359–371.
- Milford MJ, Wiles J, Wyeth GF. 2010 Solving navigational uncertainty using grid cells on robots. *PLoS Comput Biol* 6(11):e1000995. [PubMed: 21085643]
- Milner B, Corkin S, Teuber H-L. 1968 Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H.M. *Neuropsychologia* 6:215–234.
- Mitchell SJ, Ranck JB Jr. 1980 Generation of theta rhythm in medial entorhinal cortex of freely moving rats. *Brain Res* 189(1):49–66. [PubMed: 7363097]
- Mitchell SJ, Rawlins JN, Steward O, Olton DS. 1982 Medial septal area lesions disrupt theta rhythm and cholinergic staining in medial entorhinal cortex and produce impaired radial arm maze behavior in rats. *J Neurosci* 2(3):292–302. [PubMed: 7062110]
- Mizuseki K, Sirota A, Pastalkova E, Buzsaki G. 2009 Theta oscillations provide temporal windows for local circuit computation in the entorhinal-hippocampal loop. *Neuron* 64(2):267–80. [PubMed: 19874793]
- Moser EI, Moser MB. 2008 A metric for space. *Hippocampus* 18(12):1142–56. [PubMed: 19021254]
- Navratilova Z, Giocomo LM, Fellous JM, Hasselmo ME, McNaughton BL. 2012 Phase precession and variable spatial scaling in a periodic attractor map model of medial entorhinal grid cells with realistic after-spike dynamics. *Hippocampus* 22(4):772–89. [PubMed: 21484936]
- Newman EL, Climer JR, Hasselmo ME. 2014 Grid cell spatial tuning reduced following systemic muscarinic receptor blockade. *Hippocampus* 24(6):643–55. [PubMed: 24493379]
- Newman EL, Hasselmo ME. 2014 Grid cell firing properties vary as a function of theta phase locking preferences in the rat medial entorhinal cortex. *Front Syst Neurosci* 8:193. [PubMed: 25352787]
- O'Keefe J 1976 Place units in the hippocampus of the freely moving rat. *Exp Neurol* 51(1):78–109. [PubMed: 1261644]
- O'Keefe J, Burgess N. 1996 Geometric determinants of the place fields of hippocampal neurons. *Nature* 381:425–428. [PubMed: 8632799]
- O'Keefe J, Burgess N, Donnett JG, Jeffery KJ, Maguire EA. 1998 Place cells, navigational accuracy, and the human hippocampus. *Philos Trans R Soc Lond B Biol Sci* 353(1373):1333–40. [PubMed: 9770226]
- O'Keefe J, Nadel L. 1978 *The Hippocampus as a Cognitive Map*. Oxford, UK: Oxford University Press.
- O'Keefe J, Recce ML. 1993 Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3:317–330. [PubMed: 8353611]
- Olton DS, Becker JT, Handelmann GE. 1979 Hippocampus, space and memory. *Behav Brain Sci* 2:313–365.
- Olton DS, Wible CG, Shapiro ML. 1986 Mnemonic theories of hippocampal function. *Behav Neurosci* 100(6):852–5. [PubMed: 3545260]
- Pastalkova E, Itskov V, Amarasingham A, Buzsaki G. 2008 Internally generated cell assembly sequences in the rat hippocampus. *Science* 321(5894):1322–7. [PubMed: 18772431]
- Pastoll H, Ramsden HL, Nolan MF. 2012 Intrinsic electrophysiological properties of entorhinal cortex stellate cells and their contribution to grid cell firing fields. *Front Neural Circuits* 6:17. [PubMed: 22536175]
- Ranck JBJ. 1984 Head-direction cells in the deep cell layers of dorsal presubiculum in freely moving rats. *Soc. Neurosci. Abstr* 10:599.

