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150115

Neural Maps of Space:
How do we know where we are?

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How do we know where we are?

Knowing where we are is an ability that we often take for granted

How and where does the brain compute position?

What are the elements? How do they interact?

How are distances and directions calculated? Does the brain have a coordinate system? If so, how is it generated?

How do we decide about where to go?

Problem:

The brain is a complex network consisting of almost 100 billion neurons, each with about 10 000 connections

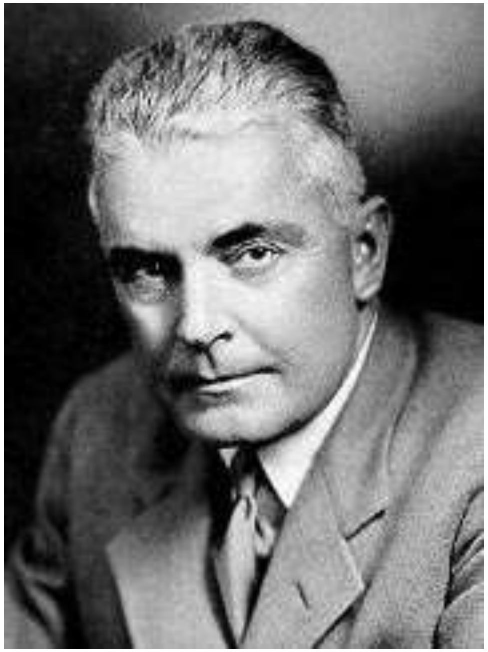
Can we ever understand how neural activity in such a large network gives rise to behavior?

Yes, we are on track.

To understand how the physiology-psychology border has eventually been broken, let us step back almost 100 years

First we needed to determine the <u>laws of behaviour</u>:

Early 1900s: Behaviorism played a significant role in the development of experimental psychology



John B. Watson
(1878-1958)

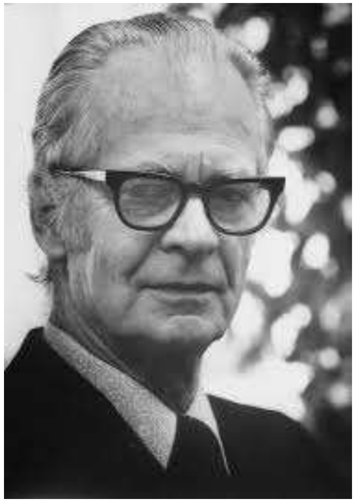
Clark L. Hull
(1984-1952)

Burrhus F. Skinner
(1904-1990)

S-R-S-R-S-R-….

Behaviorists looked for the elements of behavior – described in stimulus-response relationships…

… with considerable success!



B. F. Skinner
(1904-1990)

Using the laws of behavior, Skinner could *get* animals to do almost anything

Pigeons playing ping-pong (BF Skinner Foundation)
https://www.youtube.com/watch?v=vGazyH6fQQ4

But was this too simple? Was it all about stimulus-response relationships?

Edward C. Tolman had a more global view of behavior. He suggested that knowledge is based on **map-like** structures (cognitive maps)

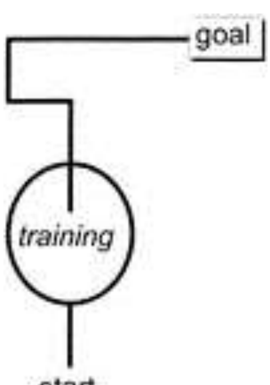
E.C. Tolman (1886-1959)

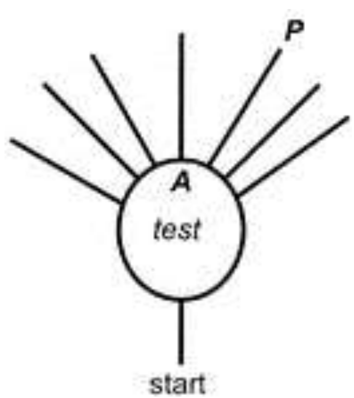
S-S-S-S--....

S-S-S-S-....

S-S-S-S-....

Tolman's shortcut-experiment:



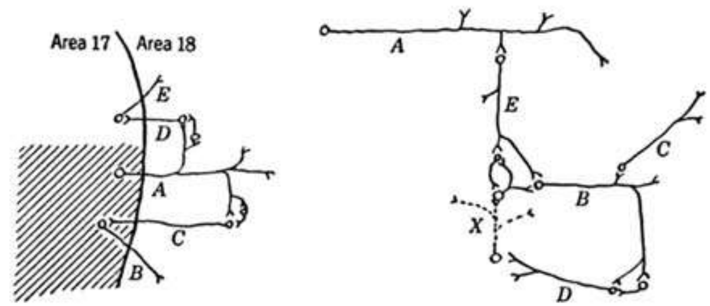


The ability to take shortcuts and detours suggests that information is not stored as pure stimulus-response sequences. Instead Tolman suggested that knowledge is stored in a map-like representation.

How could the brain create such maps – and behaviours?

Karl Spencer Lashley
(1890-1958)

Donald O. Hebb
(1904-1985)



Hebb´s cell assembly concept (1949)

Behaviorists treated the brain as a ´black box´.

