Coding of space and time in entorhinal cortex

Michael E. Hasselmo

Center for Systems Neuroscience
Department of Psychological
and Brain Sciences
Boston University

Simons Institute for the theory of computing,
Representation, coding and computation in neural circuits
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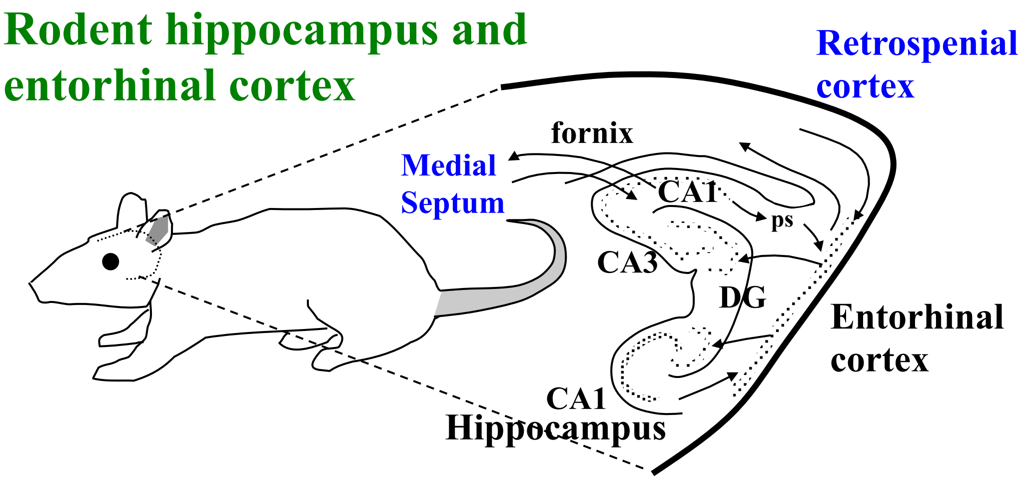
NIMH R01 MH60013, NIMH R01 MH6149 (Program officer: Andrew Rossi).
ONR MURI grant N00014-16-1-2832 (Program officer: Tom McKenna)

Mechanisms for coding spatiotemporal trajectories in entorhinal cortex



Convergent influence of
subcortical input
(theta rhythmic, speed, head direction)
and
cortical input
(sensory cues)

Talk outline:

1. **Medial septal input important for grid cells and time cells**
2. **Theta cycle skipping and head direction**
3. **Visual coding of environment boundaries**

Talk outline:

1. Medial septal input important for grid cells and time cells
2. Theta cycle skipping and head direction
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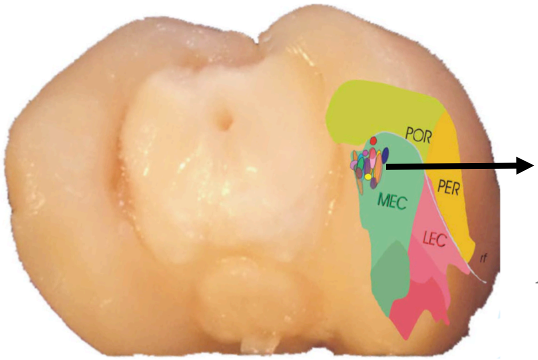
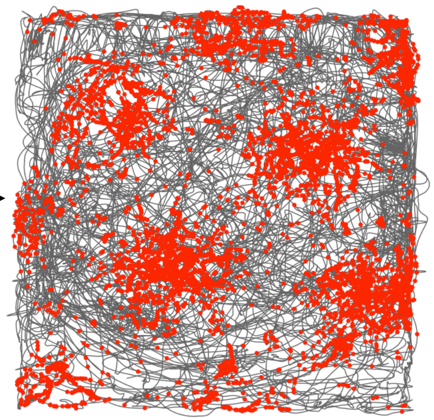
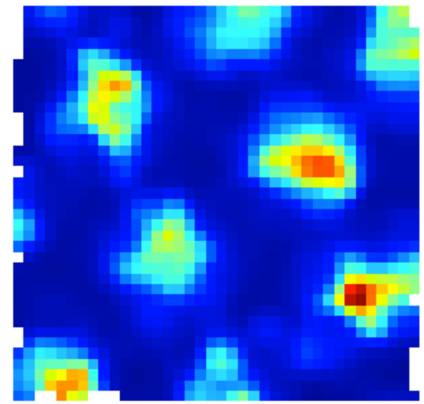
Grid cells discovered in entorhinal cortex in the lab of Edvard and May-Britt Moser (Nobel prize)

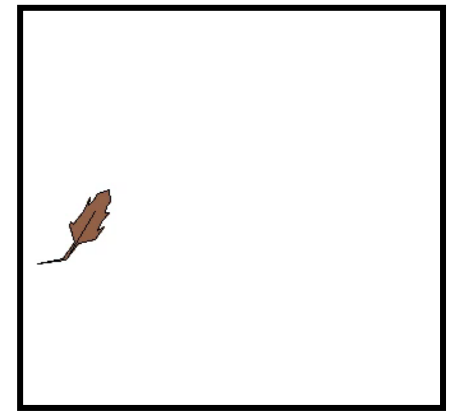




Trajectory plot



Firing rate plot



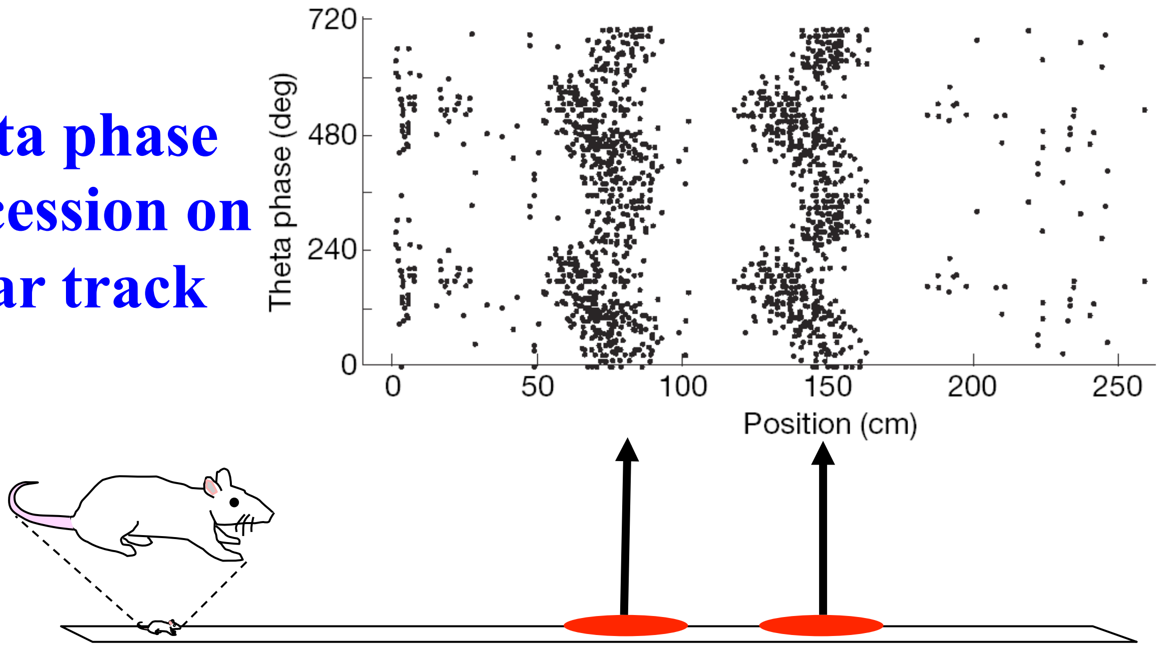
← 1 meter →

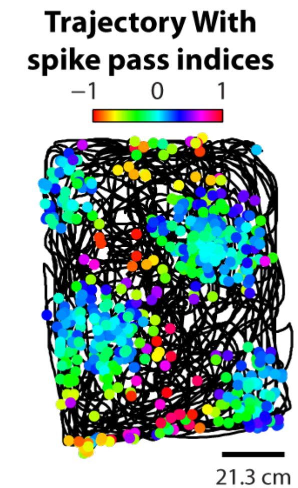
Gray: Rat foraging trajectory
Red: Location when spike is fired

Grid cells discovered in Moser lab: Hafting, Fyhn, Molder, Moser, Moser (2005), *Nature*. *(Data shown here from Mark Brandon, Caitlin Monaghan)*

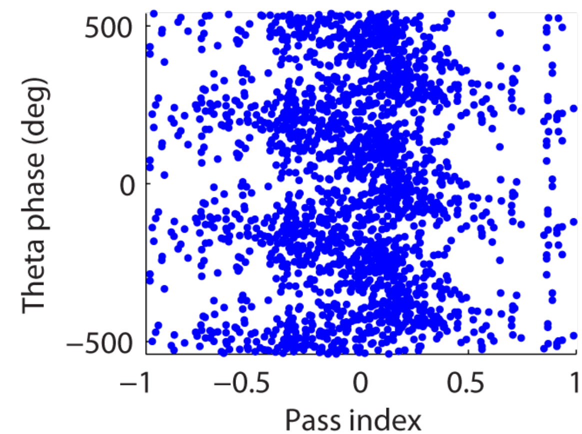
Grid cell firing with theta rhythm suggests functional role of theta

Theta phase precession on linear track



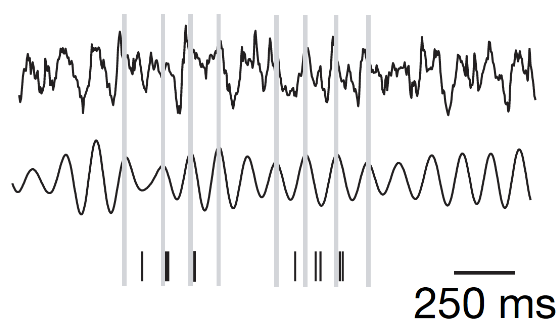


Hafting, Fyhn, Bonnevie, Moser, Moser (2008)



Grid cell theta phase Precession in layer II

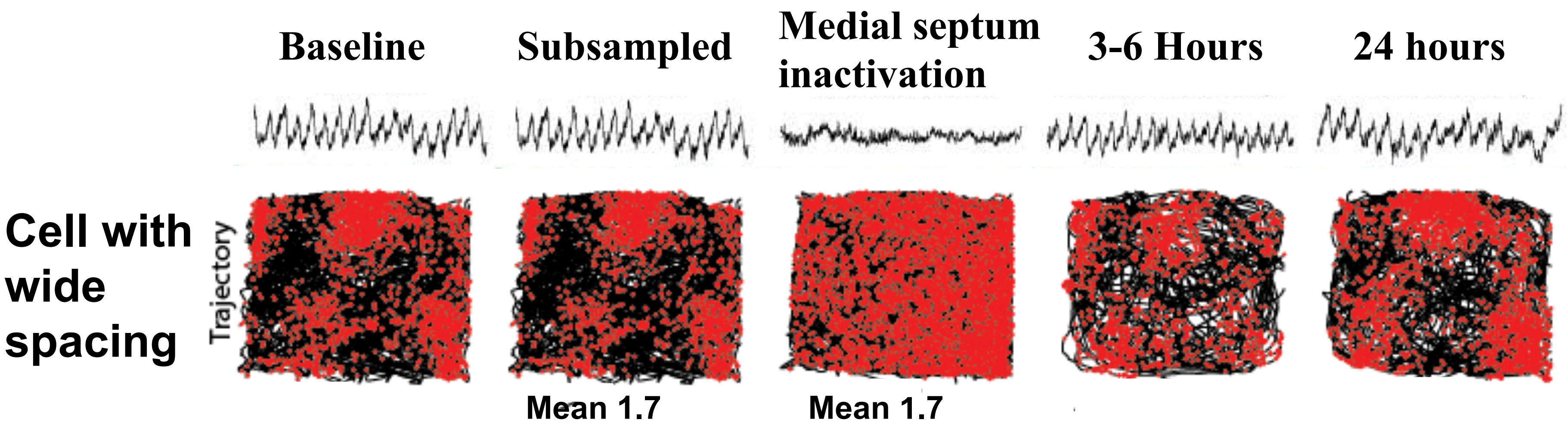
Relative to ~8 Hz Theta rhythm



Phase precession in 2D environment:

Climer, Newman, Hasselmo (2013)

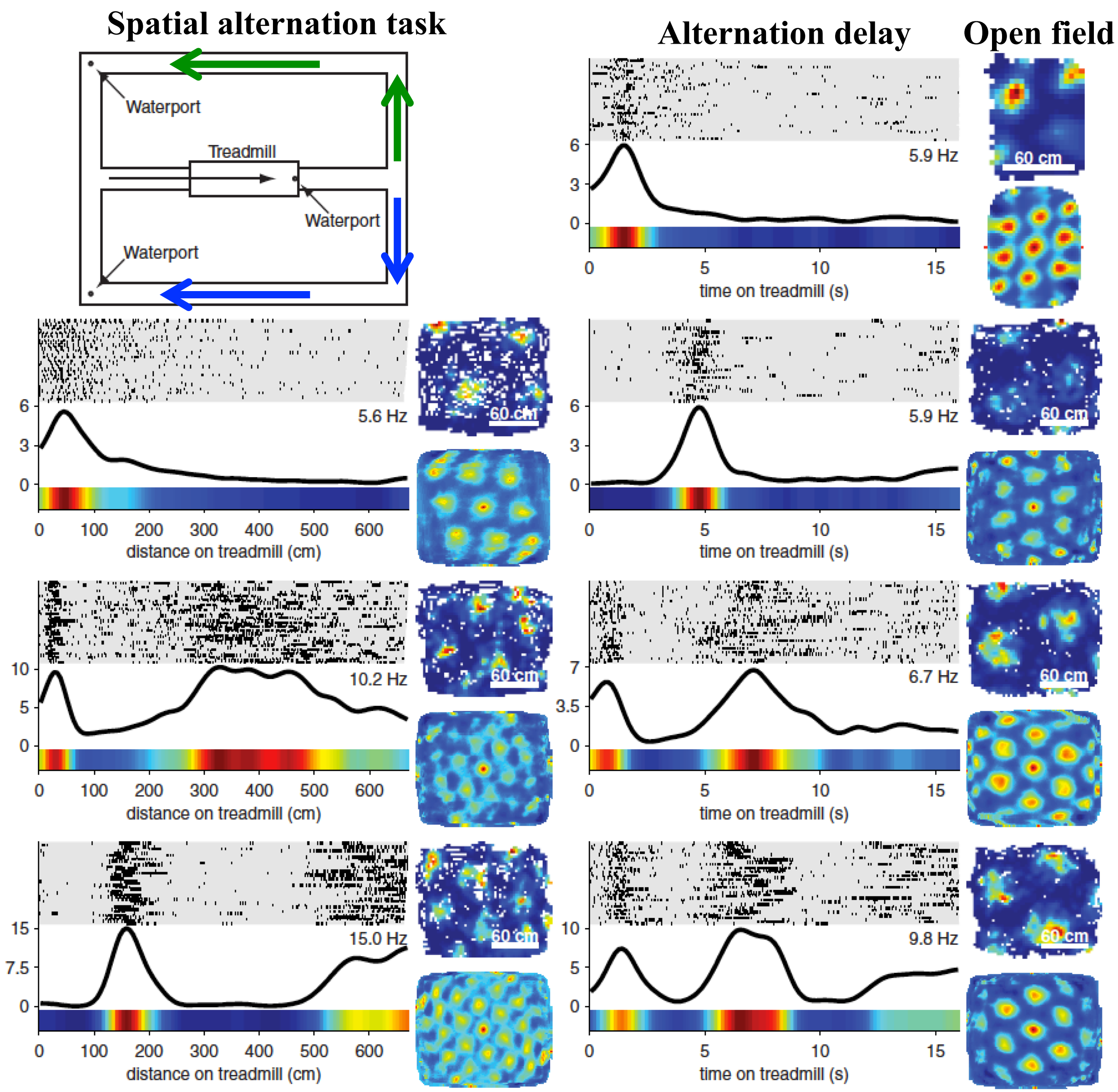
Loss of grid cell periodicity during loss of theta rhythm

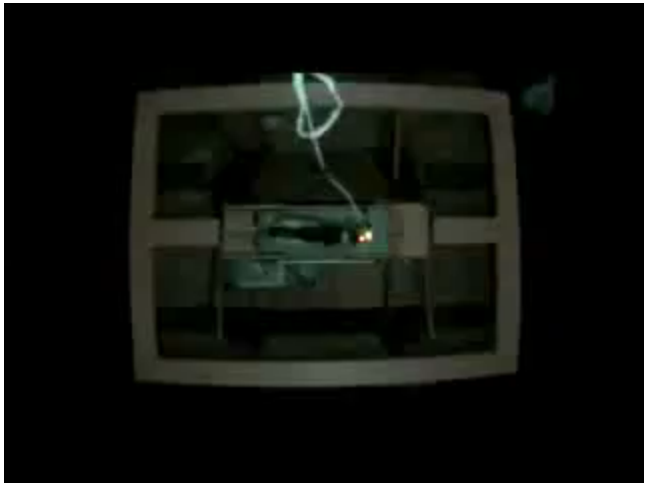


Brandon, Bogaard, Libby, Connerney, Gupta, Hasselmo (2011) Reduction of theta rhythm dissociates grid cell spatial periodicity from directional tuning. *Science*, 332: 595-599.