- Raudies F, Brandon MP, William Chapman G, Hasselmo ME. 2014 Head direction is coded more strongly than movement direction in a population of entorhinal neurons. *Brain Res.*
- Raudies F, Hasselmo ME. 2012 Modeling boundary vector cell firing given optic flow as a cue. *PLoS Comput Biol* 8(6):e1002553. [PubMed: 22761557]
- Raudies F, Mingolla E, Hasselmo ME. 2012 Modeling the influence of optic flow on grid cell firing in the absence of other cues. *J Comput Neurosci* 33(3):475–93. [PubMed: 22555390]
- Sargolini F, Fyhn M, Hafting T, McNaughton BL, Witter MP, Moser MB, Moser EI. 2006 Conjunctive representation of position, direction, and velocity in entorhinal cortex. *Science* 312(5774):758–62. [PubMed: 16675704]
- Savelli F, Yoganarasimha D, Knierim JJ. 2008 Influence of boundary removal on the spatial representations of the medial entorhinal cortex. *Hippocampus* 18(12):1270–82. [PubMed: 19021262]
- Schmidt-Hieber C, Haussler M. 2013 Cellular mechanisms of spatial navigation in the medial entorhinal cortex. *Nat Neurosci* 16(3):325–31. [PubMed: 23396102]
- Scoville WB, Milner B. 1957 Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiatry* 20:11–21.
- Shankar KH, Howard MW. 2012 A scale-invariant internal representation of time. *Neural Comput* 24(1):134–93. [PubMed: 21919782]
- Shay CF, Boardman IS, James NM, Hasselmo ME. 2012 Voltage dependence of subthreshold resonance frequency in layer II of medial entorhinal cortex. *Hippocampus* 22(8):1733–49. [PubMed: 22368047]
- Sherrill KR, Erdem UM, Ross RS, Brown TI, Hasselmo ME, Stern CE. 2013 Hippocampus and retrosplenial cortex combine path integration signals for successful navigation. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 33:19304–19313. [PubMed: 24305826]
- Si B, Kropff E, Treves A. 2012 Grid alignment in entorhinal cortex. *Biol Cybern* 106(8-9):483–506. [PubMed: 22892761]
- Skaggs WE, McNaughton BL, Wilson MA, Barnes CA. 1996 Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* 6(2):149–172. [PubMed: 8797016]
- Solstad T, Boccaro CN, Kropff E, Moser MB, Moser EI. 2008 Representation of geometric borders in the entorhinal cortex. *Science* 322(5909):1865–8. [PubMed: 19095945]
- Stensola H, Stensola T, Solstad T, Froland K, Moser MB, Moser EI. 2012 The entorhinal grid map is discretized. *Nature* 492(7427):72–8. [PubMed: 23222610]
- Taube JS, Bassett JP. 2003 Persistent neural activity in head direction cells. *Cereb Cortex* 13(11):1162–72. [PubMed: 14576208]
- Taube JS, Goodridge JP, Golob EJ, Dudchenko PA, Stackman RW. 1996 Processing the head direction cell signal: a review and commentary. *Brain Res. Bull* 40(5-6):477–484. [PubMed: 8886377]
- Taube JS, Muller RU, Ranck JB Jr. 1990a Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. *J Neurosci* 10(2):420–35. [PubMed: 2303851]
- Taube JS, Muller RU, Ranck JB Jr. 1990b Head-direction cells recorded from the postsubiculum in freely moving rats. II. Effects of environmental manipulations. *J Neurosci* 10(2):436–47. [PubMed: 2303852]
- Tiganj Z, Hasselmo ME, Howard MW. 2015 A simple biophysically plausible model for long time constants in single neurons. *Hippocampus* 25(1):27–37. [PubMed: 25113022]
- Varga V, Hangya B, Kranitz K, Ludanyi A, Zemankovics R, Katona I, Shigemoto R, Freund TF, Borhegyi Z. 2008 The presence of pacemaker HCN channels identifies theta rhythmic GABAergic neurons in the medial septum. *J Physiol* 586(16):3893–915. [PubMed: 18565991]
- Wang Y, Romani S, Lustig B, Leonardo A, Pastalkova E. 2015 Theta sequences are essential for internally generated hippocampal firing fields. *Nat Neurosci* 18(2):282–8. [PubMed: 25531571]
- Welday AC, Shlifer IG, Bloom ML, Zhang K, Blair HT. 2011 Cosine directional tuning of theta cell burst frequencies: evidence for spatial coding by oscillatory interference. *J Neurosci* 31(45):16157–76. [PubMed: 22072668]

- Wills TJ, Barry C, Cacucci F. 2012 The abrupt development of adult-like grid cell firing in the medial entorhinal cortex. *Front Neural Circuits* 6:21. [PubMed: 22557949]
- Yartsev MM, Witter MP, Ulanovsky N. 2011 Grid cells without theta oscillations in the entorhinal cortex of bats. *Nature* 479(7371):103–7. [PubMed: 22051680]

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