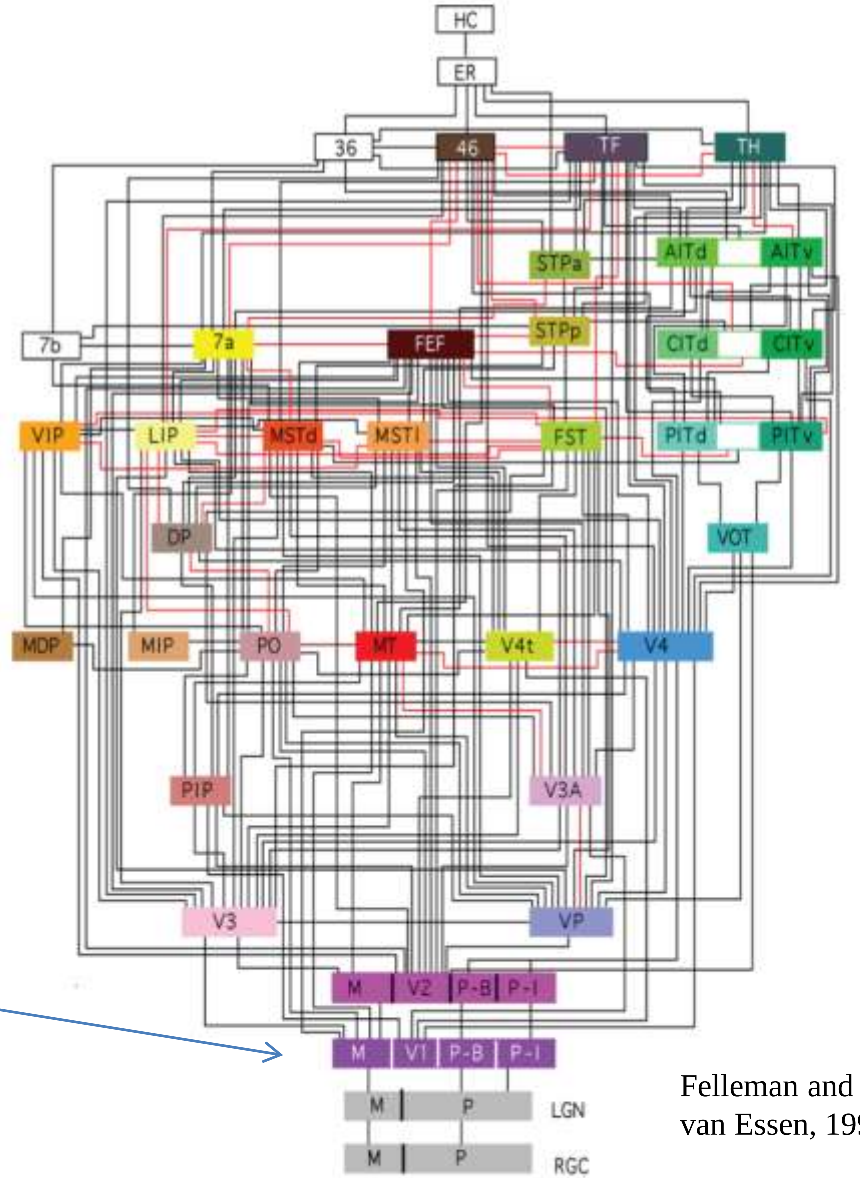
But with Lashley and especially Hebb concepts for a neuroscience of behaviour – that involved the cortex - were introduced.

1959 -: Physiology:

Significant progress towards understanding <u>sensory</u> behaviour was made at the 'low end' of the cortex, near the sensory receptors

J. Wrinn, Harvard Public Affairs

David H. Hubel (1926-2013) and Torsten N. Wiesel (1924)

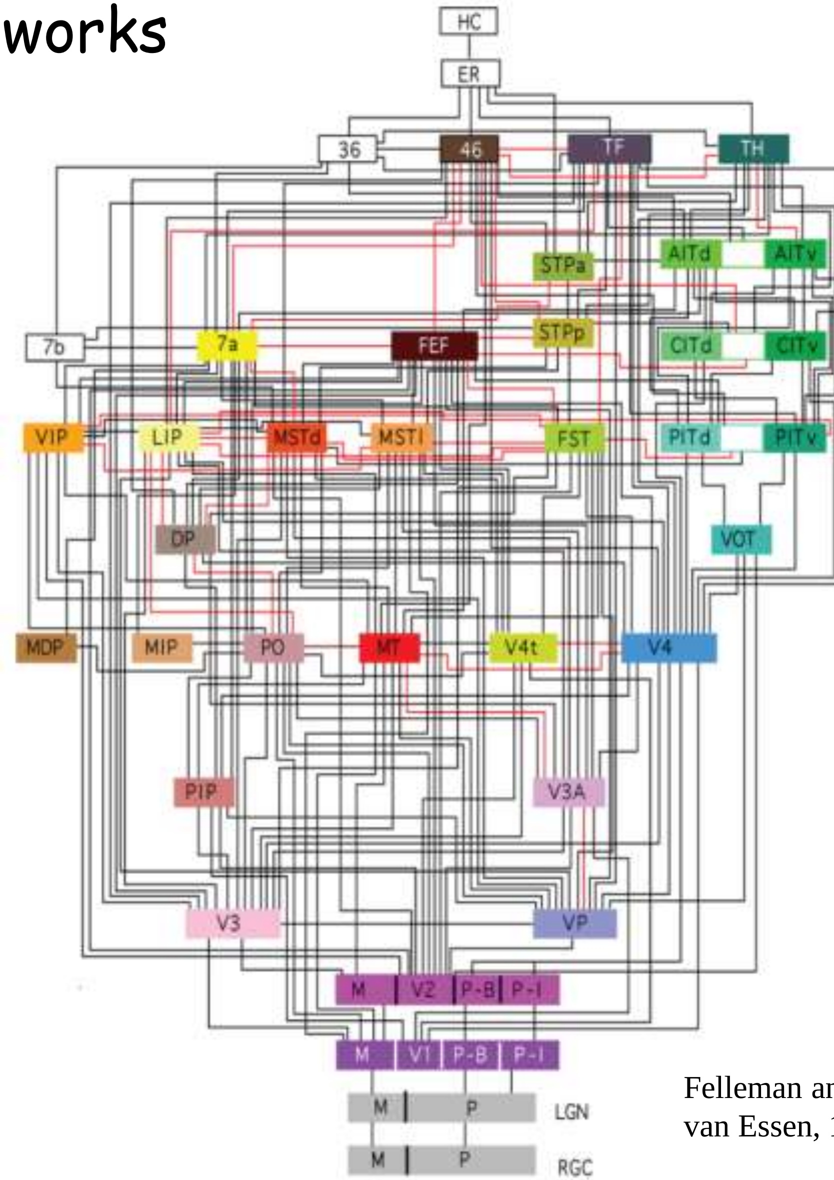


Felleman and van Essen, 1991

Understanding how the cortex works

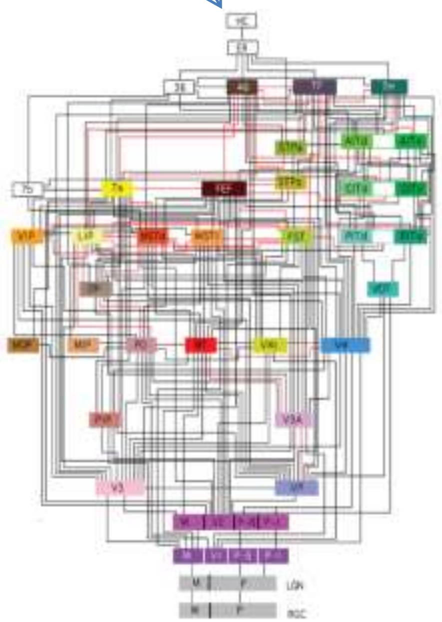
But, more than 50 years later, as we move upwards, clear correlates to the outside world tend to get lost…

Yet, with our training in psychology, the upper levels is what we wanted to understand.