With lidocaine: Koenig, Linder, Leutgeb, Leutgeb (2011)

Grid cells in entorhinal cortex fire as time cells during delayed spatial alternation and show multiple firing fields



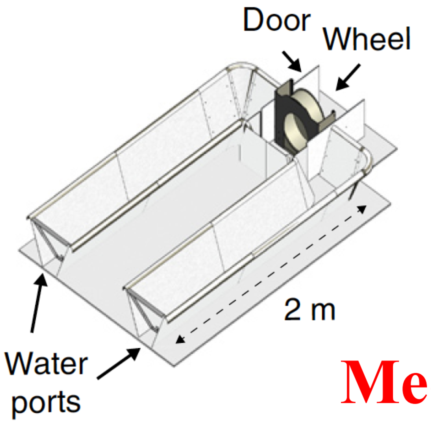


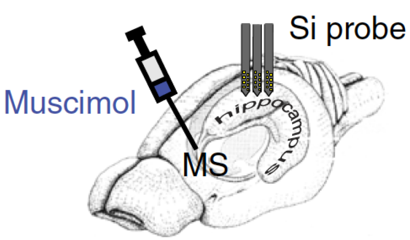
Kraus, Brandon, Robinson, Connerney, Hasselmo, Eichenbaum (2015) *Neuron*, 88: 578-589

Hippocampal time cells shown by Pastalkova, Amarasingham, Itskov, Buzsaki (2008).

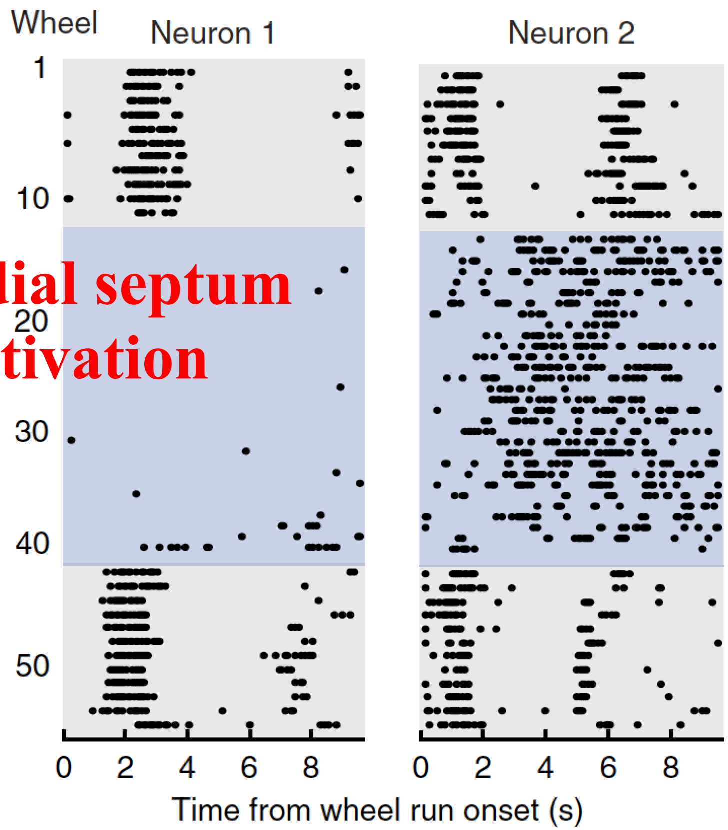
Kraus, Robinson, White, Eichenbaum, Hasselmo Neuron, 2013, 78: 1090-1101

Medial septum inactivation blocks hippocampal time cells



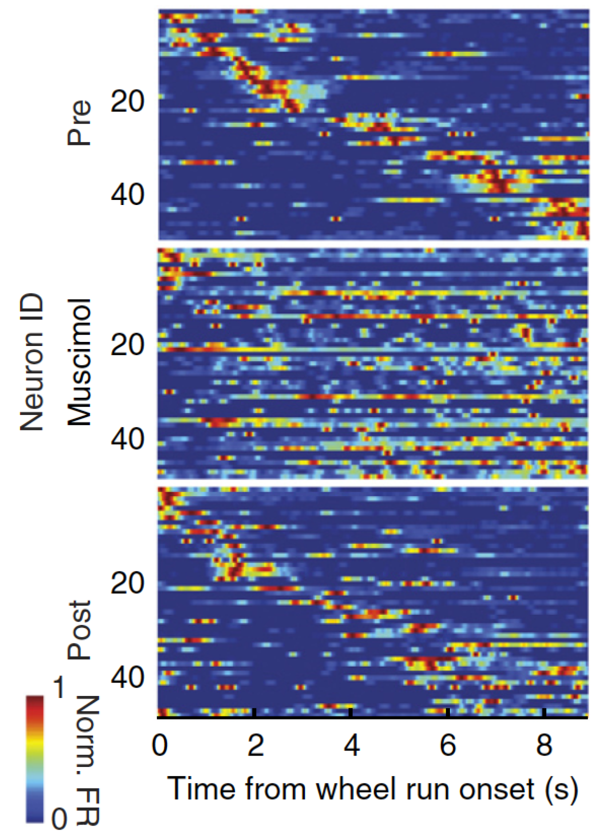


Time cells



Medial septum inactivation

Time cells

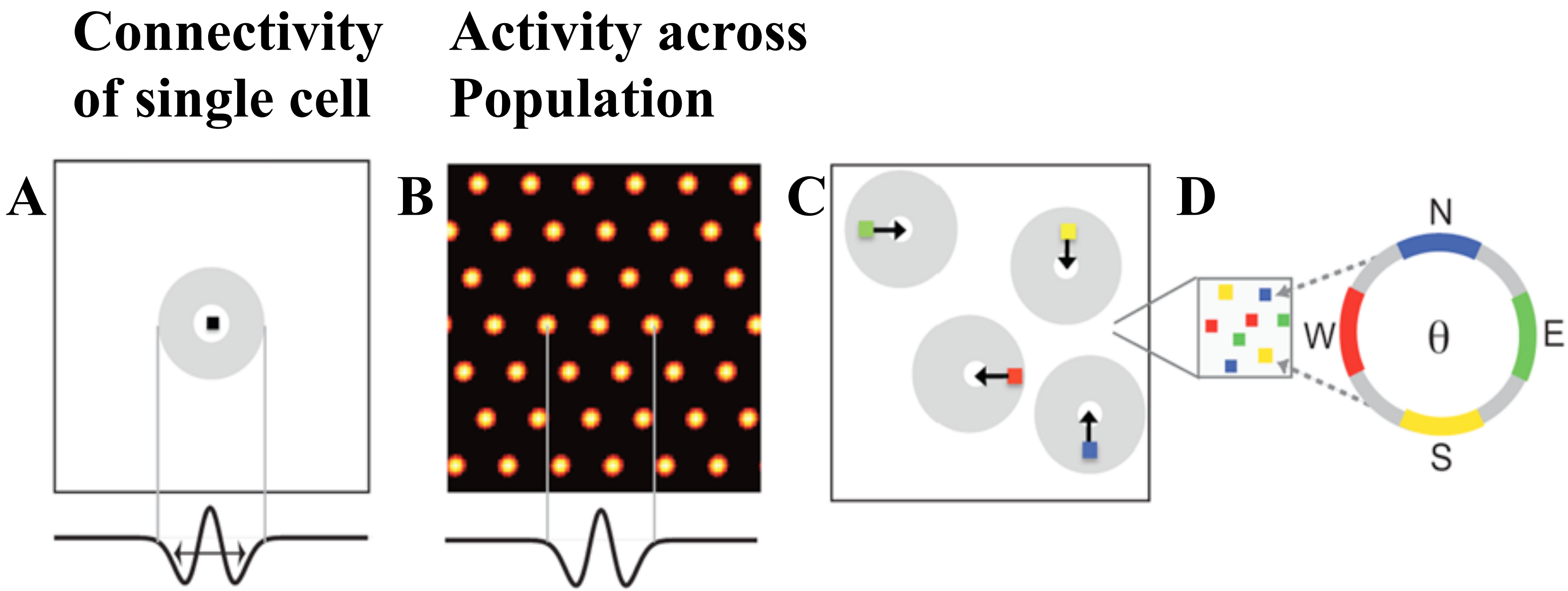


Wang, Romani, Lustig, Leonard, Pastalkova (2014)

Attractor models of grid cells integrate velocity (speed and direction)

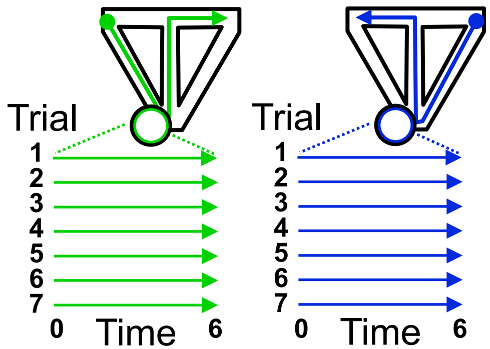
Consistent with much data, but have only simulated theta precession in 1-D

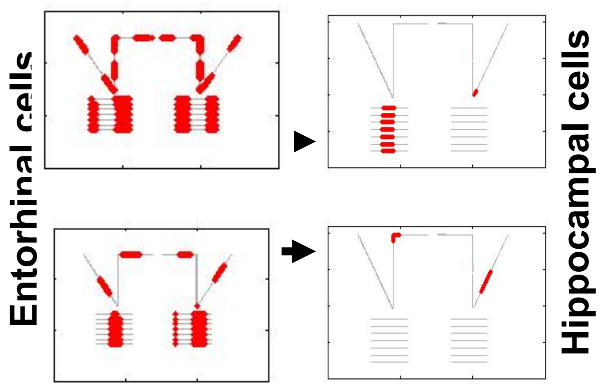
Figure from Burak and Fiete, 2009



Fuhs and Touretzky, 2006; Guanella et al., 2007; Fiete, Burak, Brookings, 2008; Burak and Fiete, 2009; Yoon, Barry, Buice, Burgess, Fiete, 2013; Couey et al., 2013; Bonnevie et al., 2013; Pastoll et al. 2013; Widloski and Fiete, 2014

Oscillatory interference model (Burgess, Barry, O'Keefe, 2007) simulates coding of location and time by grid cells. (But bat data shows absence of theta rhythmicity)



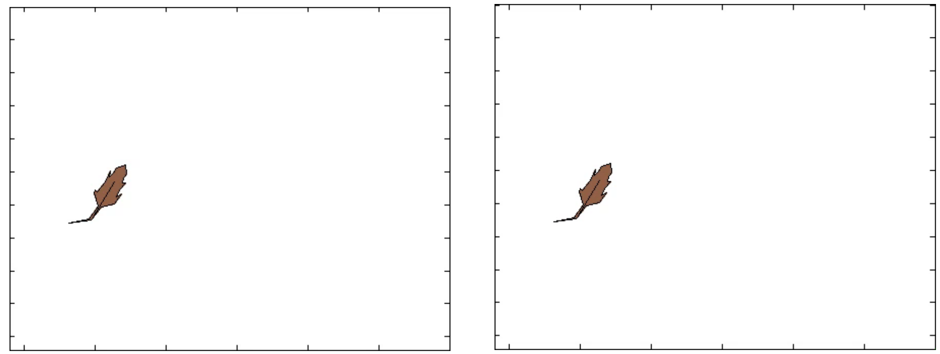


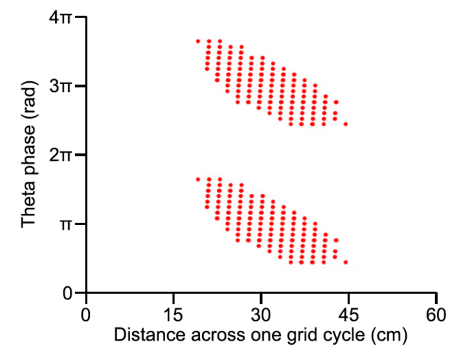
Simulates multiple firing fields in space and time

Figure: Hasselmo, *Hippocampus,* 2008
Using model by Burgess, Barry, O'Keefe, 2007

Simulates grid cell spatial periodicity

Data **Model**

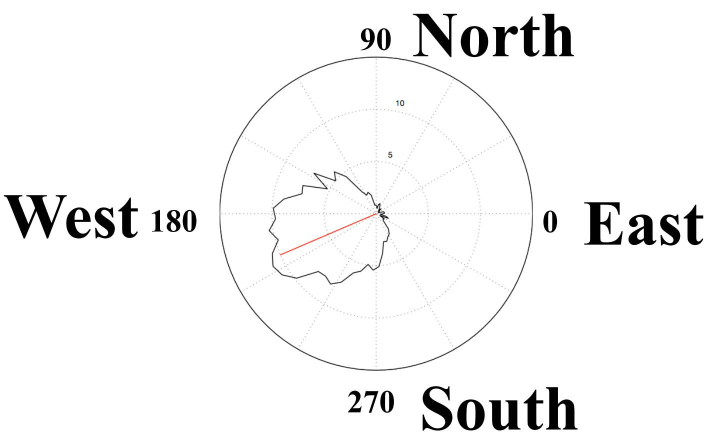




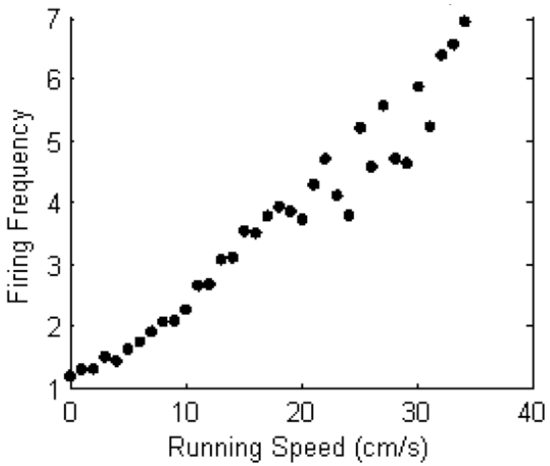
Simulates theta phase precession as essential functional component
Burgess, 2008; Climer et al. 2013; Bush & Burgess, 2014

