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Sources of the Spatial Code Within the Hippocampus

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The entorhinal cortex is further divided into medial (MEC) and lateral (LEC) regions. These are distinct regions, with different single-cell physiologies and different targets within the hippocampus. The medial ECIII projects to parts of region CA1 that are more proximal to CA3 [5,6], whereas the lateral ECIII targets cells more distant from CA3 (Figure 1). Thus, a key question has been what kinds of afferent information arrives from ECII compared with ECIII, and from the MEC compared with the LEC.

**Major recent advances**

To determine the role of direct ECIII input to region CA1 Brun *et al.* [7] recorded place cells in region CA1 after completely disconnecting CA3 and CA1. This effectively
To distinguish differences between lateral versus medial entorhinal input, Hargreaves and colleagues [9] recorded in both areas in the open field. They found cells with strong spatial modulation in the MEC but not in the LEC. Concurrent work in the MEC revealed the intriguing phenomenon of ‘grid cells’ [4, 10–12]. In contrast to place cells, which fire when a rat is at a single, particular location, a grid cell fires when a rat is at any of multiple different locations in the environment that are distributed in a hexagonal array. These results indicate that the MEC may convey spatial information, whereas the LEC encodes information about objects and items [9, 13].

The discovery of grid cells has driven a range of recent research. Several models have been proposed to explain how MEC grid cells might provide a basis for driving hippocampal place-cell activities [14–17]. These models are supported by data showing that hippocampal place cell populations acquire new spatial representations (i.e. remapping) concurrent with simultaneous changes in the spatial phase and orientation of entorhinal grid cells [11]. In addition to grid-cell input to the hippocampus, a context signal [18] (concerning landmark configuration or behavioural requirements) could account for remapping of place cells while the orientation, phase and spacing of the grid cells remain consistent with each other. A separate input of this sort to place cells could drive the experiencedependent expansion in grid-cell dimensions that is associated with changes in environment boundaries [19].

If the entorhinal cortex grid cells provide the input for place cells, one would predict a scaling of the sizes of the spatial receptive fields of place cells (spatial scaling) along the dorsal-to-ventral axis of the hippocampus similar to the spatial scaling of grid cells [10]. Such spatial scaling was indeed demonstrated recently in the hippocampus [20], in which remarkably large firing fields (up to 10 meters long) were found in the ventral hippocampus. The largest firing fields are consistent with very large grid receptive fields found in the ventral regions of the entorhinal cortex [21].

Questions about the input that causes grid cells to fire and the mechanism that generates the firing pattern have been addressed by models that effectively simulate grid-cell firing patterns. These models are of two competing types. One is the ‘oscillatory interference model’ [22, 23]. This proposes the interaction of oscillations that occur at slightly different frequencies, causing a beat frequency equal to the difference of the frequencies. In this model, grid cells depend on input from head-direction cells, consistent with the selective input from areas containing head-direction cells to medial, but not to lateral, entorhinal cortex. Modulation of oscillation frequency by cells sensitive to head direction and running speed, reported to have been found in the postsubiculum and hippocampus, can cause interference which results in a two-dimensional pattern of grid-cell firing. This model generates a realistic representation of both grid-cell firing and the phenomenon of theta-phase precession [22], and is supported by experimental data showing theta-phase precession in grid cells in ECII [12]. Theta-phase precession is the observation that, as an animal moves through the firing field of a place cell or grid cell, spikes in the electroencephalogram (EEG) gradually shift from late to early phases of theta-frequency oscillations [12, 24]. The model also accounts for the change in time course of theta-phase precession observed in the large firing fields in ventral entorhinal cortex and hippocampus [22, 25].

The oscillatory interference model also predicts that changes in spatial scaling in grid cells along the dorsal to ventral axis of the MEC [4, 10] arise from differences in the intrinsic oscillation properties of neurons [2, 22]. This prediction is supported by intracellular data showing differences in membrane potential oscillation frequency and resonance along the MEC dorsal to ventral axis.
Other experimental data support predictions of this model in regard to changes in intrinsic spiking frequency [28] and decreased theta-rhythm frequency in novel environments [29].

The experimentally observed absence of theta-phase precession in grid cells of ECIII [12] suggests that some grid responses do not arise from oscillatory interference, but might arise from 'attractor dynamics'. In attractor dynamic models, excitatory synaptic feedback between entorhinal neurons in the presence of background inhibition causes a subset of these cells to fire as grid cells [14,30]. Published attractor dynamic models of grid cells do not yet simulate theta-phase precession, but can account for the activity of grid cells apart from precession. These models can account for recent ECIII data showing discrete, rather than continuous, scaling of grid cells at different dorsal to ventral positions [19].