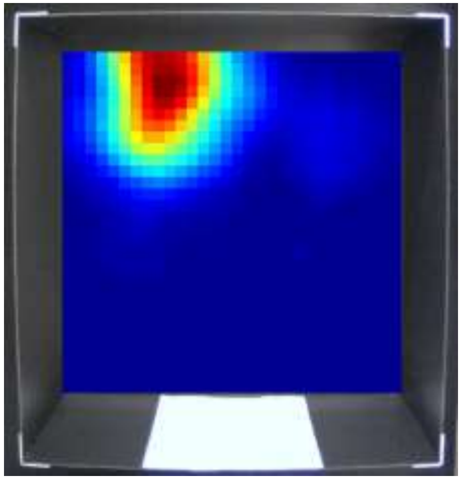
Felleman and van Essen, 1991

There are a few exceptions to the lack of external correlations, one of which is the neural circuitry for space



The hippocampus contains place cells (O´Keefe and Dostrovsky, 1971).

Their firing is clearly related to a property of the outside world – the animal´s location.

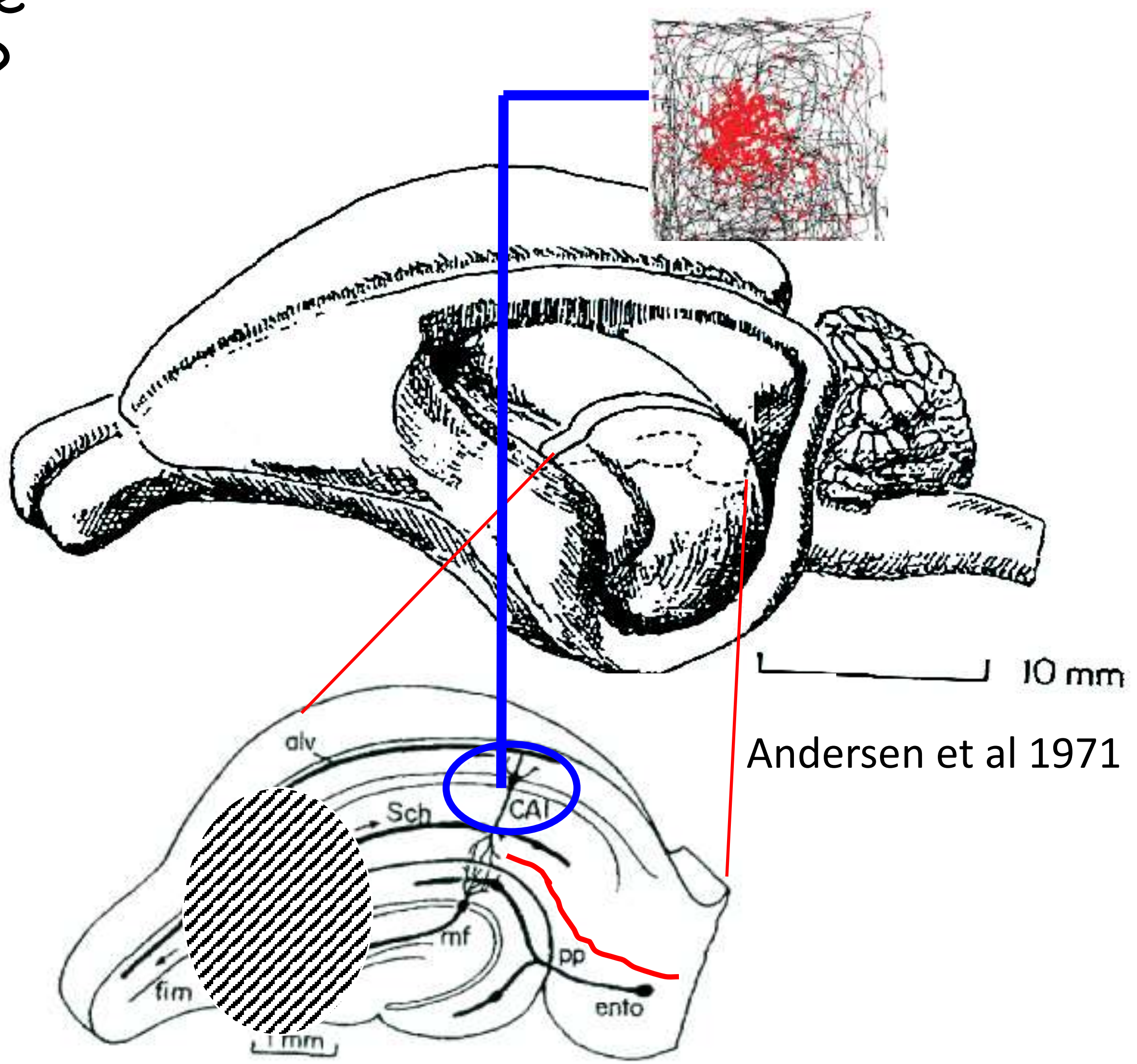


The Hippocampus as a Tolmanian Cognitive Map

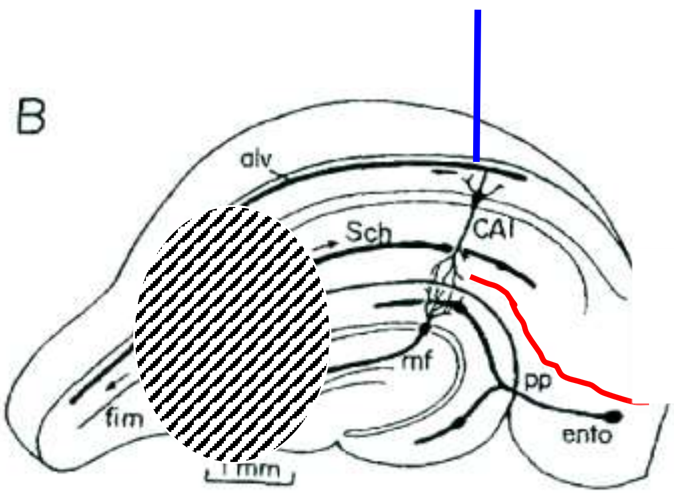
Trondheim 1996-:

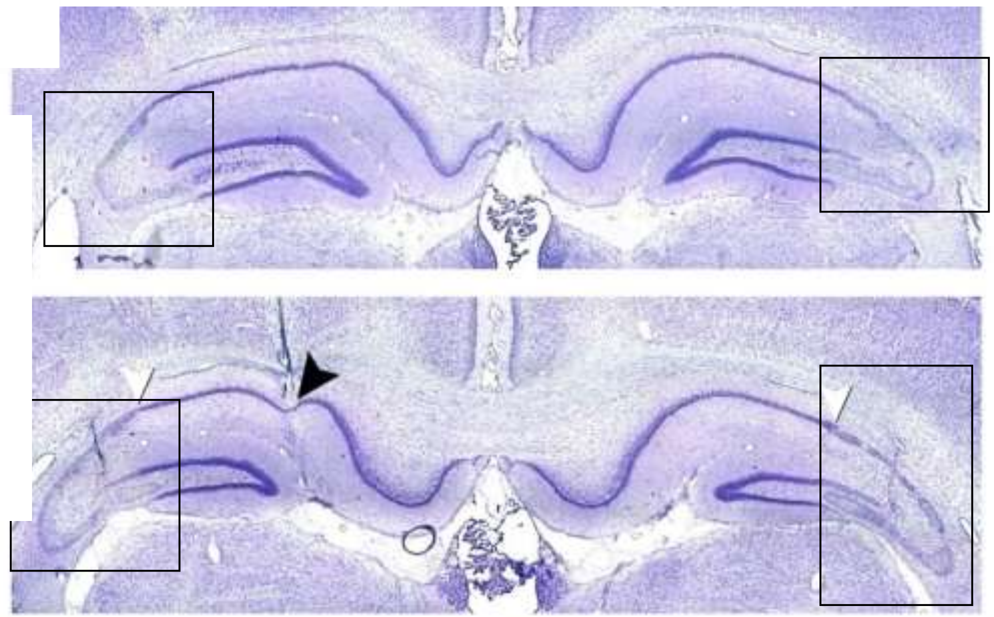
Where and how was the place signal generated?

The hippocampus:

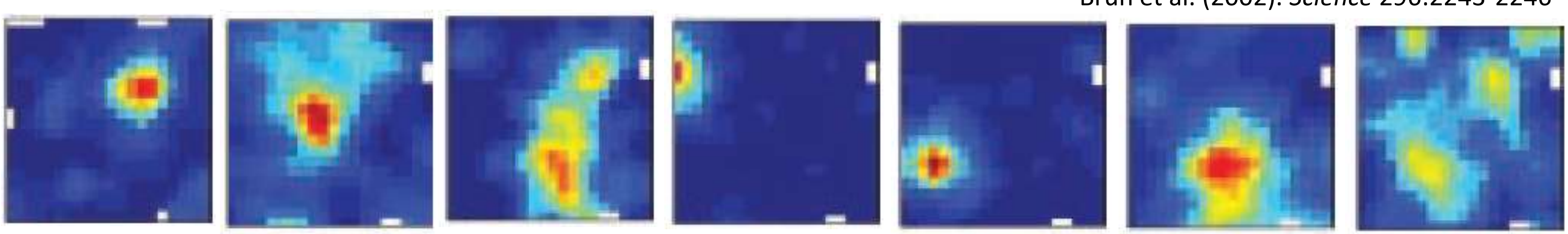


CA1 cells continued to express place fields after lesion of the intrinsic hippocampal pathway, suggesting that the source of the place signal is external