Grid cell and time cell models: integration of velocity to code location requires coding of direction and speed

Example of head direction cell



200 degrees = preferred direction



Firing rate with head direction

Previously demonstrated by:
Taube, Muller, Ranck, 1990
Sargolini et al., 2006

Firing rate with running speed

Hinman, Brandon, Chapman, Hasselmo, 2016

Other studies:
O'Keefe et al., 1998; Wills et al., 2012; Kropff et al., 2015

Entorhinal cells code running speed in two different ways

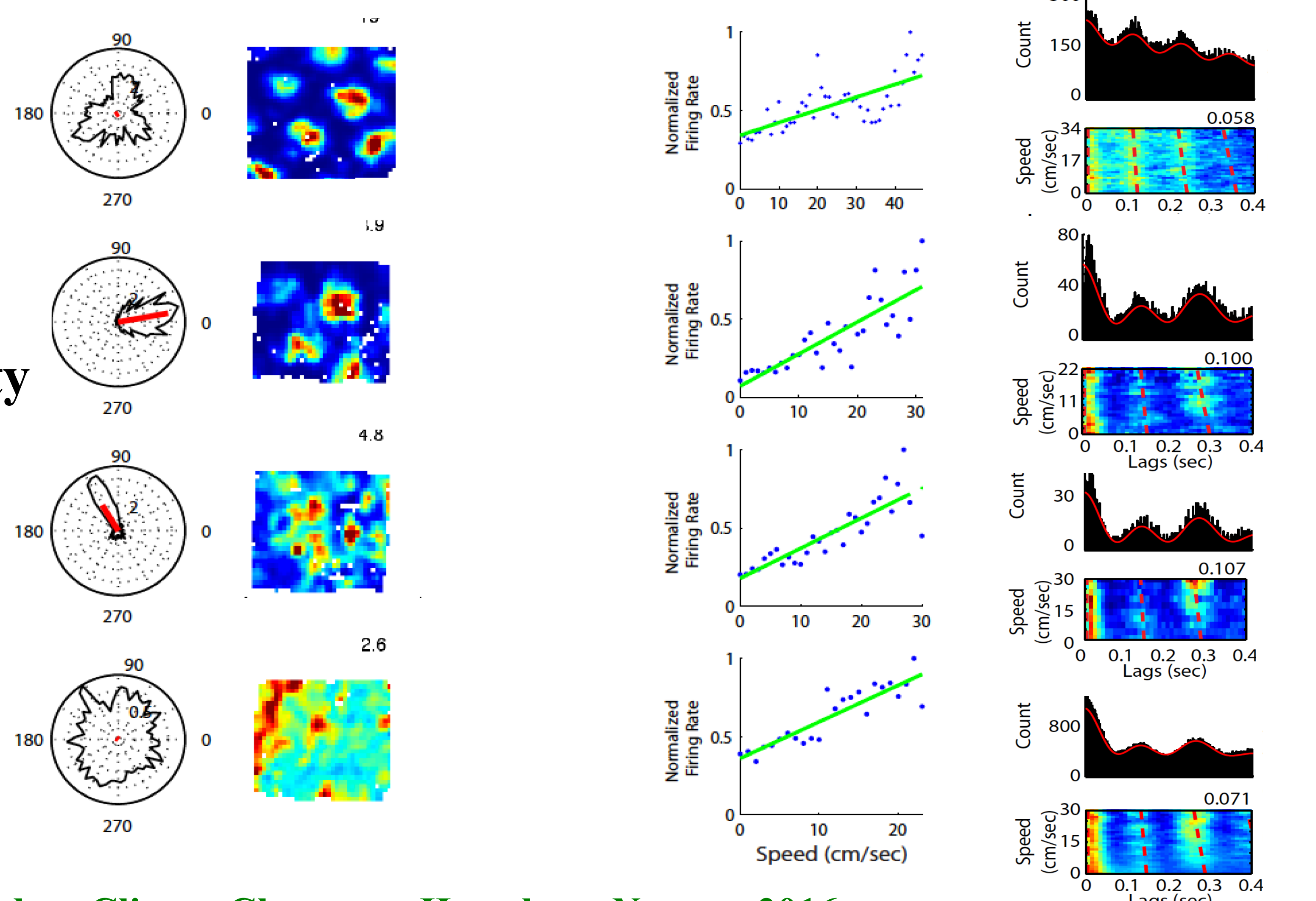
Spiking vs Head dir. | **Spatial plot** | **Firing rate vs speed** | **Theta rhythmicity vs speed**

Grid cell

Grid cell with head dir selectivity

Head dir. cell

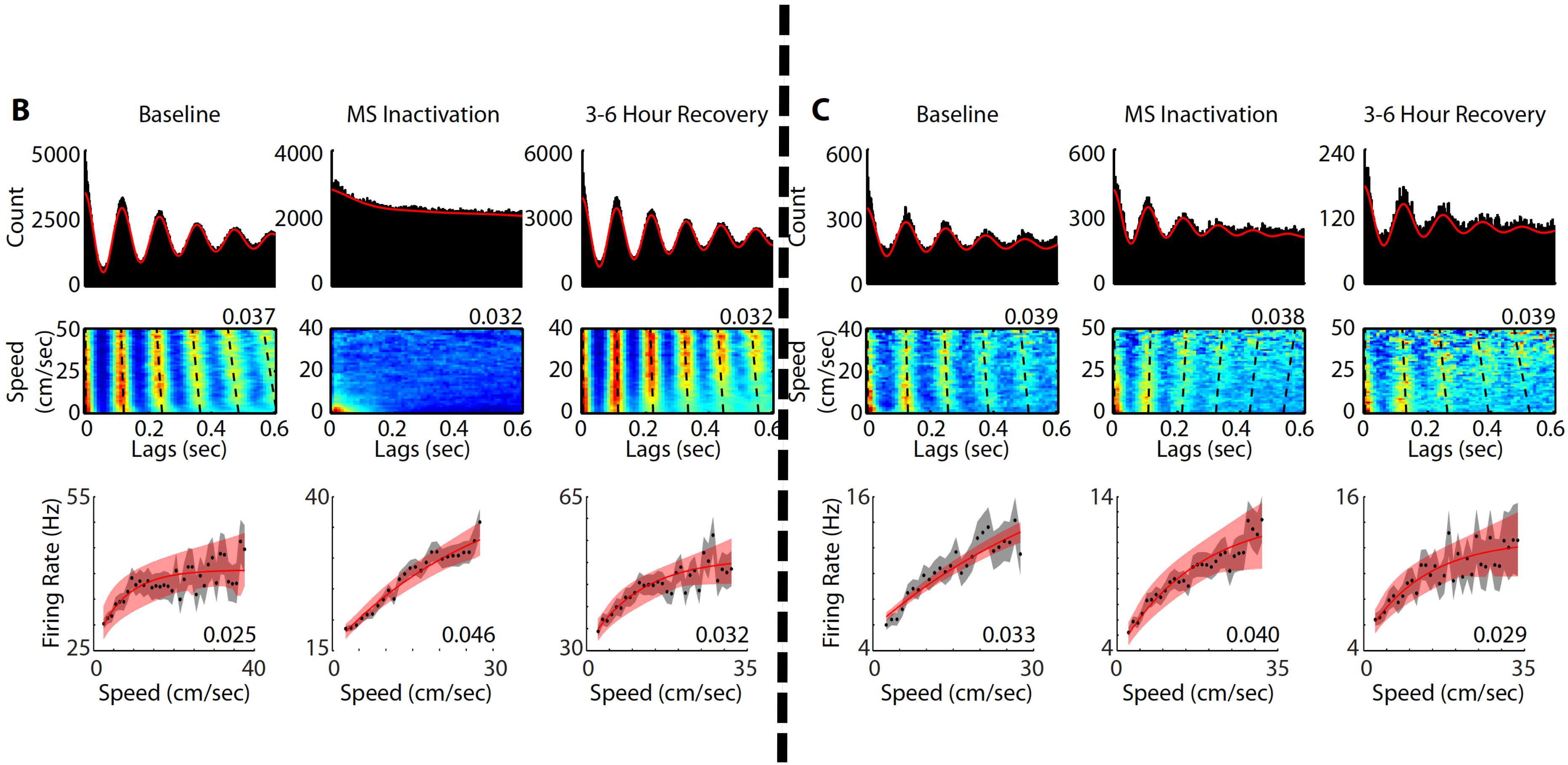
Speed cell



Hinman, Brandon, Climer, Chapman, Hasselmo, *Neuron*, 2016

Also Jeewajee et al, 2008; Kemere et al., 2013; Kropff et al., 2015

Medial septum inactivation causes loss of theta rhythmicity relationship to speed (but not loss of firing rate vs speed)

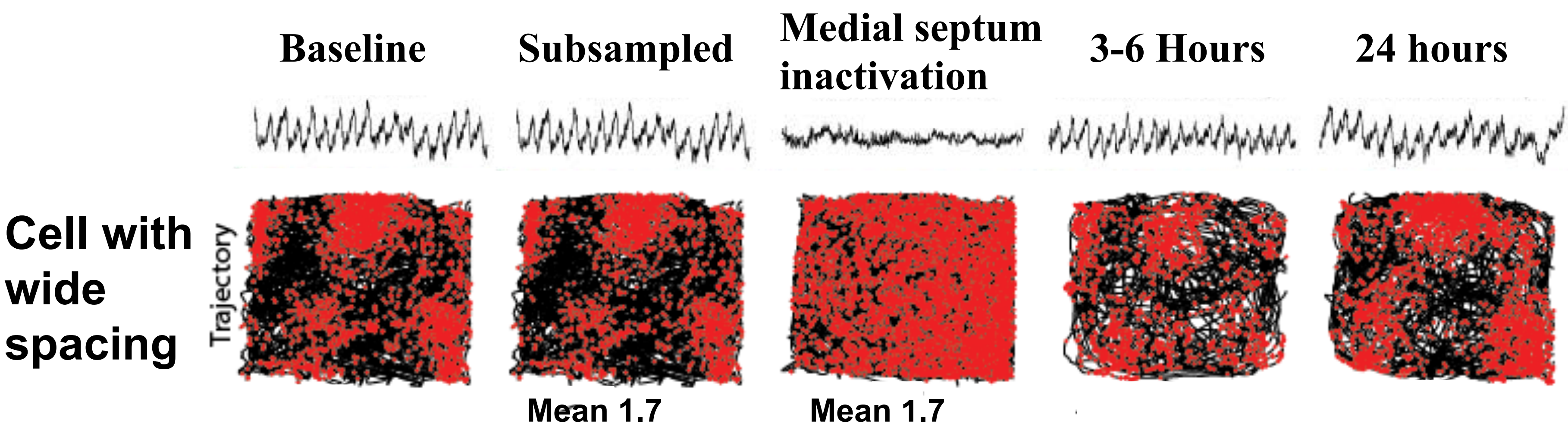


Two different speed codes: firing rate is NOT sensitive

Theta rhythmicity of firing IS sensitive to medial septum inactivation

Hinman, Brandon, Climer, Chapman, Hasselmo, *Neuron* 2016

Loss of grid cell periodicity during loss of theta rhythmicity in EEG may be due to loss of speed modulation of spiking rhythmicity



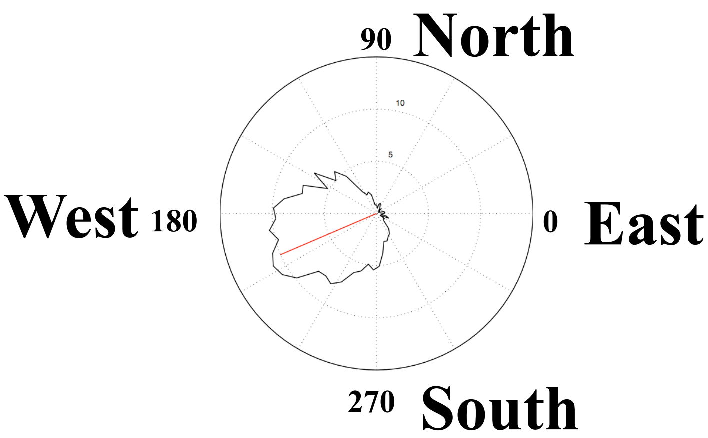
Supports a role of theta rhythm in generating grid cells

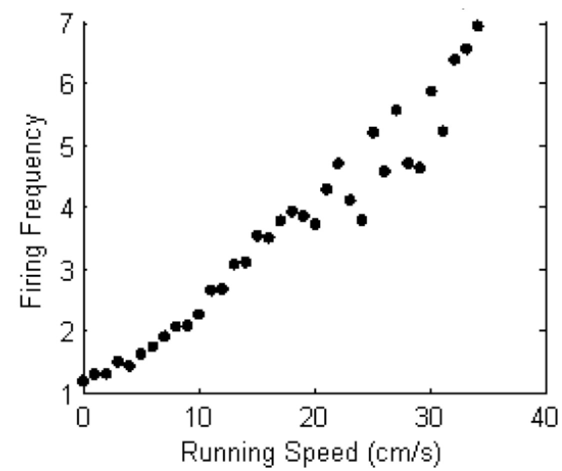
Brandon, Bogaard, Libby, Connerney, Gupta, Hasselmo (2011) Reduction of theta rhythm dissociates grid cell spatial periodicity from directional tuning. *Science*, 332: 595-599.