**Future directions**

Future studies should resolve important remaining questions about the entorhinal input to the hippocampus. For example, more extensive data is needed to understand the type of information supplied by the LEC - in contrast to the strongly spatially coded information supplied by the MEC. Future studies could also test for differences in spatial specificity of firing within CA1 that is associated with the segregation of medial input to CA1 cells closer to region CA3 and lateral input to cells more distant from CA3.

More data are needed to select between possible mechanisms of grid-cell firing, in order to test further predictions of the oscillatory interference model versus those of attractor dynamic models. Both these proposed mechanisms might contribute to grid-cell firing, or they might be supplemented by other physiological properties, including the time course of spike-frequency adaptation [31] or the frequency of stable persistent spiking [32,33].

A remaining issue is whether MEC cells are providing the hippocampus with rigid spatial information or with a more flexible representation that can allow the hippocampus to disambiguate information about distinct episodic memories. Lesion studies have shown that the MEC is necessary for spatial navigation [34]; however, it is not clear how the MEC participates in non-spatial episodic encoding. One recent study has shown that some cells in the MEC can distinguish between sequences on a T-maze alternation task [35].

Models of oscillatory interference using phase reset [22,32,36] (that is, restarting of oscillations) can account for context-dependent (that is, task specific) firing [32,36] of both entorhinal neurons [35,37,38] and hippocampal neurons [39-42]. Future studies can test the predictions of these models to determine whether the same mechanisms contribute to both regular spatial firing and to context-dependent firing in specific tasks.

The full circuit of grid cells, place cells and head-direction cells provides a continuous code of spatial location and movement direction that has been used to effectively model the episodic encoding and retrieval of spatial trajectories [33,43]. In other words, this circuit forms the memories of where animal has been and supports the recall of these previously taken paths. The anatomical and physiological data on the interactions between these regions provide a detailed functional perspective on potential circuit-level mechanisms of episodic memory.

**Abbreviations**

EC, entorhinal cortex; ECII, layer 2 of the entorhinal cortex; ECIII, layer 3 of the entorhinal cortex; EEG, electroencephalogram; DG, dentate gyrus; LEC, lateral entorhinal cortex; MEC, medial entorhinal cortex

**Competing interests**

The authors declare that they have no competing interests.

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**References**

1. O'Keefe J, Burgess N: Geometric determinants of the place fields of hippocampal neurons. *Nature* 1996, 381:425-8.

2. O'Keefe J, Burgess N: Dual phase and rate coding in hippocampal place cells: theoretical significance and relationship to entorhinal grid cells. *Hippocampus* 2005, 15:853-66.

3. Taube JS, Muller RU, Ranck JB Jr: Head-direction cells recorded from the postsubiculum in freely moving rats. I. Description and quantitative analysis. *J Neurosci* 1990, 10:420-35.

4. Sargolini F, Fyhn M, Hafting T, McNaughton BL, Witter MP, Moser MB, Moser EI: Conjunctive representation of position, direction, and velocity in entorhinal cortex. *Science* 2006, 312:758-62.

5. Amaral DG, Witter MP: The three-dimensional organization of the hippocampal formation - A review of anatomical data. *Neuroscience* 1989, 31:571-91.

6. Witter MP, Groenewegen Hj, Lopes da Silva FH, Lohman AH: Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region. *Prog Neurobiol* 1989, 33:161-253.

7. Brun VH, Otnass MK, Molden S, Steffenach HA, Witter MP, Moser MB, Moser EI: Place cells and place recognition maintained by direct entorhinal-hippocampal circuitry. *Science* 2002, 296:2243-6.
8. Brun VH, Leutgeb S, Wu HQ, Schwarz R, Witter MP, Moser El, Moser MB: Impaired spatial representation in CA1 after lesion of direct input from entorhinal cortex. Neuron 2008, 57:290-302.

F1000 Factor 6.0 Must Read
Evaluated by James Knierim 29 Jan 2008

9. Hargreaves EL, Rao G, Lee I, Knierim JJ: Major dissociation between medial and lateral entorhinal input to dorsal hippocampus. Science 2005, 308:1792-4.