Brun et al. (2002). *Science* 296:2243-2246

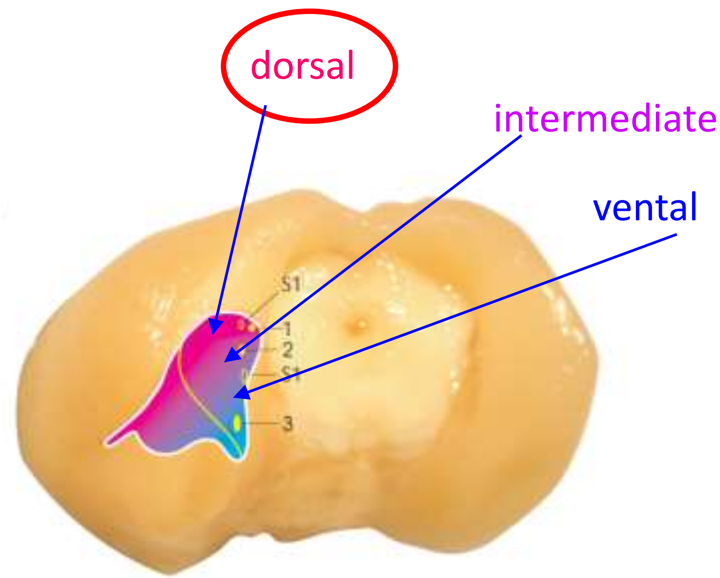


Best candidate: the entorhinal cortex

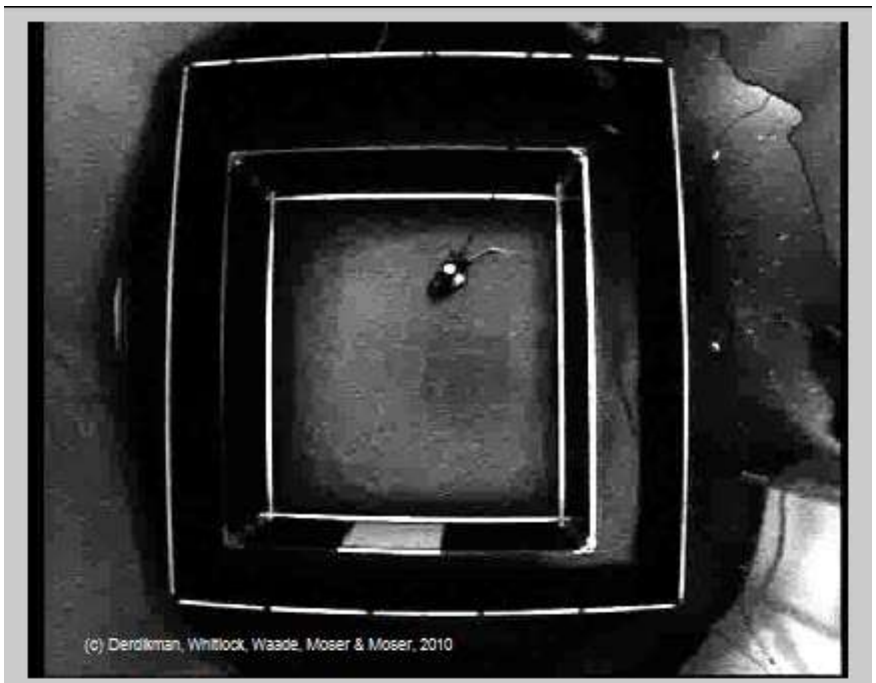
Moving out of the hippocampus

We recorded from **dorsal medial entorhinal cortex**, which provides the strongest input to the dorsal hippocampus where the place cells were found

Entorhinal cortex of a rat brain (seen from behind):



Fyhn et al. (2004). *Science* 305:1258-1264

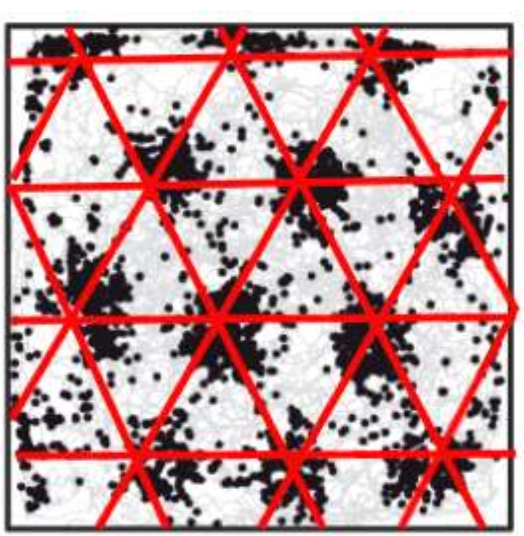


Entorhinal cells had multiple fields and the fields exhibited a regular pattern. But what was the pattern?

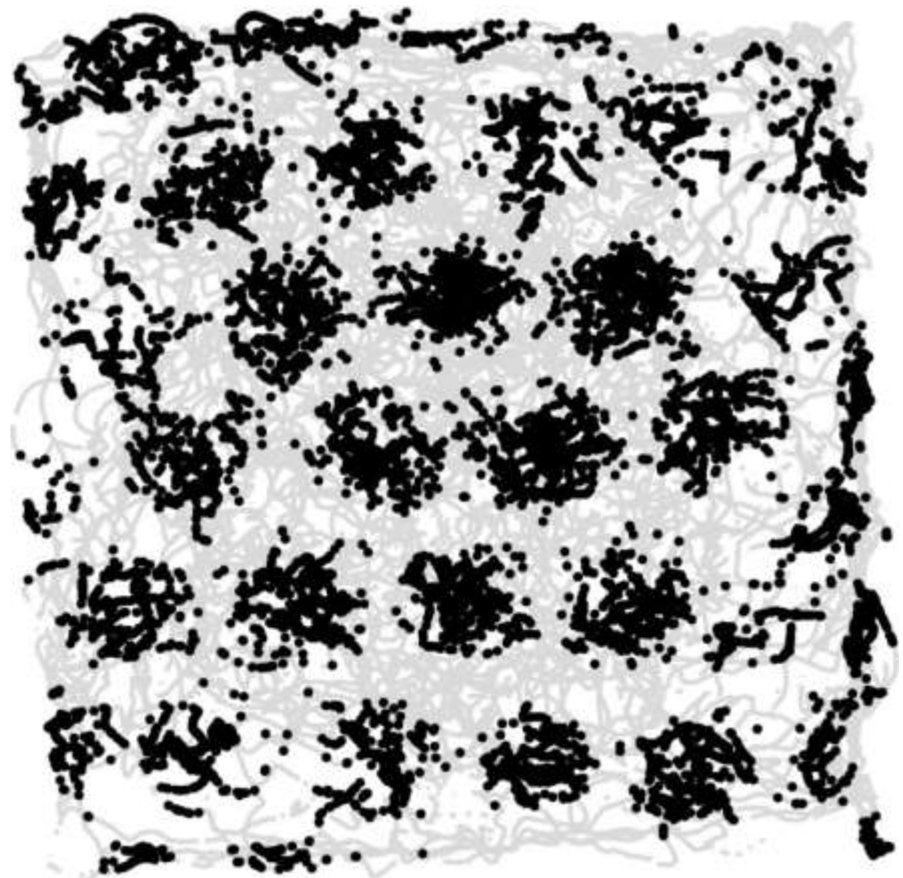
Entorhinal cells had spatial fields with a periodic hexagonal (triangular) structure

The fields formed a grid that covered the entire space available to the animal.