With lidocaine:, Koenig, Linder, Leutgeb, Leutgeb (2011)

Grid cell models: integration of velocity to code location requires coding of movement direction and speed

Example of HEAD direction cell





200 degrees = preferred direction

Firing rate with HEAD direction

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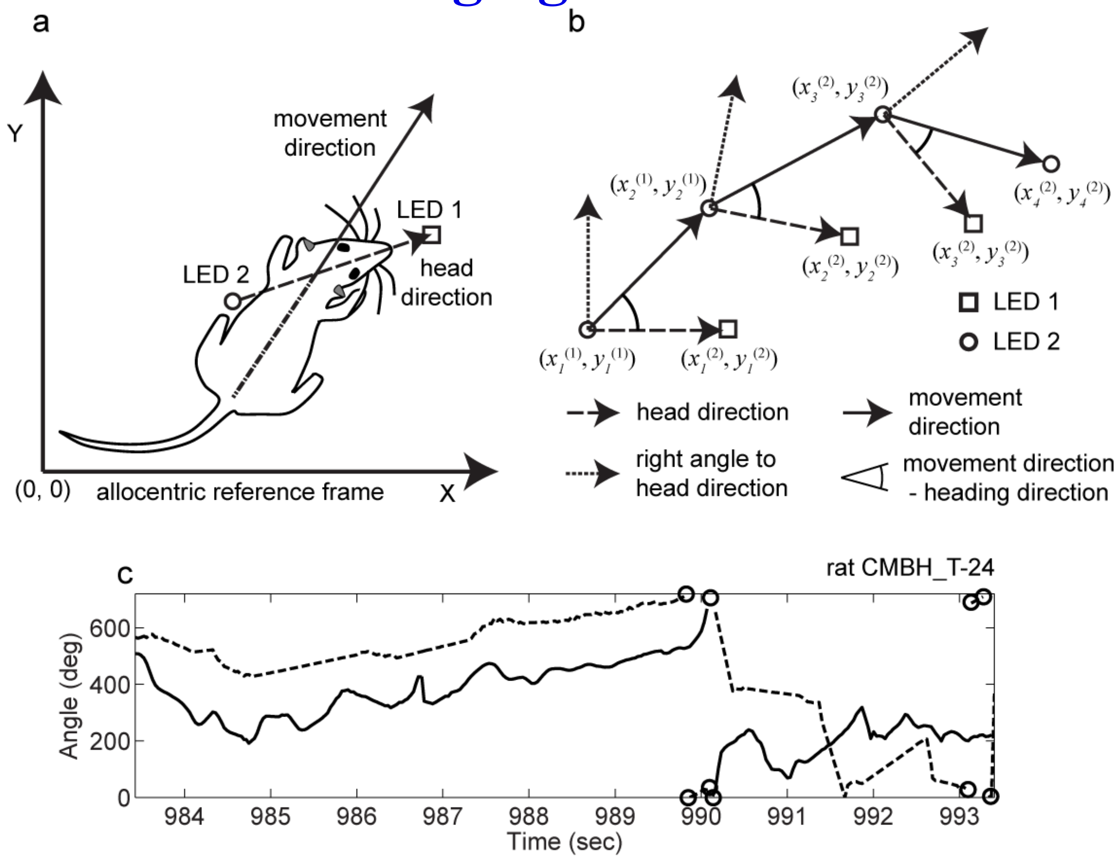
Sargolini et al., 2006

Firing rate with running speed

Hinman, Brandon, Chapman, Hasselmo, 2016

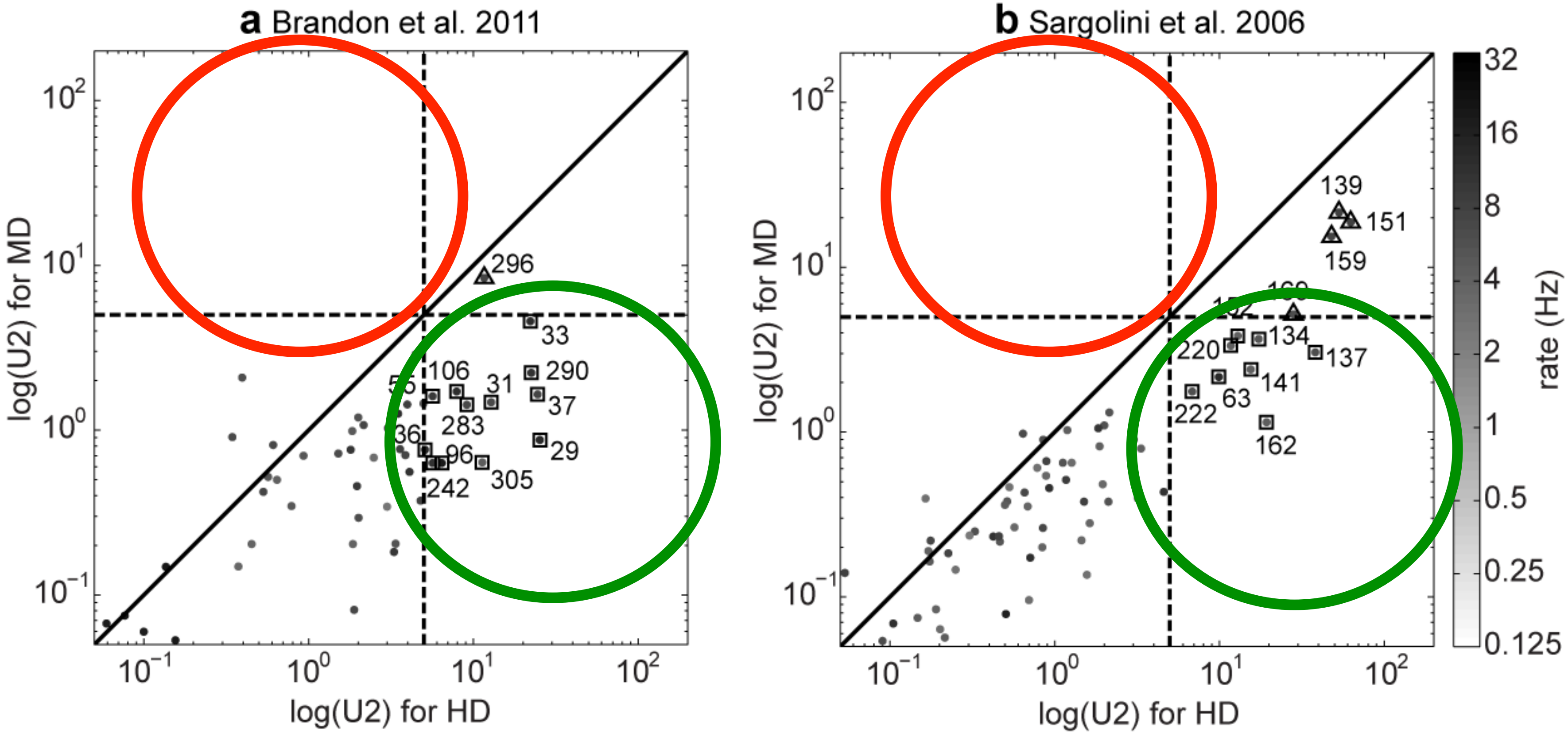
Other studies:
O'Keefe et al., 1998; Wills et al., 2012; Kropff et al., 2015

Movement direction does not equal head direction during rat foraging behavior



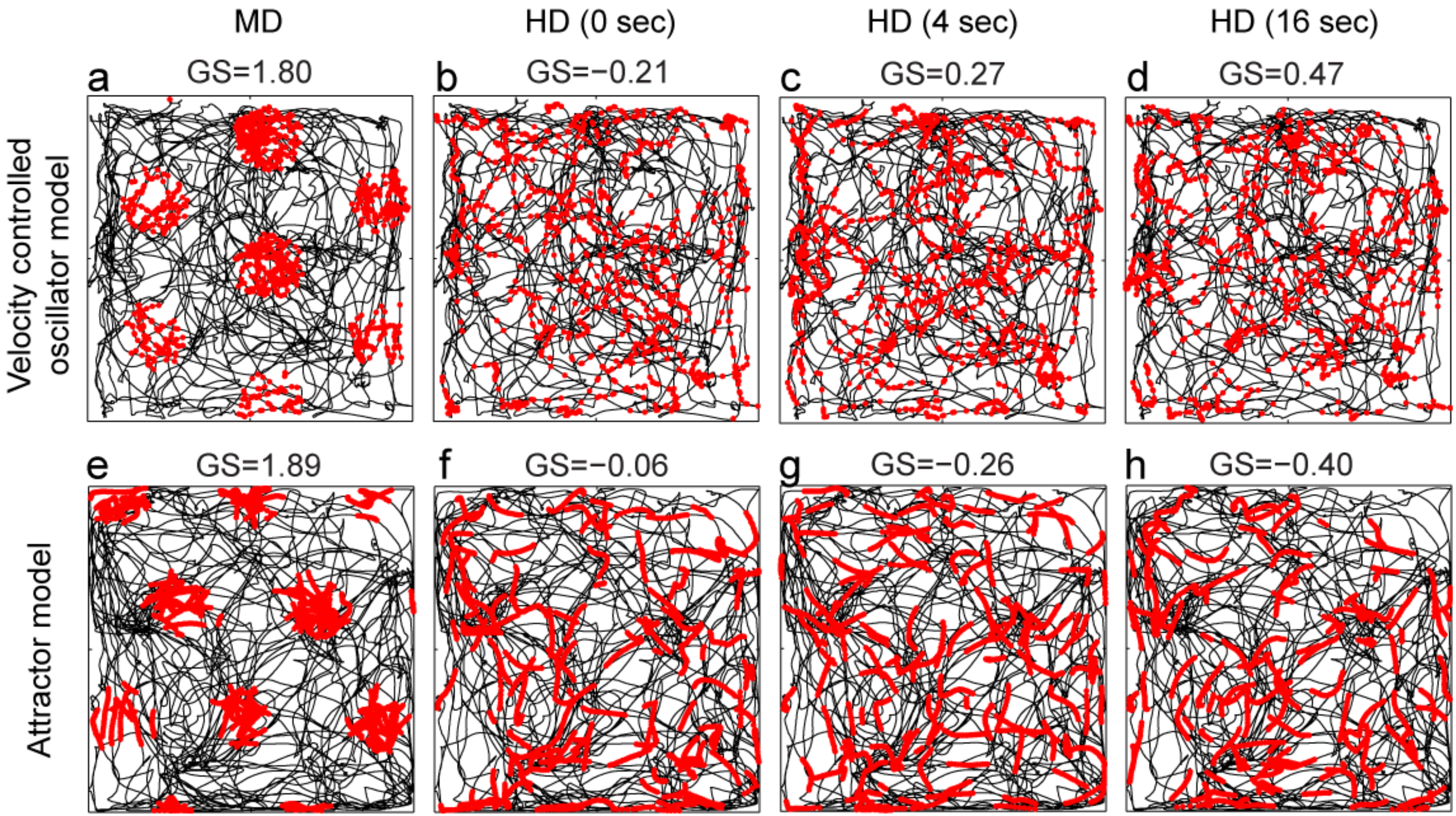
Raudies, Brandon, Chapman, Hasselmo (2015)

Many cells show tuning to head direction alone
No cells show tuning to movement direction alone
A few cells show tuning to both in entorhinal cortex



Raudies, Brandon, Chapman, Hasselmo (2015)

Grid cell models require movement direction (MD). Most models fail when using head direction (HD)



Movement direction input

No grid fields with head direction input

Raudies, Brandon, Chapman, Hasselmo (2015)

Questions:

1. **What role does theta rhythm play in generation of grid cells and time cells?**
2. **Why is head direction coded more strongly than movement direction?**
   (e.g. stronger influence of sensory input than path integration?)

Talk outline:

1. Medial septal input important for grid cells and time cells
2. Theta cycle skipping and head direction
3. Visual coding of environment boundaries

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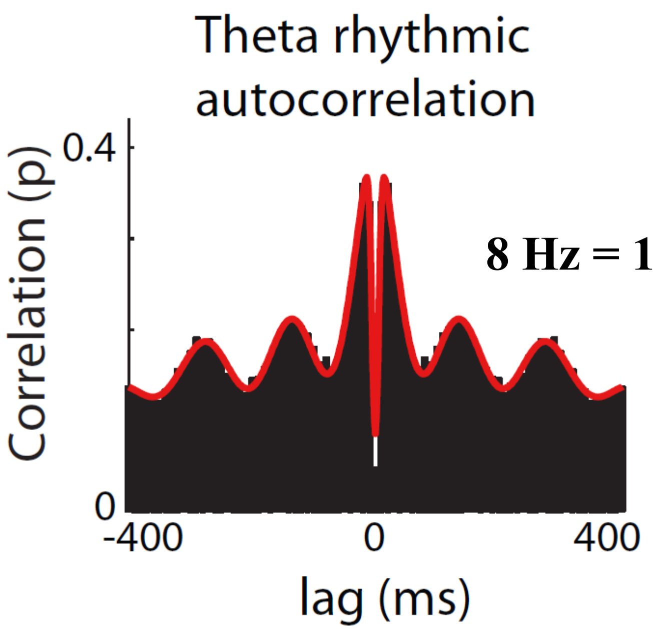
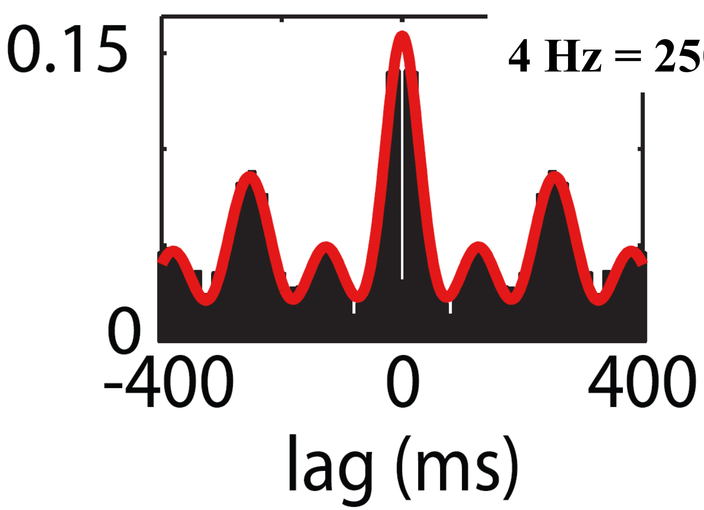
Data on entorhinal cells shows theta cycle skipping



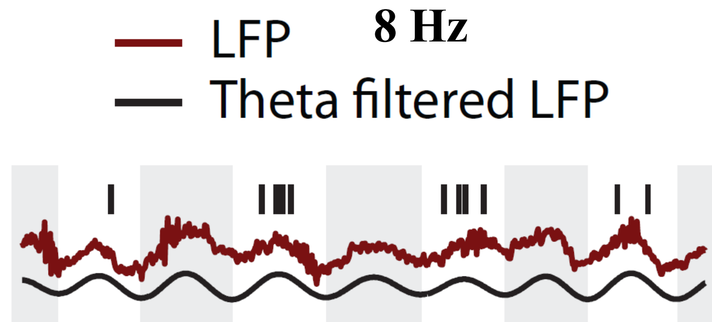
8 Hz = 125 msec

Entorhinal: Jeffery, Donnett, O'Keefe (1995)
Deshmukh, Yoganarasimha, Voicu, Knierim (2010)
Septum: King, Recce, O'Keefe (1998);
Varga et al. (2008)