F1000 Factor 8.0 Exceptional
Evaluated by Edvard I Moser 21 Jun 2005, Anthony Wagner 20 Jul 2005

10. Hafing T, Fyn M, Molden S, Moser MB, Moser El: Microstructure of a spatial map in the entorhinal cortex. Nature 2005, 436:801-6.

F1000 Factor 10.4 Exceptional
Evaluated by James Knierim 9 Mar 2007, Howard Eichenbaum 9 Mar 2007

11. Fyn M, Hafing T, Treves A, Moser MB, Moser El: Hippocampal remapping and grid realignment in entorhinal cortex. Nature 2007, 446:190-4.

F1000 Factor 8.0 Exceptional
Evaluated by James Knierim 9 Mar 2007, Howard Eichenbaum 9 Mar 2007

12. Hafing T, Fyn M, Bonnevie T, Moser MB, Moser El: Hippocampus-independent phase precession in entorhinal grid cells. Nature 2008, 453:1246-52.

F1000 Factor 8.2 Exceptional
Evaluated by Mayank Mehta 30 Jul 2008, Neil Burgess 18 Aug 2008, James Knierim 9 Sep 2008

13. Eichenbaum H, Lipton P: Towards a functional organization of the medial temporal lobe memory system: Role of the parahippocampal and medial entorhinal cortical areas. Hippocampus 2008, 18:1314-24.

14. Fuhs MC, Touretzky DS: A spin glass model of path integration in rat medial entorhinal cortex. J Neurosci 2006, 26:4266-76.

F1000 Factor 4.8 Must Read
Evaluated by James Knierim 27 Apr 2006, Michael E Hasselmo 10 Oct 2006

15. Solstad T, Moser El, Enevoll GT: From grid cells to place cells: a mathematical model. Hippocampus 2006, 16:1026-31.

16. Rolls ET, Stringer SM, Elliot T: Entorhinal cortex grid cells can map to hippocampal place cells by competitive learning. Network 2006, 17:447-65.

17. Molter C, Yamaguchi Y: Entorhinal theta phase precession sculpts dentate gyrus place fields. Hippocampus 2008, 18:919-30.

18. Hayman R, Jeffery KJ: Generating partial remapping of hippocampal place fields from entorhinal grids. Hippocampus 2008, 18 (in press).

19. Barry C, Hayman R, Burgess N, Jeffery KJ: Experience-dependent rescaling of entorhinal grids. Nat Neurosci 2007, 10:682-4.

F1000 Factor 6.7 Must Read
Evaluated by Edvard I Moser 15 May 2007, James Knierim 21 May 2007, Wendy Suzuki 15 Jun 2007, Michael E Hasselmo 18 Jul 2007

20. Kjelstrup KB, Solstad T, Brun VH, Hafing T, Leutgeb S, Witter MP, Moser El, Moser MB: Finite scale of spatial representation in the hippocampus. Science 2008, 321:140-3.

F1000 Factor 8.2 Exceptional
Evaluated by David P Woller 10 Jul 2008, Neil Burgess 21 Jul 2008, Michael E Hasselmo 15 Aug 2008, James Knierim 9 Sep 2008

21. Brun VH, Solstad T, Kjelstrup KB, Fyn M, Witter MP, Moser El, Moser MB: Progressive increase in grid scale from dorsal to ventral medial entorhinal cortex. Hippocampus 2008, 18:1200-12.

22. Burgess N, Barry C, O’Keefe J: An oscillatory interference model of grid cell firing. Hippocampus 2007, 17:801-12.

F1000 Factor 8.2 Exceptional
Evaluated by Michael E Hasselmo 18 Jul 2007, Edvard I Moser 24 Jul 2007, Misha Tsodyks 8 Oct 2007

23. Hasselmo ME, Giocomo LM, Zilli EA: Grid cell firing may arise from interference of theta frequency membrane potential oscillations in single neurons. Hippocampus 2007, 17:1252-71.

24. O’Keefe J, Recce ML: Phase relationship between hippocampal place units and the EEG theta rhythm. Hippocampus 1993, 3:317-30.

25. Hasselmo ME: Neuroscience. The scale of experience. Science 2008, 321:46-7.

26. Giocomo LM, Hasselmo ME: Computation by oscillations: implications of experimental data for theoretical models of grid cells. Hippocampus 2008, 18:1186-99.