We called them grid cells



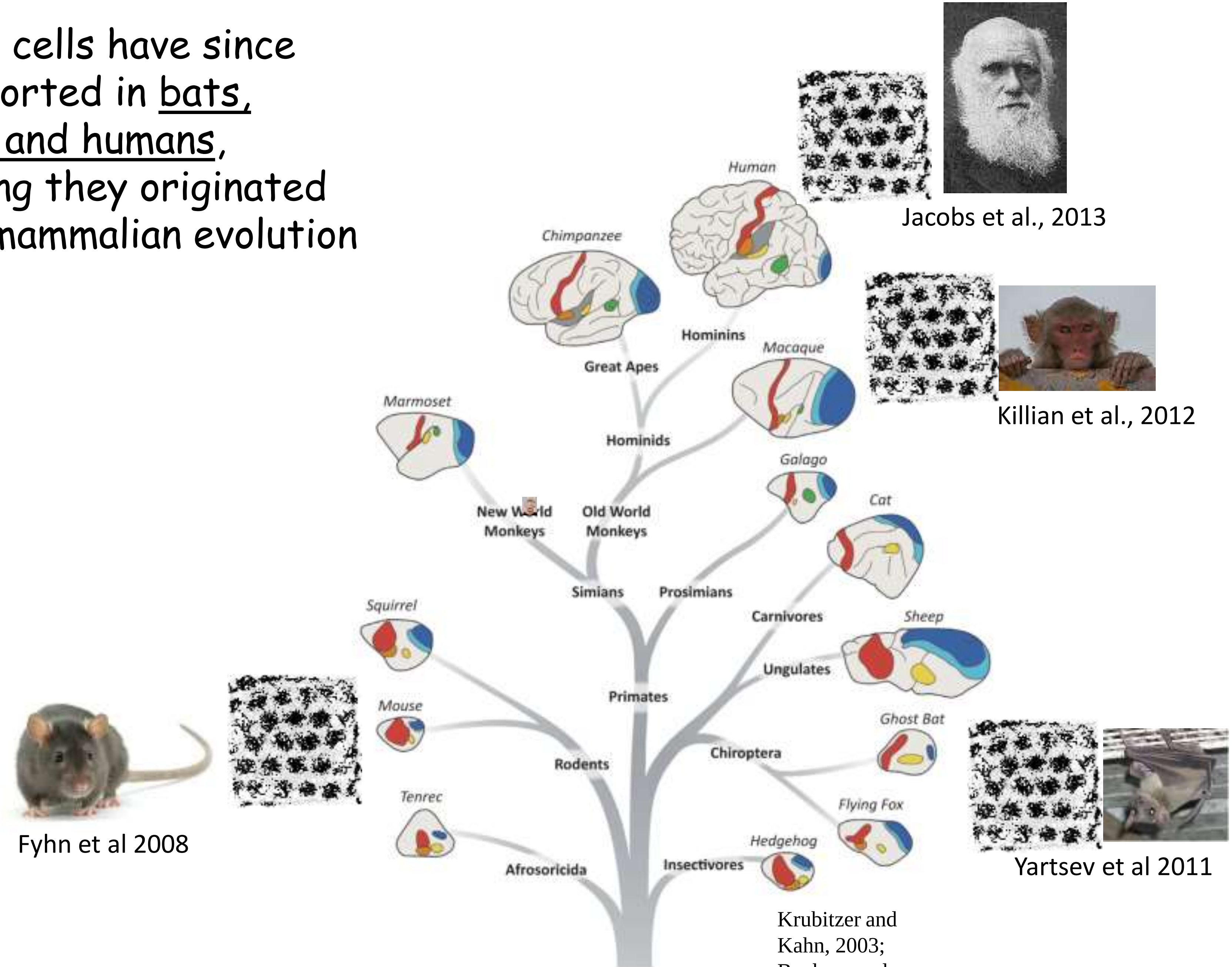
Hafting et al. (2005). *Nature* 436:801-806



220 cm wide box

Stensola et al. *Nature*, 492, 72-78 (2012)

Grid-like cells have since been reported in <u>bats, monkeys and humans</u>, suggesting they originated early in mammalian evolution



Jacobs et al., 2013

Killian et al., 2012

Yartsev et al 2011

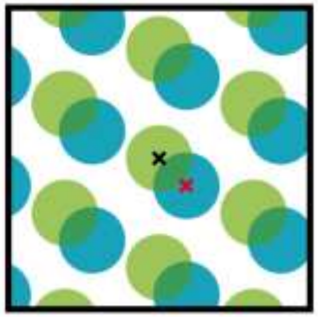
Fyhn et al 2008

Krubitzer and Kahn, 2003; Buckner and Krienen, 2013

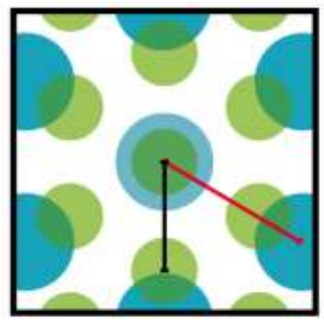
How are grid cells mapped onto the brain?