Theta cycle skipping autocorrelation



4 Hz = 250 msec →

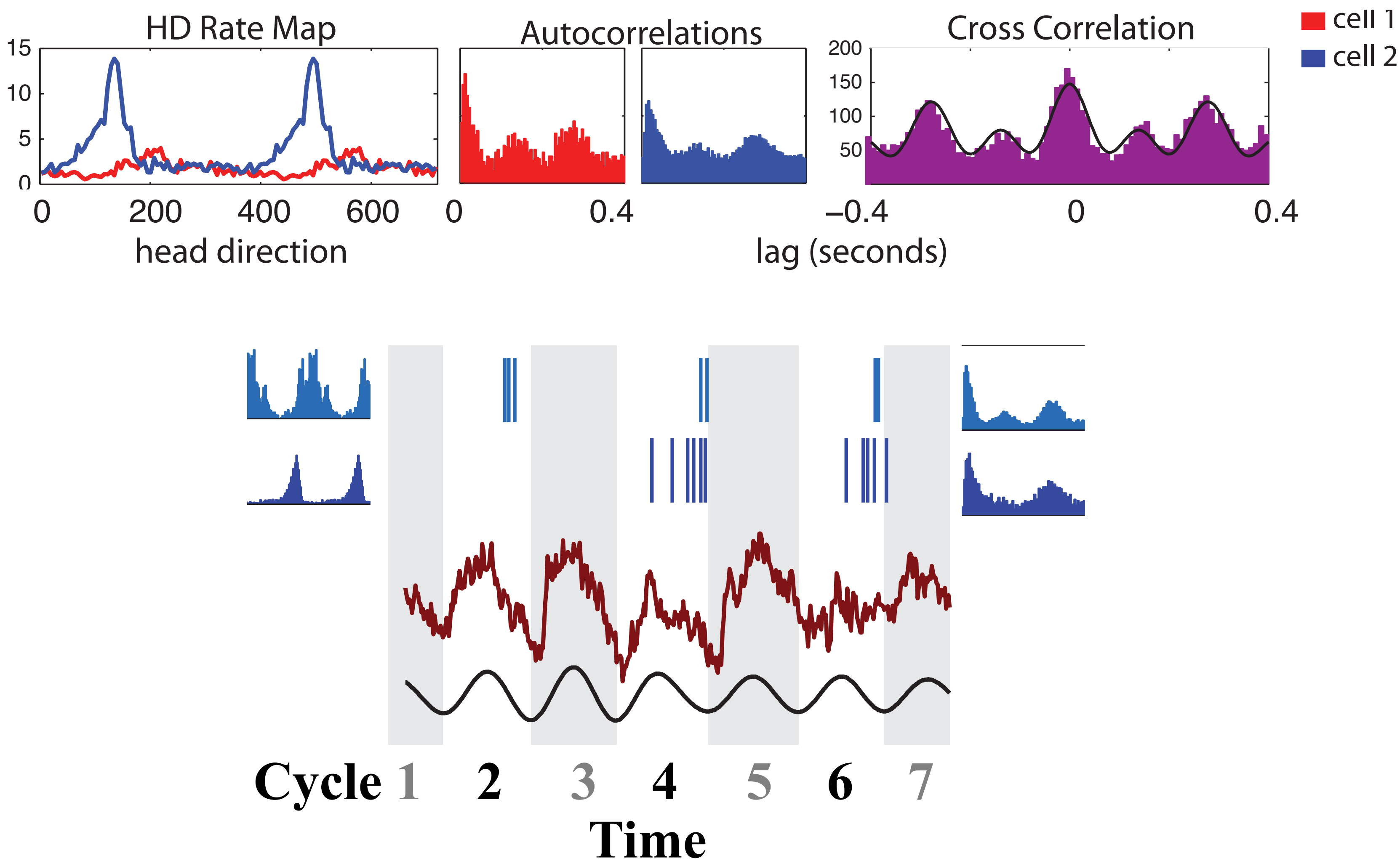


Theta cycle 1 **2** 3 **4** 5 **6** 7 **8** 9

Time →

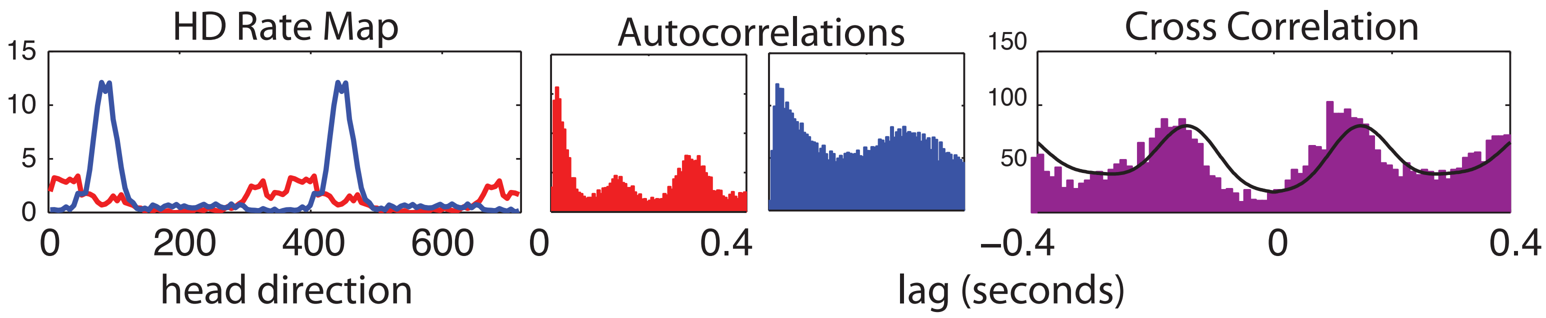
Brandon, Bogaard, Schultheiss, Hasselmo, (2013) *Nature Neuroscience*, 16(6):738-748

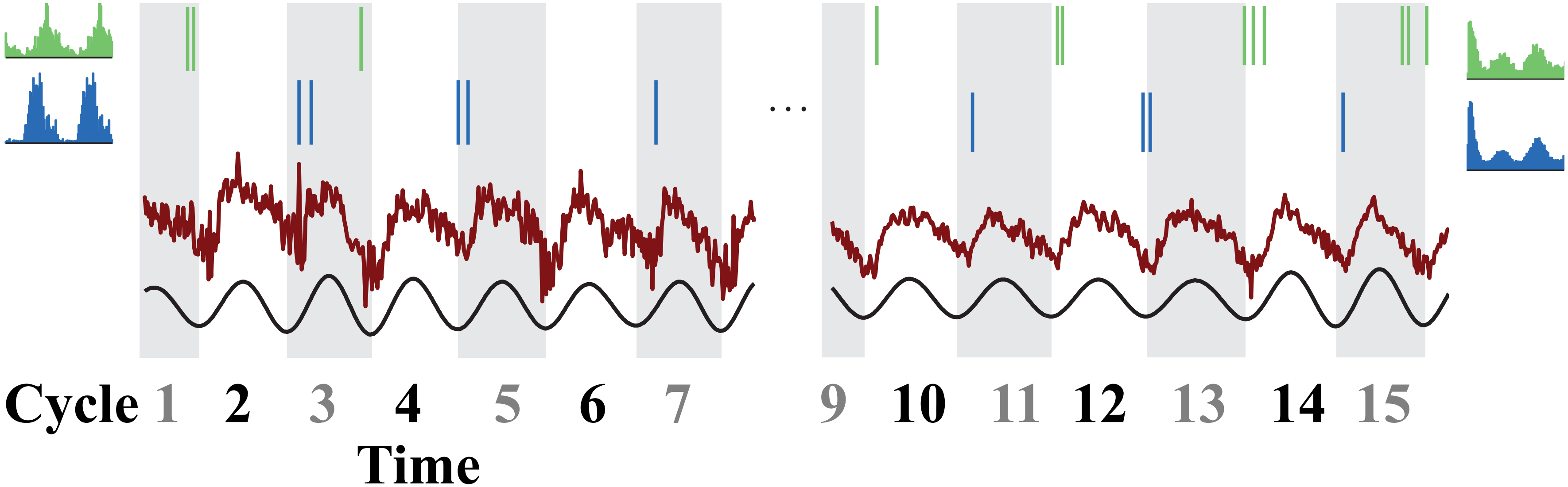
Cross-correlation of spiking - synchronous cycle skipping



Brandon, Bogaard, Schultheiss, Hasselmo, (2013) *Nature Neuroscience*, 16(6):738-748

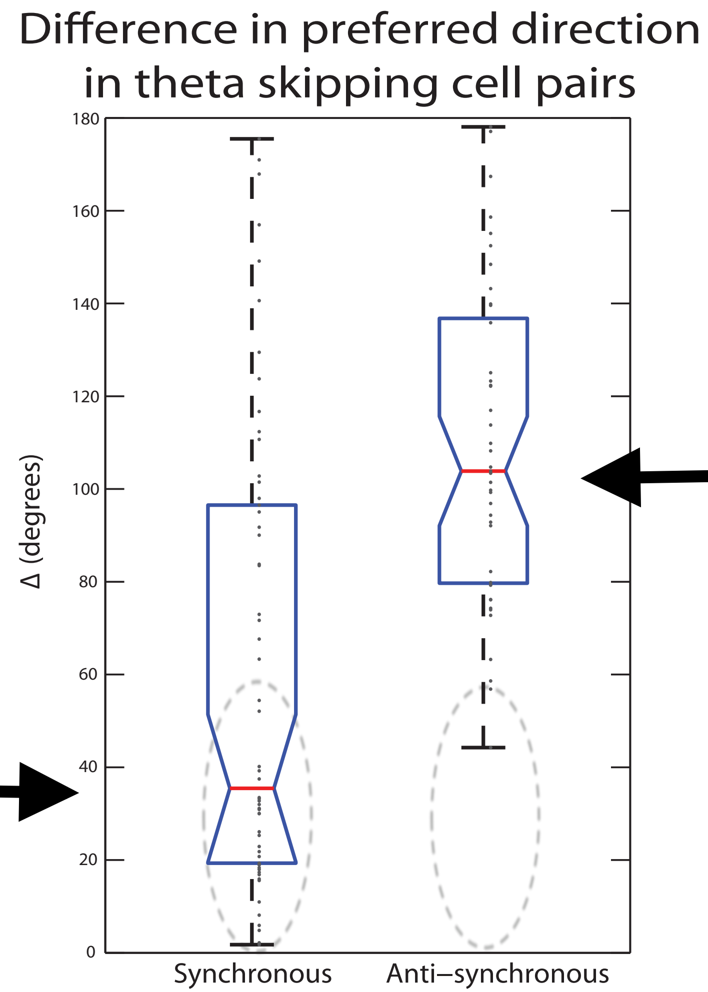
Cross-correlations of spiking – anti-synchronous cycle skipping





Brandon, Bogaard, Schultheiss, Hasselmo, (2013) *Nature Neuroscience*, 16(6):738-748

Difference in preferred Head Direction tuning



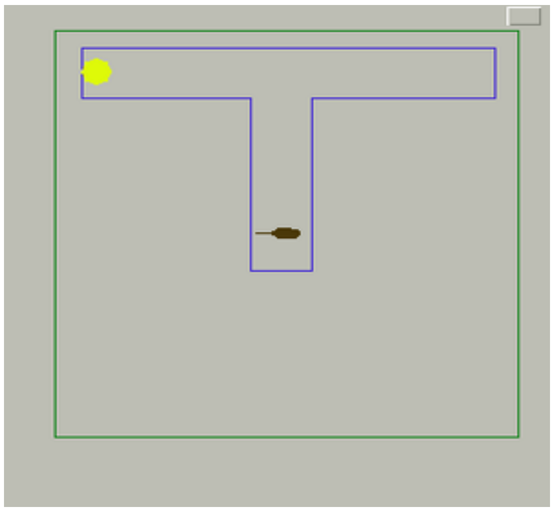
Synchronous pairs have similar head direction tunings

Anti-synchronous pairs differ in head direction tuning

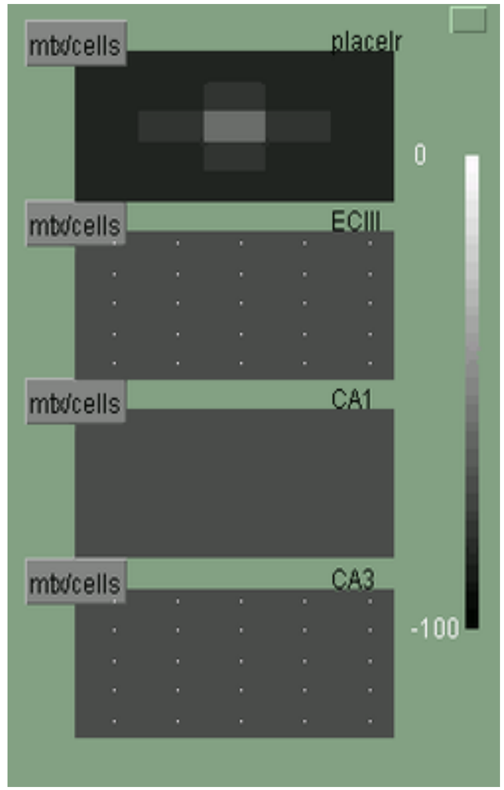
(No pairs are closer than 40 degrees)

Brandon, Bogaard, Schultheiss, Hasselmo, (2013) *Nature Neuroscience*, 16(6):738-748

Encoding and retrieval works best on separate phases of theta rhythm



Separation of encoding and retrieval



Theta rhythm

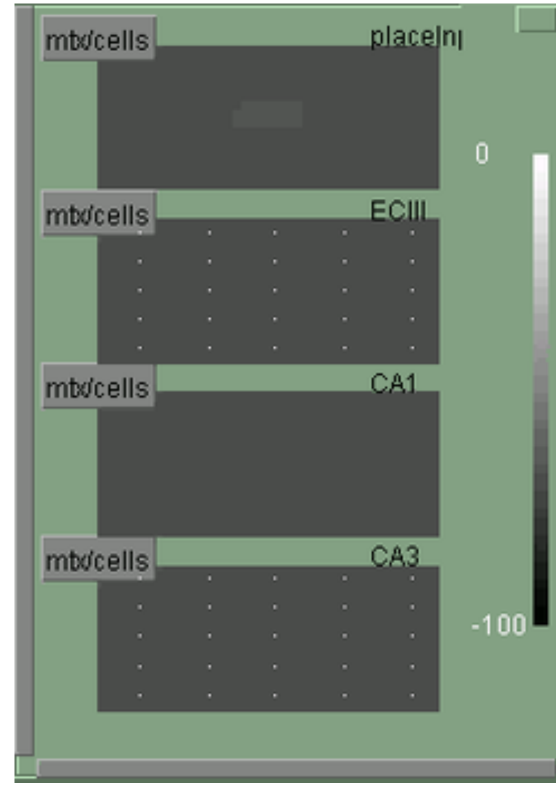
Place

EC

CA1

CA3

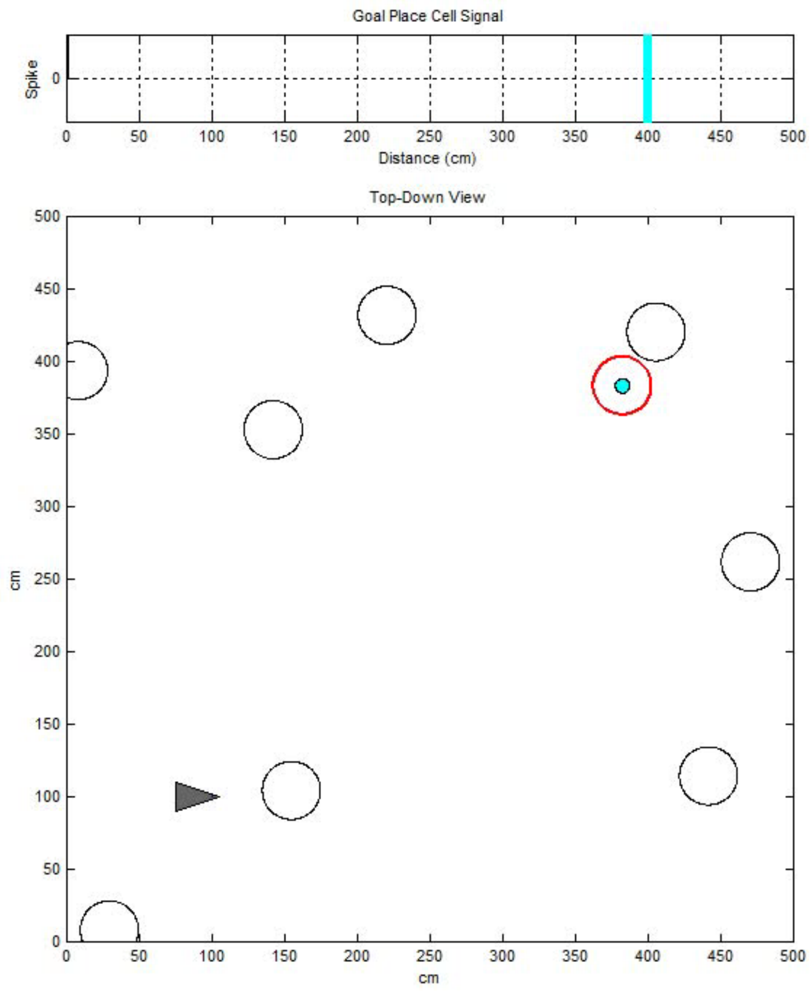
Retrieval during encoding causes interference