27. Giocomo LM, Zilli EA, Fransen E, Hasselmo ME: Temporal frequency of subthreshold oscillations scales with entorhinal grid cell field spacing. Science 2007, 315:1719-22.

F1000 Factor 8.0 Exceptional
Evaluated by Edvard I Moser 28 Mar 2007, James Knierim 4 Apr 2007

28. Jeewajee A, Barry C, O’Keefe J, Burgess N: Grid cells and theta as oscillatory interference: electrophysiological data from freely moving rats. Hippocampus 2008, 18:1175-85.

29. Jeewajee A, Lever C, Burton S, O’Keefe J, Burgess N: Environmental novelty is signaled by reduction of the hippocampal theta frequency. Hippocampus 2008, 18:340-8.

F1000 Factor 3.0 Recommended
Evaluated by Edvard I Moser with Dori Derdikman 17 Nov 2008

30. McNaughton BL, Battaglia FP, Jensen O, Moser El, Moser MB: Path integration and the neural basis of the ‘cognitive map’. Nat Rev Neurosci 2006, 7:663-78.

F1000 Factor 4.8 Must Read
Evaluated by James Knierim 14 Aug 2006, John Lisman 2 Nov 2006

31. Kropff E, Treves A: The emergence of grid cells: Intelligent design or just adaptation? Hippocampus 2008, 18:125-69.

32. Hasselmo ME: Grid cell mechanisms and function: Contributions of entorhinal persistent spiking and phase resetting. Hippocampus 2008, 18:1213-29.

33. Hasselmo ME, Brandon MP: Linking cellular mechanisms to behavior: entorhinal persistent spiking and membrane potential oscillations may underlie path integration, grid cell firing, and episodic memory. Neural Plast 2008, 2008, 658323.

34. Steffenach HA, Witter M, Moser MB, Moser El: Spatial memory in the rat requires the dorsolateral band of the entorhinal cortex. Neuroanatomy 2005, 45:301-13.

F1000 Factor 3.0 Recommended
Evaluated by James Knierim 24 Jan 2005

35. Lipton PA, White JA, Eichenbaum H: Disambiguation of overlapping experiences by neurons in the medial entorhinal cortex. J Neurosci 2000, 20:169-78.

F1000 Factor 6.7 Must Read
Evaluated by James Knierim 14 Aug 2006, John Lisman 2 Nov 2006

36. Hasselmo ME: Arc length coding by interference of theta frequency oscillations may underlie context-dependent hippocampal unit data and episodic memory function. Learn Mem 2007, 14:782-94.

37. Derdikman D, Fyn M, Hafing T, Moser El, Moser El: Breaking up the entorhinal grid in a hairpin maze. Soc Neurosci Abs 2006, 33:68.10.

38. Frank LM, Brown EN, Wilson M: Trajectory encoding in the hippocampus and entorhinal cortex. Neuron 2000, 27:169-78.

F1000 Factor 9.0 Exceptional
Evaluated by Michael E Hasselmo 15 Feb 2002

39. Lee I, Griffin AL, Zilli EA, Eichenbaum H, Hasselmo ME: Gradual translocation of spatial correlates of neuronal firing in the
hippocampus toward prospective reward locations. Neuron 2006, 51:639-50.

F1000 Factor 6.4 Must Read
Evaluated by James Knierim 22 Sep 2006, Edvard I. Moser 10 Oct 2006

40. Griffin AL, Eichenbaum H, Hasselmo ME: Spatial representations of hippocampal CA1 neurons are modulated by behavioral context in a hippocampus-dependent memory task. J Neurosci 2007, 27:2416-23.

F1000 Factor 3.0 Recommended
Evaluated by James Knierim 4 Apr 2007

41. Wood ER, Dudchenko PA, Robitsek RJ, Eichenbaum H: Hippocampal neurons encode information about different types of memory episodes occurring in the same location. Neuron 2000, 27:623-33.

F1000 Factor 9.0 Exceptional
Evaluated by Michael E Hasselmo 16 Oct 2001

42. Ferbinteanu J, Shapiro ML: Prospective and retrospective memory coding in the hippocampus. Neuron 2003, 40:1227-39.

F1000 Factor 6.5 Must Read
Evaluated by James Knierim 22 Dec 2003, Edvard I Moser 9 Jan 2004, Mark Mayford 9 Jan 2004

43. Hasselmo ME: Temporally structured replay of neural activity in a model of entorhinal-hippocampal interactions. Eur J Neurosci 2008 (in press).