Grid cells have at least three dimensions of variation

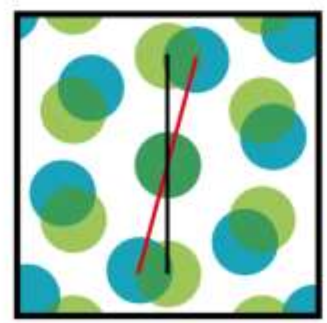
1. Phase



2. Scale

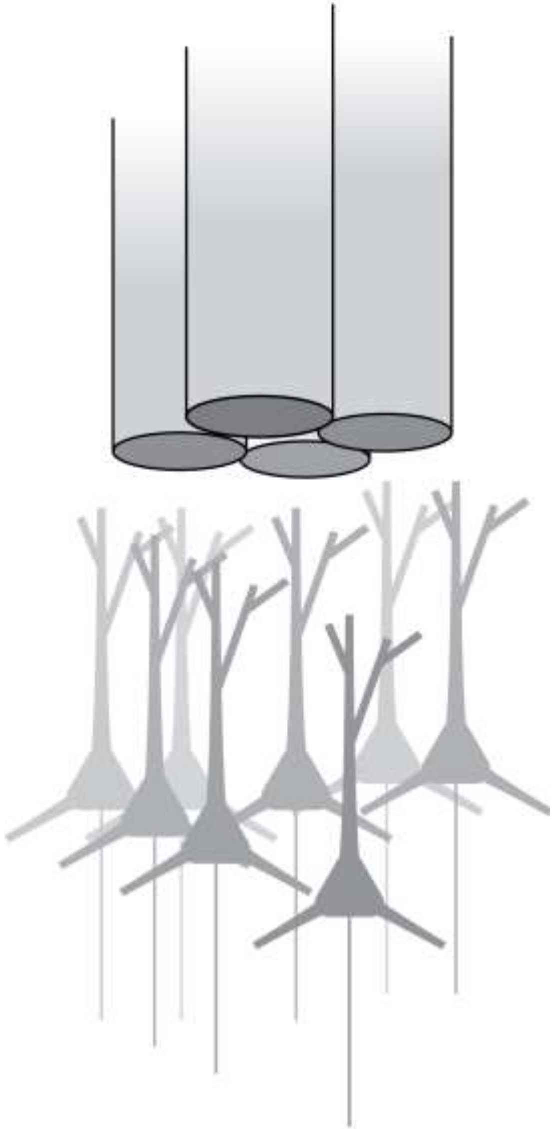


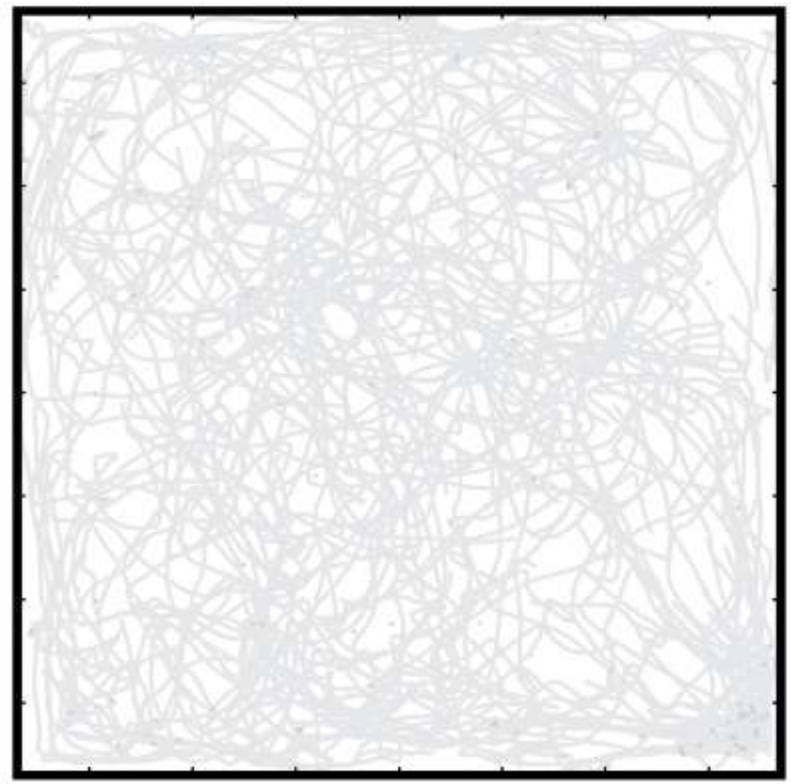
3. Orientation



Phase, scale and orientation may vary between grid cells. How are these variations expressed in cortical space?

1. Grid phase (x, y-locations) is distributed:
All phases are represented within a small cell clusters





Hafting et al. (2005). *Nature* 436:801-806
(cell from Stensola et al 2012)

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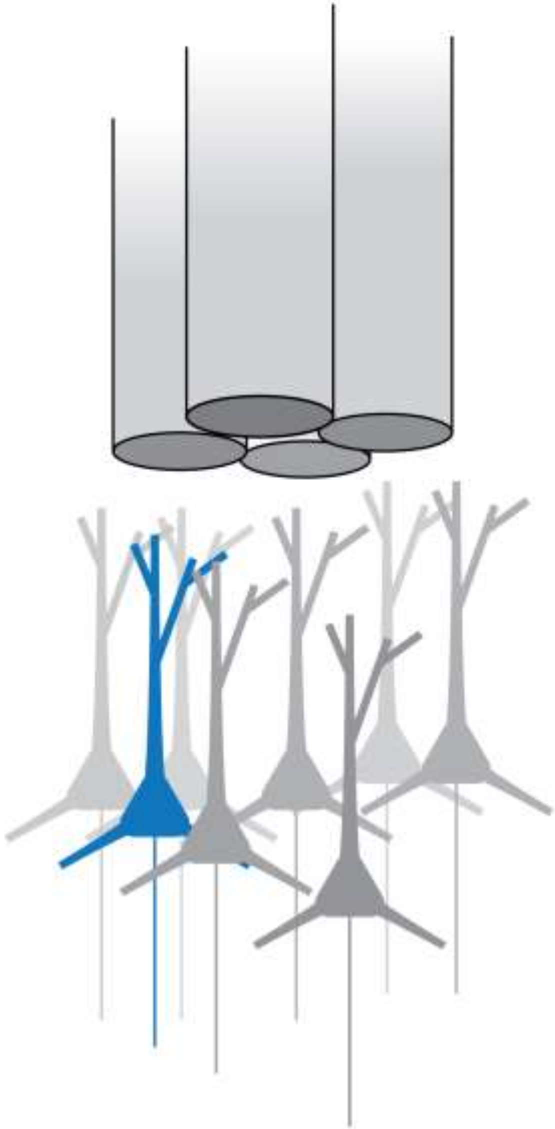