No theta rhythm (fornix lesion)

Hasselmo, Bodelon, Wyble (2002) A proposed function of the hippocampal theta rhythm: Separate phases of encoding and retrieval. Neural Comput 14:793–817.
Hasselmo and Eichenbaum (2005)

Grid cell models can simulate forward probing of trajectories to goals



- Model performs forward probe of trajectory
- If probe activates goal place then direction is chosen

Erdem and Hasselmo, (2012; 2014)
Erdem, Milford, Hasselmo, 2015

Data shows predictive activity in entorhinal cortex:
Gupta, Beer, Keller, Hasselmo (2013)
Gupta, Erdem, Hasselmo (2013)
And hippocampus:
Johnson and Redish, 2007; Pfeiffer and Foster, 2013; Kay…Frank, 2017

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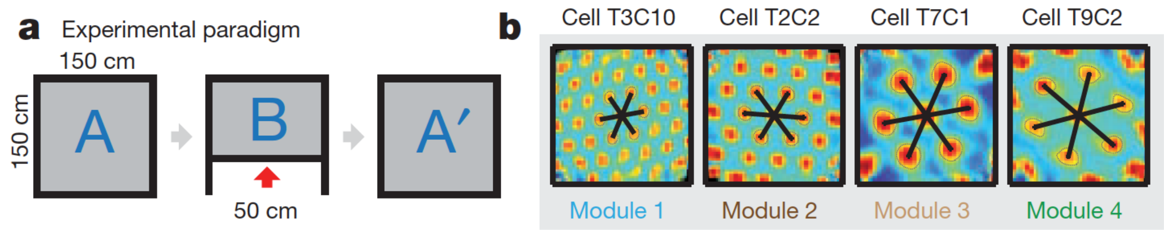
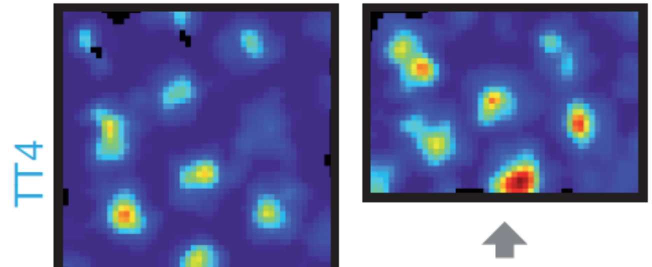
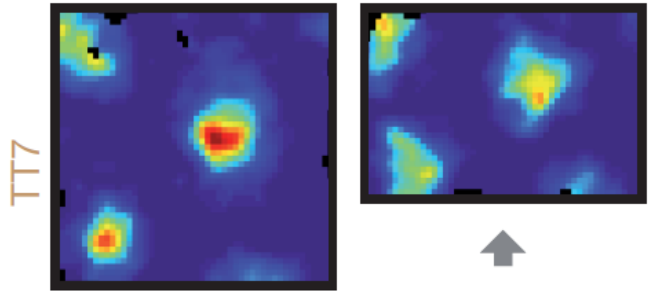
Different grid cell modules show different responses to barrier location (visual cues)



Grid cells with small spacing show **NO** rescaling



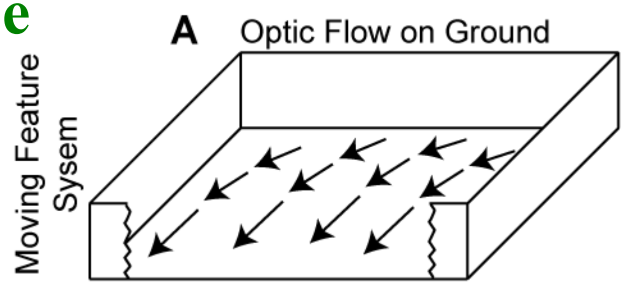
Grid cells with large spacing show large rescaling (compression)

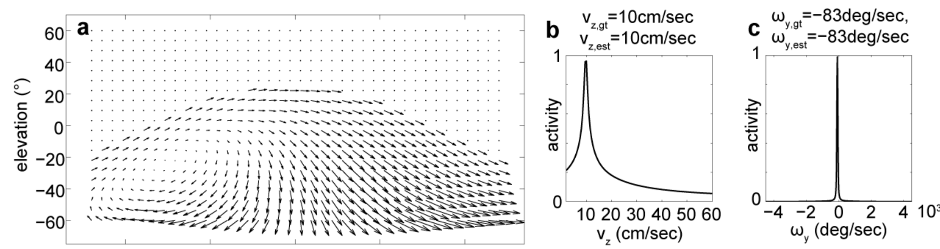


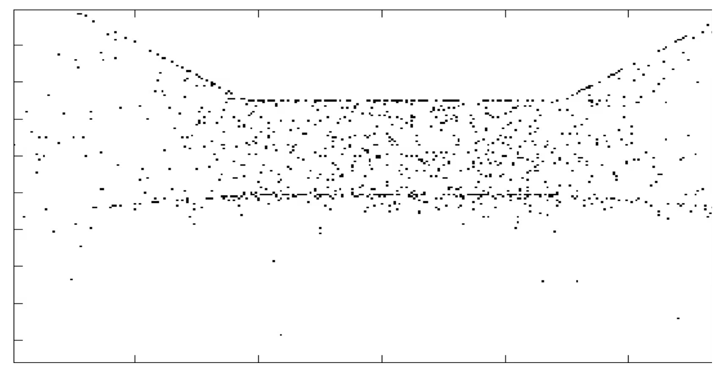
Stensola, Stensola, Solstad, Froland, Moser, Moser (2012) *Nature*
Compression first shown by:
Barry, Heyman, Burgess Jeffery (2007) *Nature Neurosci.*

Modeling influence of visual cues on different grid cell modules

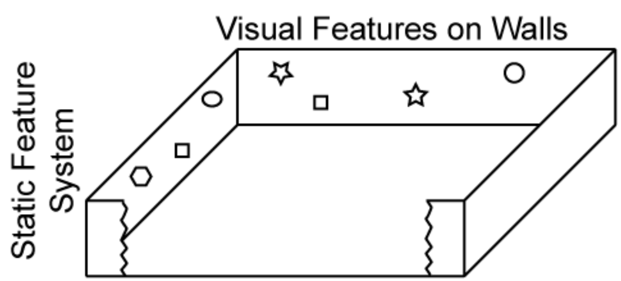
Ground plane

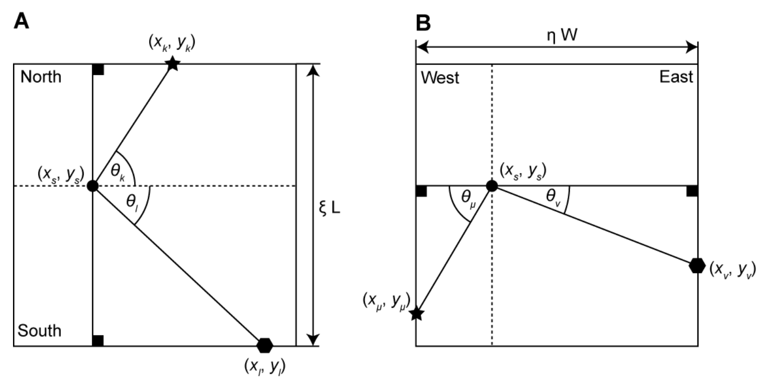






Sense of spatial location from visual cues and optic flow

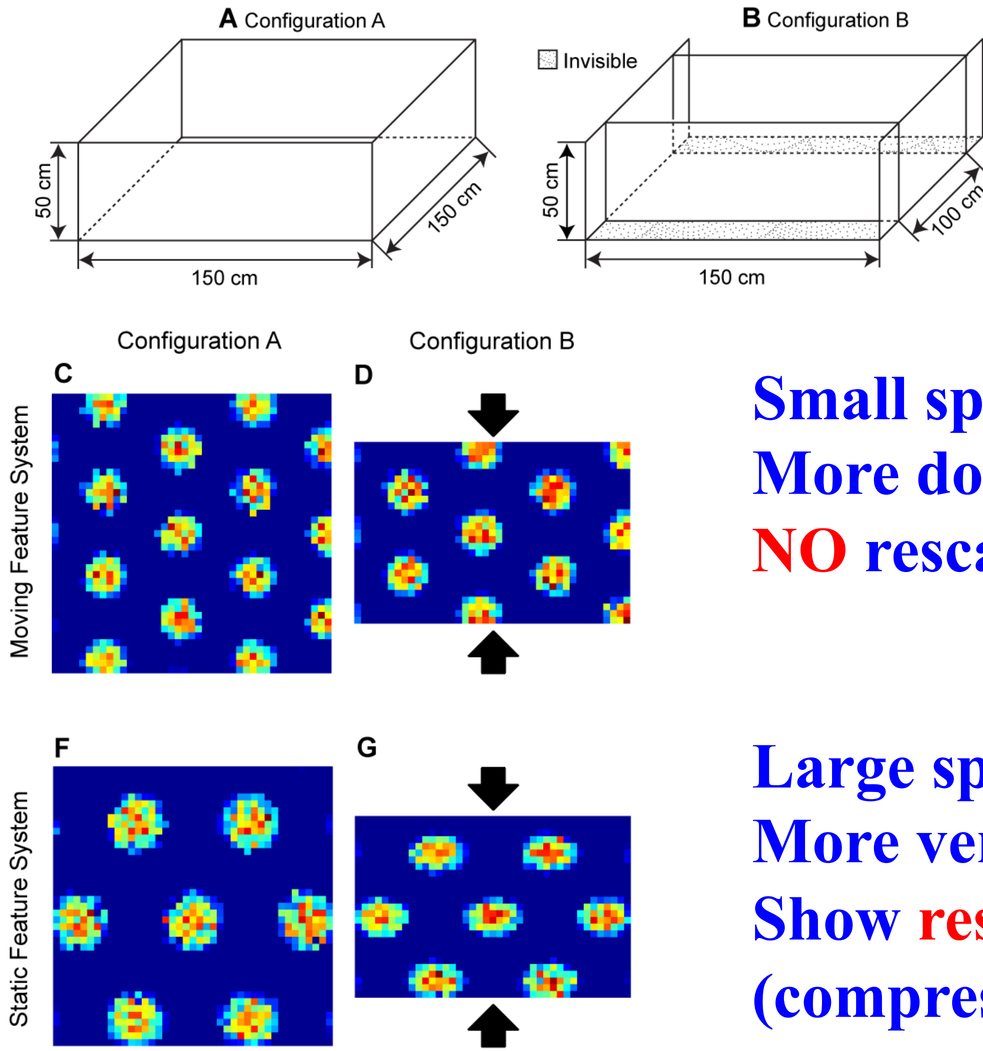




Wall features

Raudies and Hasselmo, PLoS Comp Biology, (2015) 11(11):e1004596

Model replicates differential influence of visual cues on different grid cell modules in entorhinal cortex



Ground plane
(no change in optic flow)

Small spacing cells
More dorsal
NO rescaling

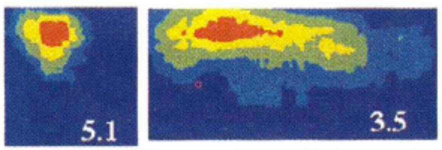
Wall features
(compression)

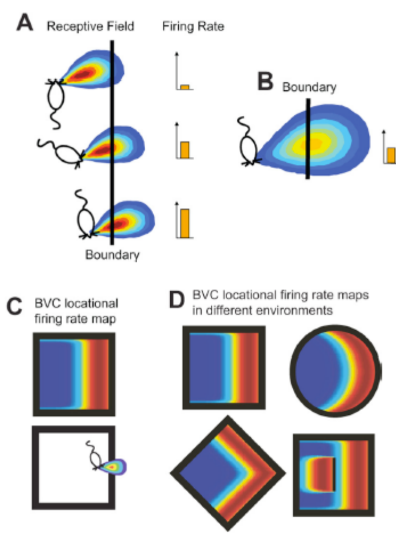
Large spacing cell
More ventral
Show rescaling (compression)

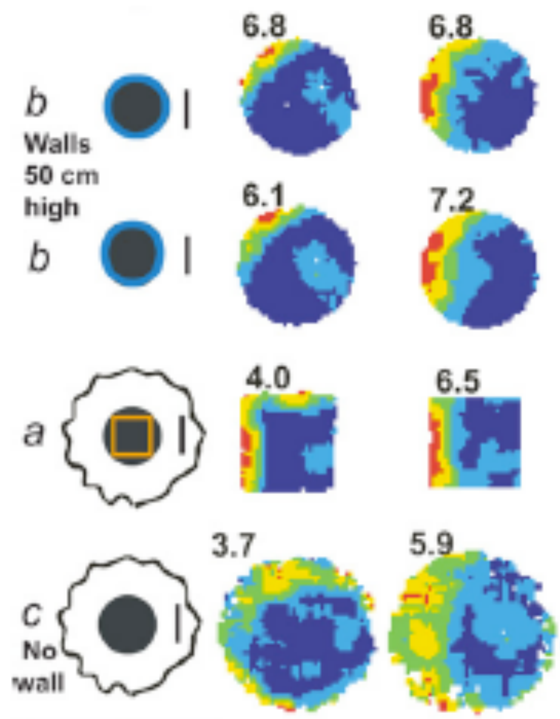
Raudies and Hasselmo, PLoS Comp Biology, (2015) 11(11):e1004596

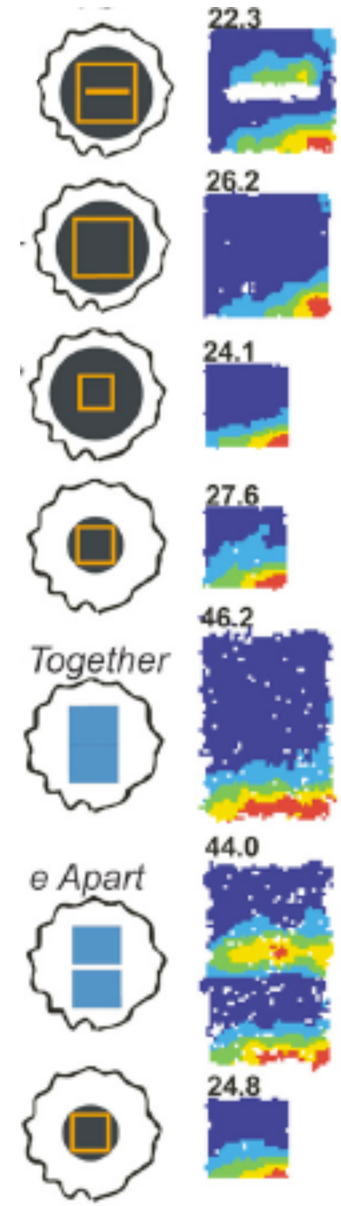
Barrier effect led to prediction of allocentric boundary cells

Prediction:
O'Keefe and Burgess, 1996
Burgess et al., 1998
Hartley et al., 2000



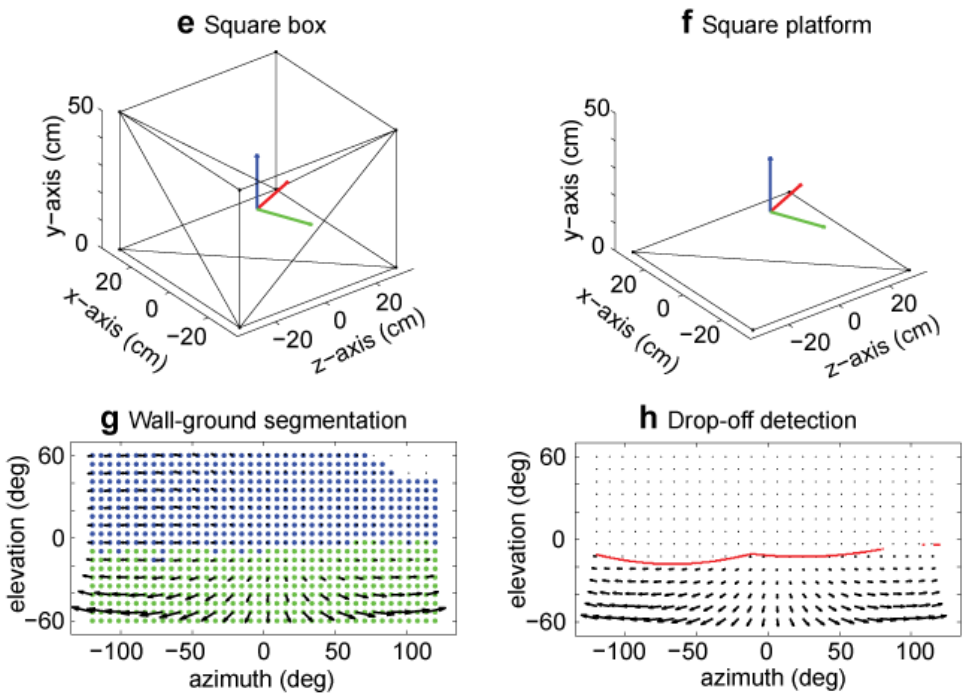




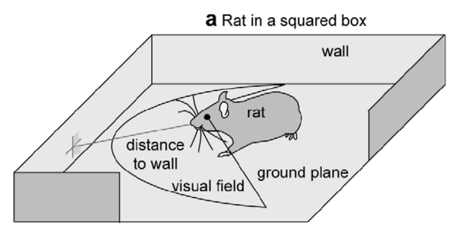


Data: Barry, Lever, O'Keefe, Burgess, 2006
Lever, Barry, Burgess, 2009
Same as Border cell: Solstad et al., 2008

Boundary responses may be driven by optic flow



Template based detection of edge (Local optic flow)
Not yet biological



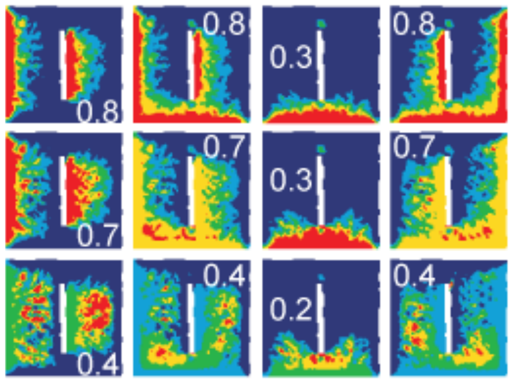
Raudies and Hasselmo (2012) Modeling boundary vector cell firing given optic flow as a cue. *PLoS Computational Biology*

Addressing data from Lever, Burton, Jeewajee, O'Keefe, Burgess (2009)

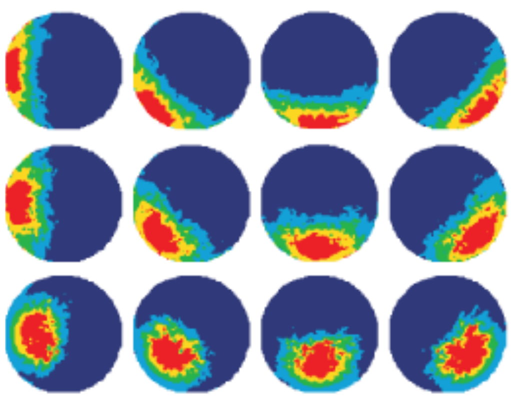
Experimental data shows predicted boundary vector cells
Can simulate based on optic flow

Modeling

Simulation

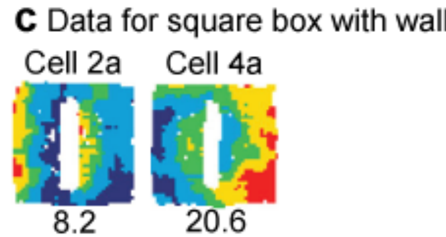


Simulation

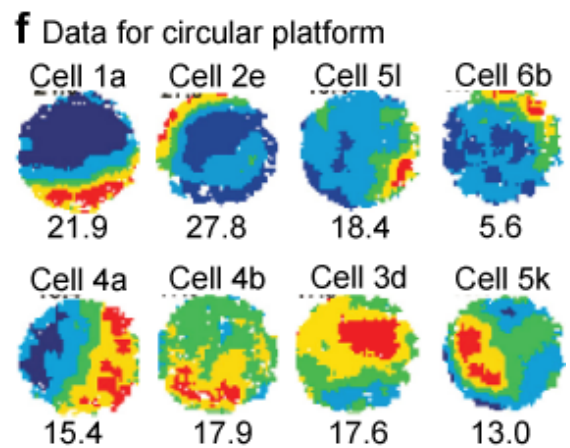


Data

Experimental data



Experimental data

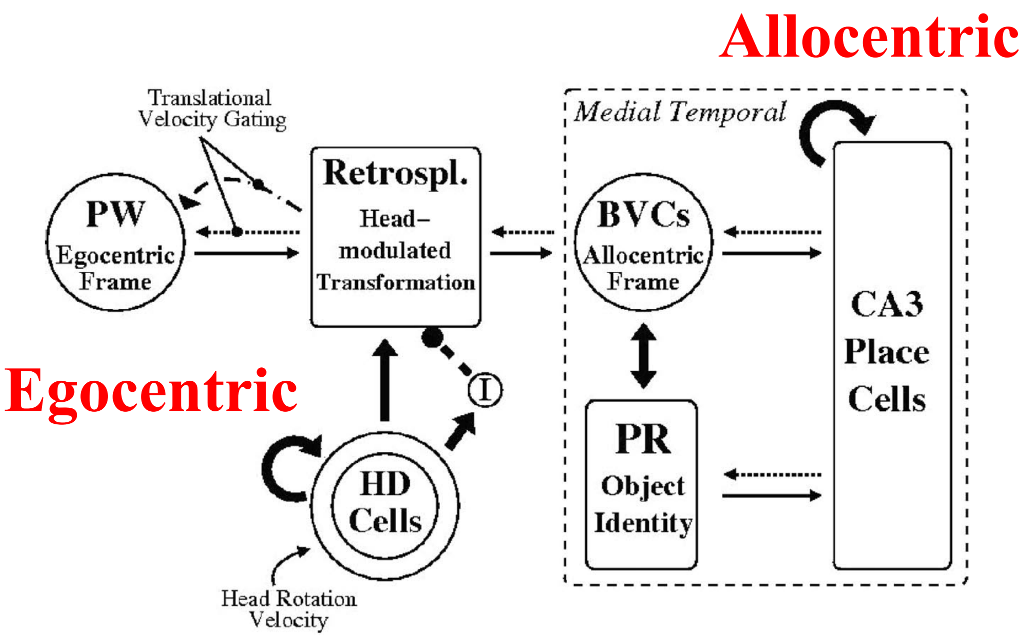


Simulation: Raudies and Hasselmo (2012) PLoS Comp Bio

Data: Lever, Burton, Jeewajee, O'Keefe, Burgess (2009)

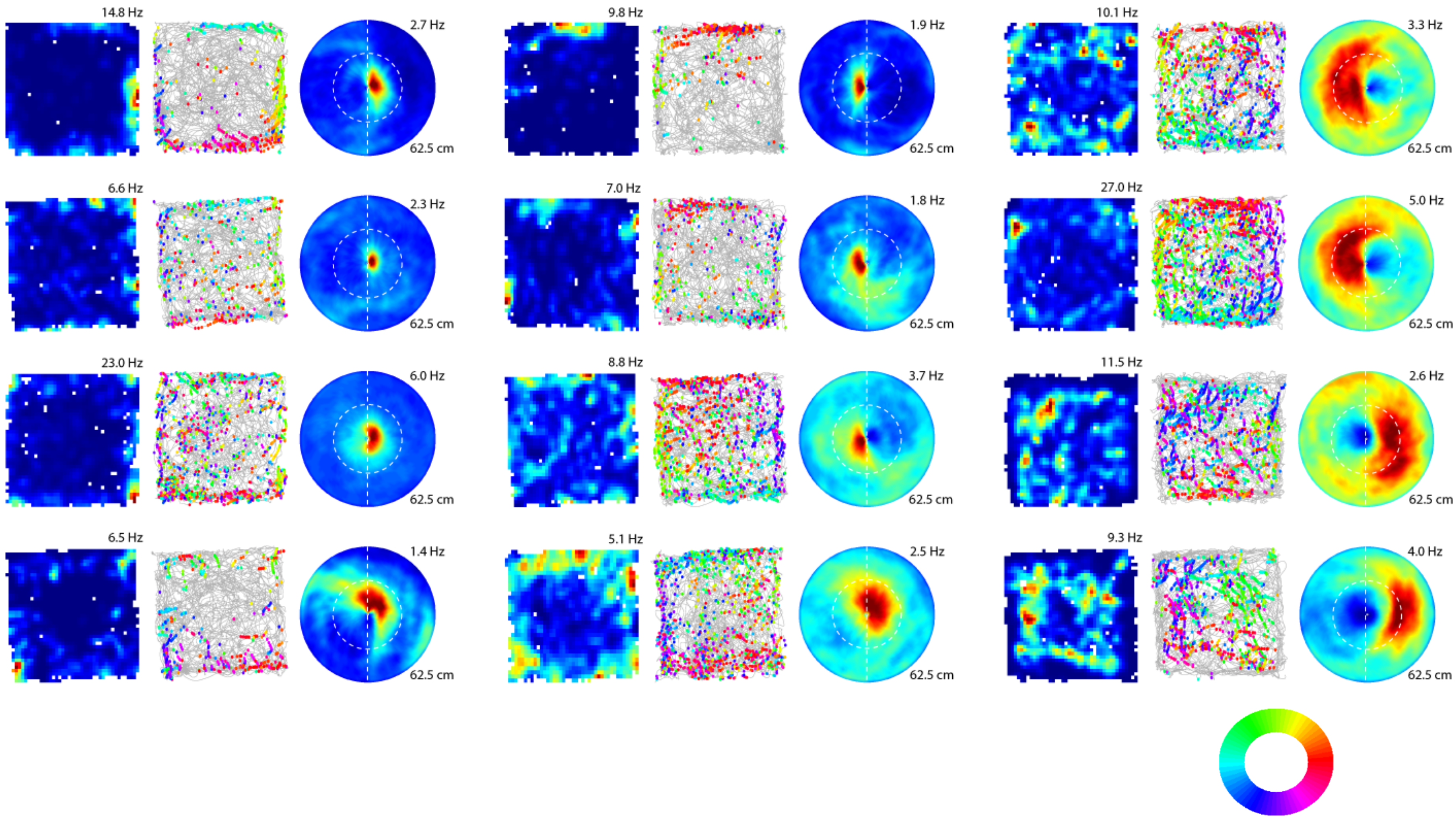
Translation from egocentric to allocentric spatial representation

"We hypothesize that a population of neurons maintains a head-centered, egocentric map of space ... This map represents the locations of all landmarks/objects that are visible from an animal's current location in space." Byrne et al., 2007



Byrne, Becker, Burgess, *Psychol. Review*, 2007

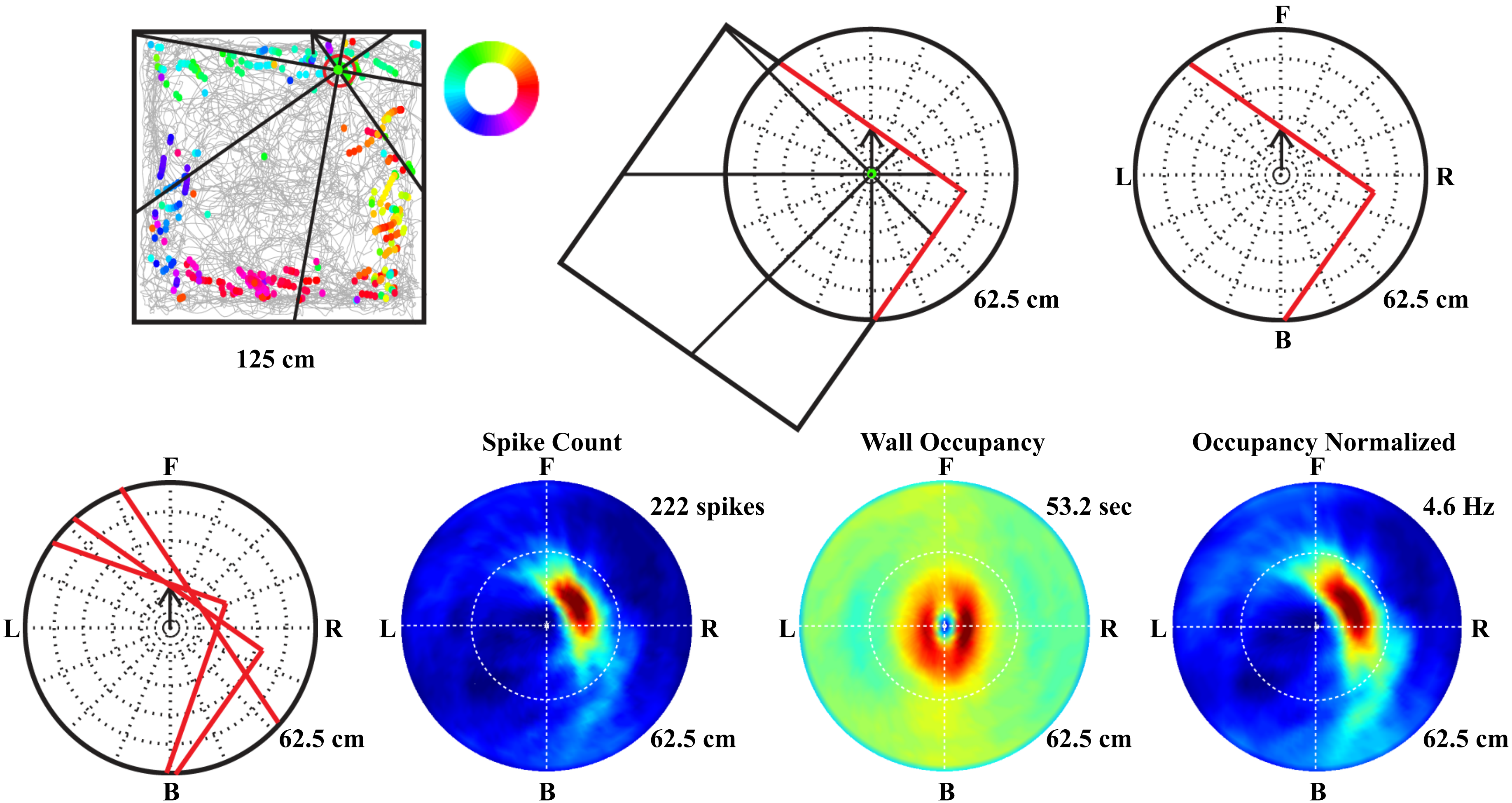
Data on Egocentric Boundary Cells (EBCs)



Jake Hinman, dorsal striatum (area gets input from retrosplenial), SFN 2016, 2017

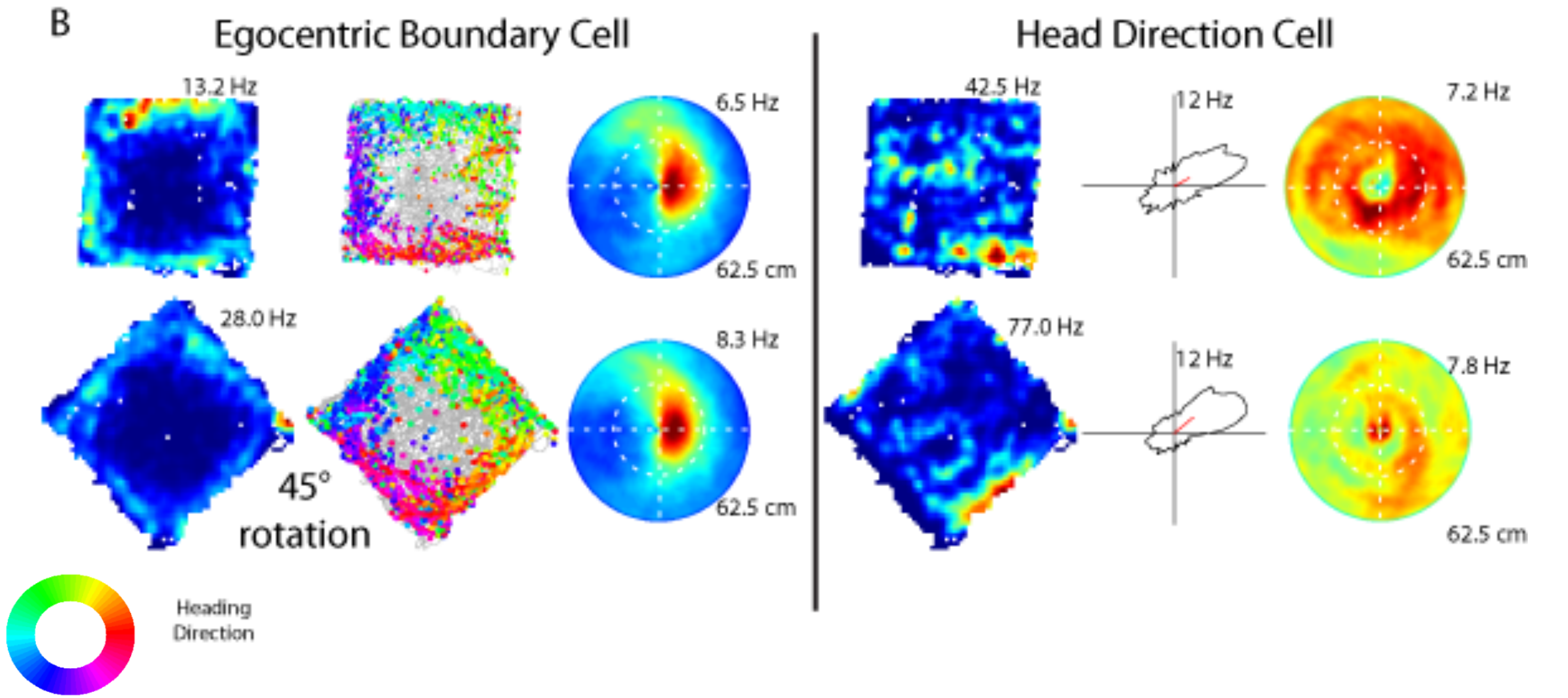
Andy Alexander, retrosplenial cortex

Generation of egocentric boundary ratemap



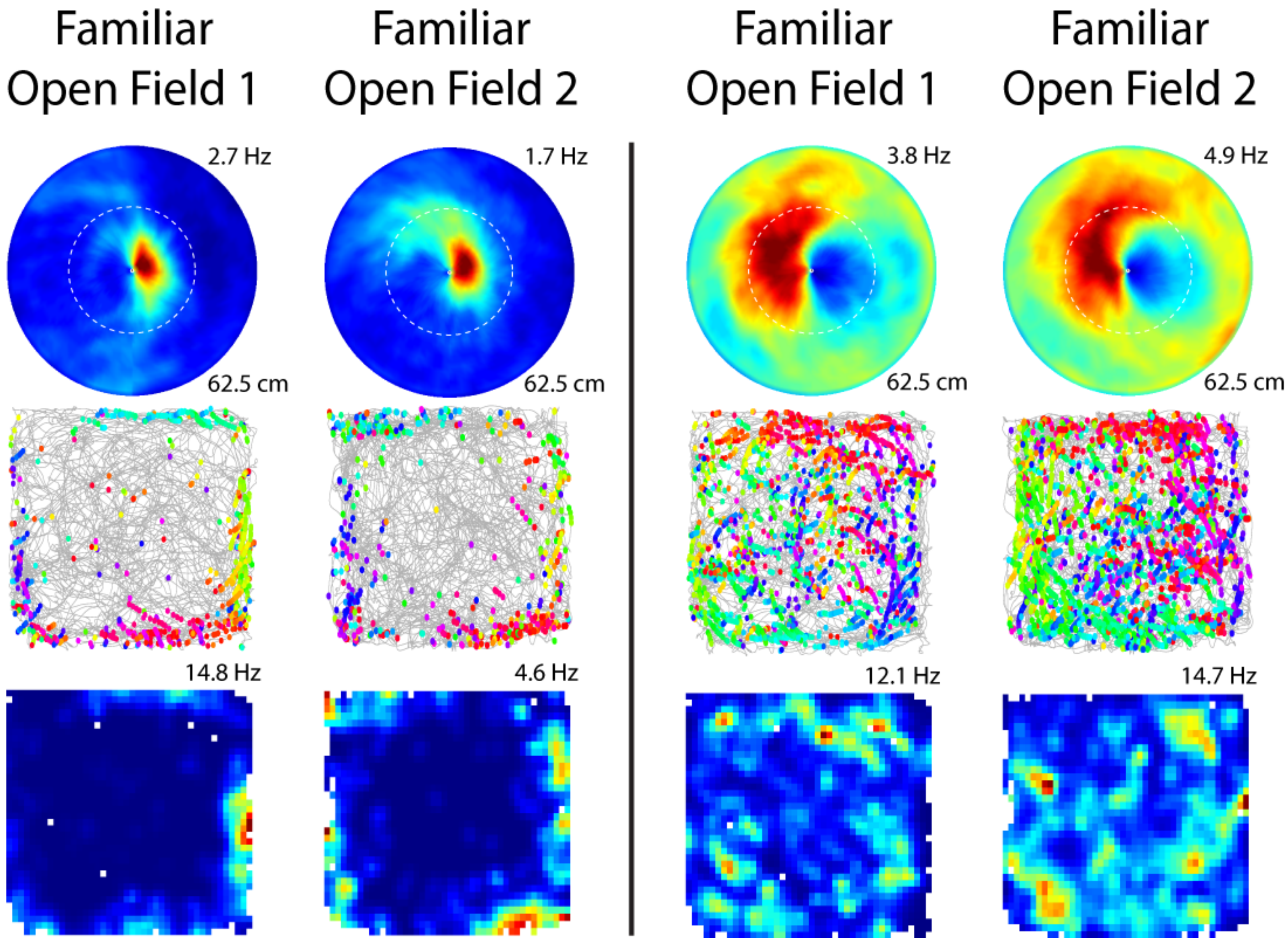
Jake Hinman, SFN 2016, 2017

Dissociating egocentric and allocentric reference frames



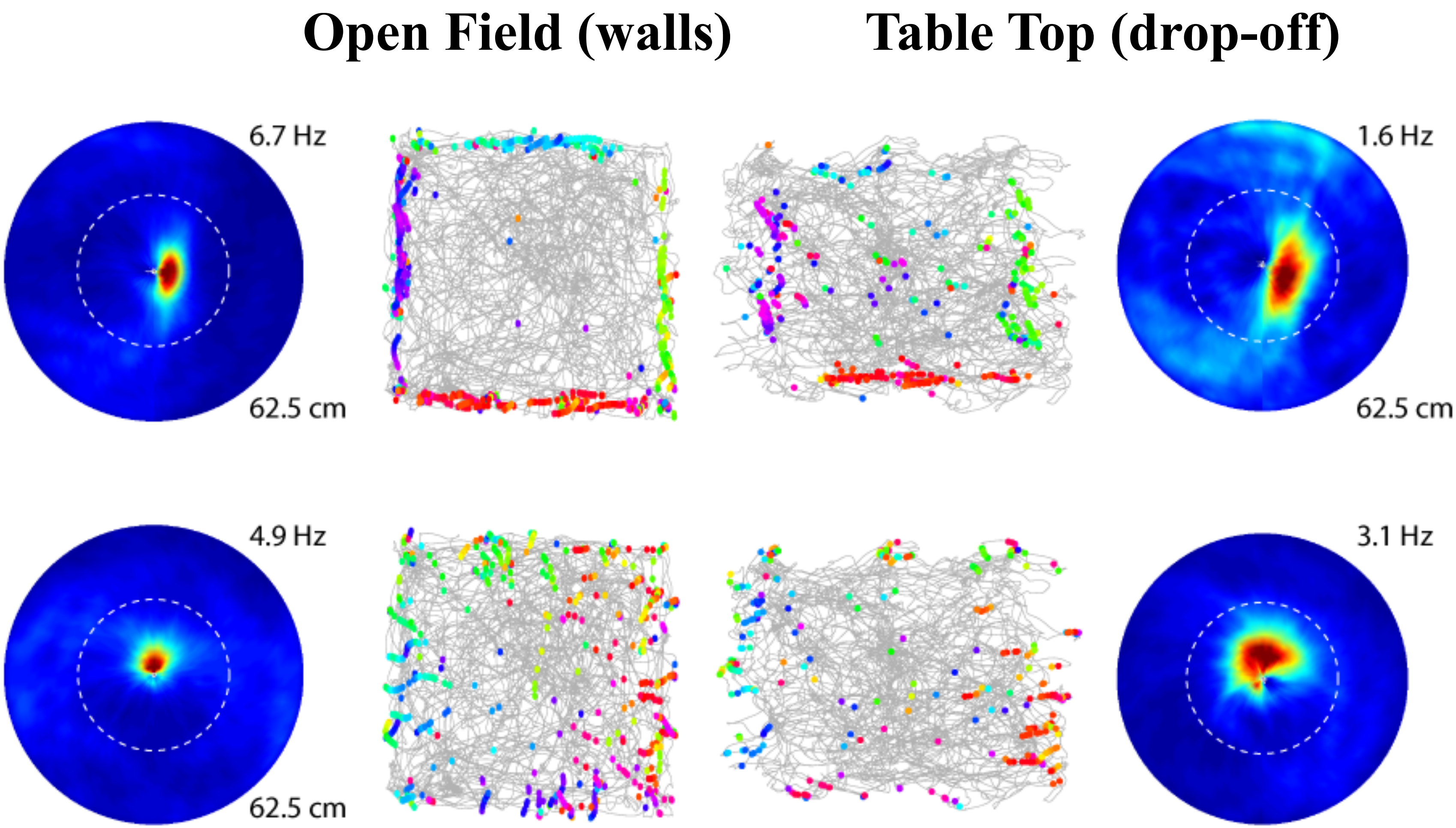
Jake Hinman, SFN 2016, 2017

Stable representation across multiple environments



Jake Hinman, SFN 2016, 2017

EBCs respond similarly to different boundary types



Jake Hinman, SFN 2016, 2017

Translation from egocentric to allocentric spatial representation

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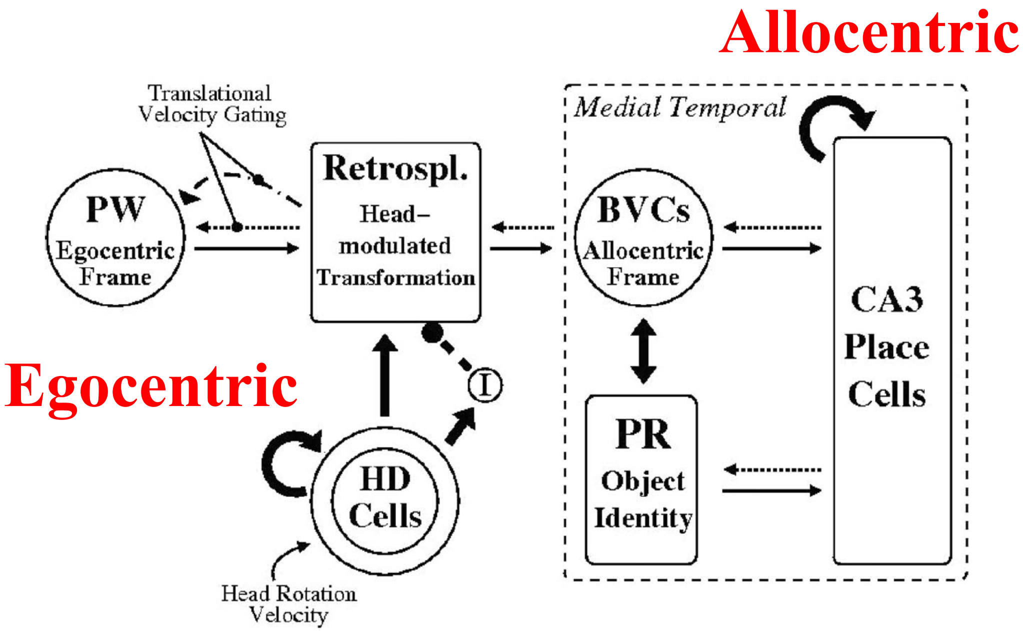

Byrne, Becker, Burgess, *Psychol. Review*, 2007

Talk outline:

1. **Medial septal input important for grid cells and time cells**
2. **Theta cycle skipping and head direction**
3. **Visual coding of environment boundaries**

Questions:

1. What role does theta rhythm play in generation of grid cells, time cells and head direction cells?
2. Why is head direction coded more strongly than movement direction (e.g. stronger influence of sensory input than path integration)?
3. How do neural circuits code position and self-motion from visual feature angle or optic flow?

Hasselmo lab members and alumni:
In vivo – unit (extracellular) recording in awake, behaving rats
Dr. Jake Hinman, Dr. Holger Dannenberg, Dr. Andy Alexander,
Alumni: Dr. Mark Brandon (McGill Univ), Andrew Bogaard (UW), Dr. Jason Climer, Dr. Ehren Newman (Indiana Univ), Dr. Kishan Gupta (UCLA), Dr. Caitlin Monaghan, William Chapman

In vitro - whole cell patch (intracellular) recording in slice preparations
Kim Young, Michael Brown, Alumni: Dr. Lisa Giocomo (Stanford University), Dr. Jim Heys (Northwestern), Dr. Motoharu Yoshida (DZNE Magdeburg),

Computational modeling of grid cell firing, memory-guided behavior and dynamics of cortical structures
Dr. Florian Raudies, Dr. Marianne Bezaire, Alunni: Dr. Vassilis Cutsuridis, Dr. Jason Climer, Dr. Murat Erdem, Dr. Eric Zilli, Dr. Michele Ferrante

Undergraduates:
Chris Libby, Michael Connerney, Stefan Linn, Ron DiTullio, Meghana Sana

Collaborators:
Prof. Howard Eichenbaum, Dr. Ben Kraus – Time cells
Prof. Chantal Stern – functional magnetic resonance imaging