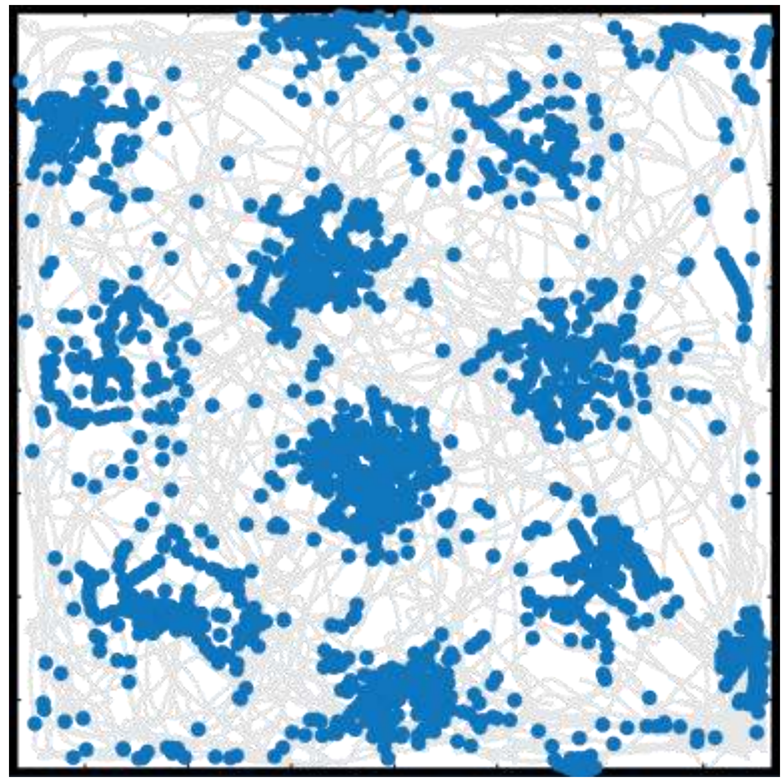

Hafting et al. (2005). *Nature* 436:801-806
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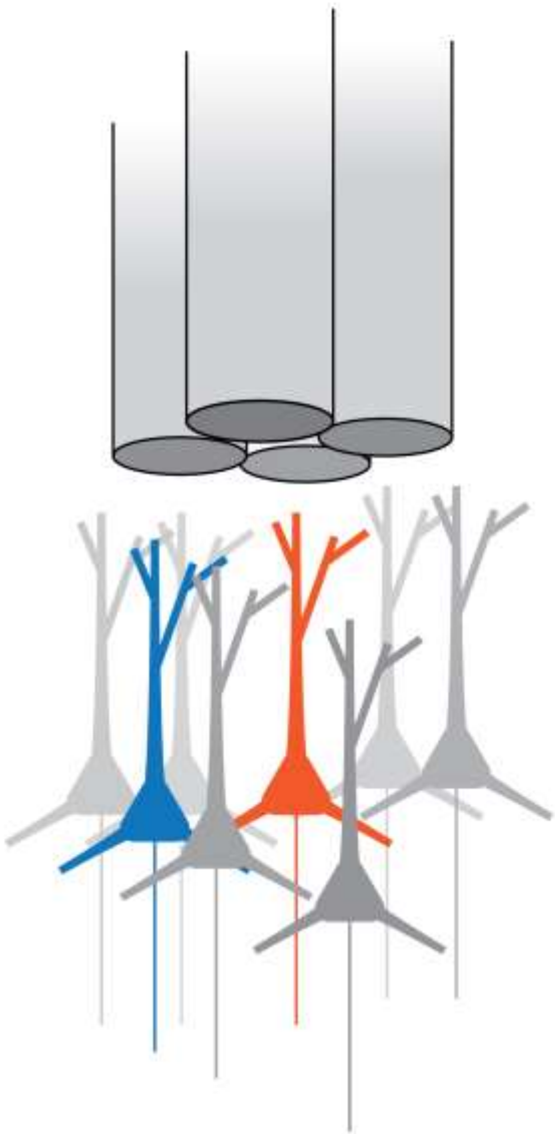

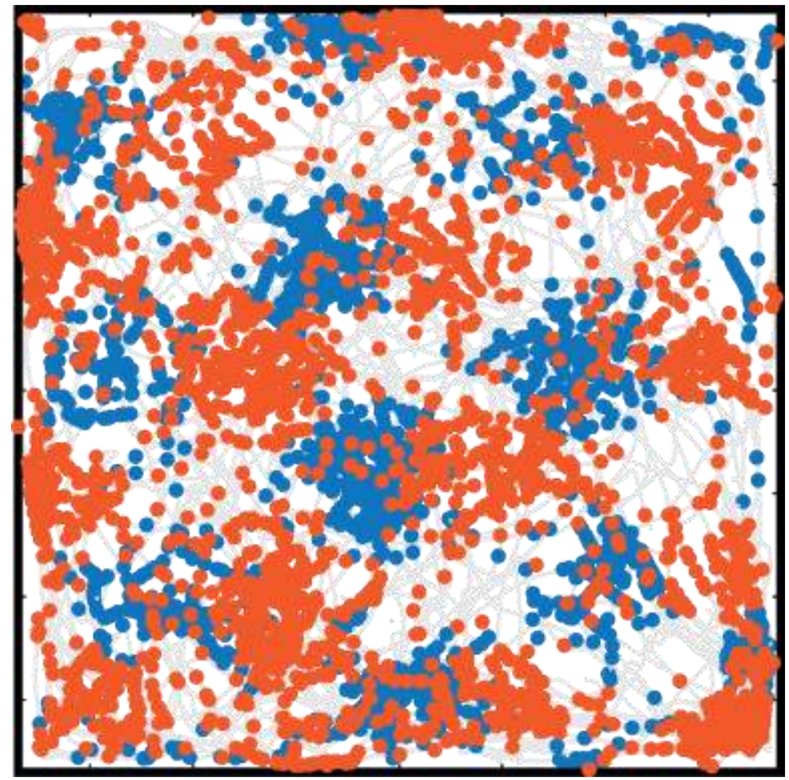

Hafting et al. (2005). *Nature* 436:801-806
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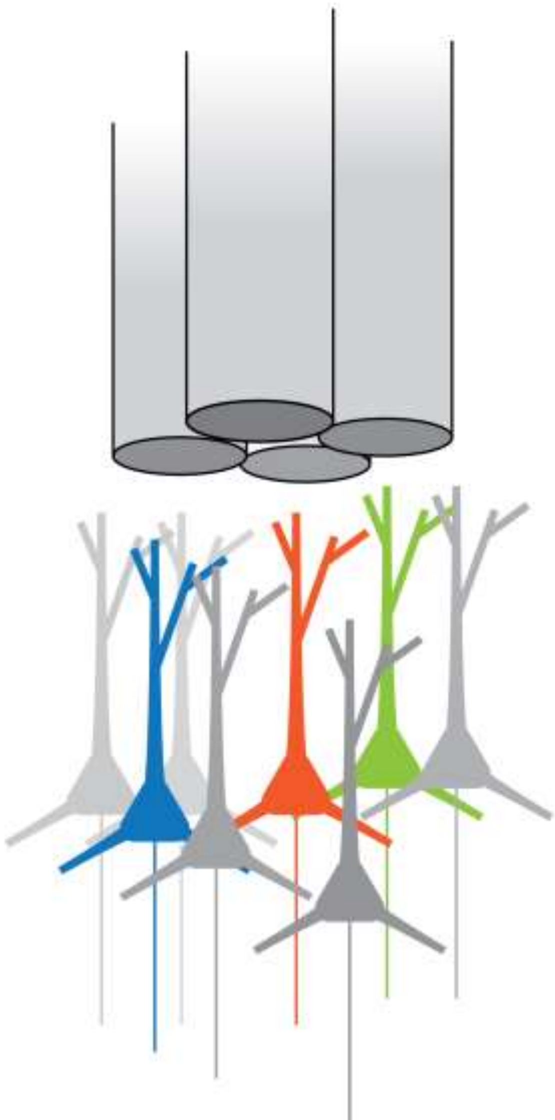
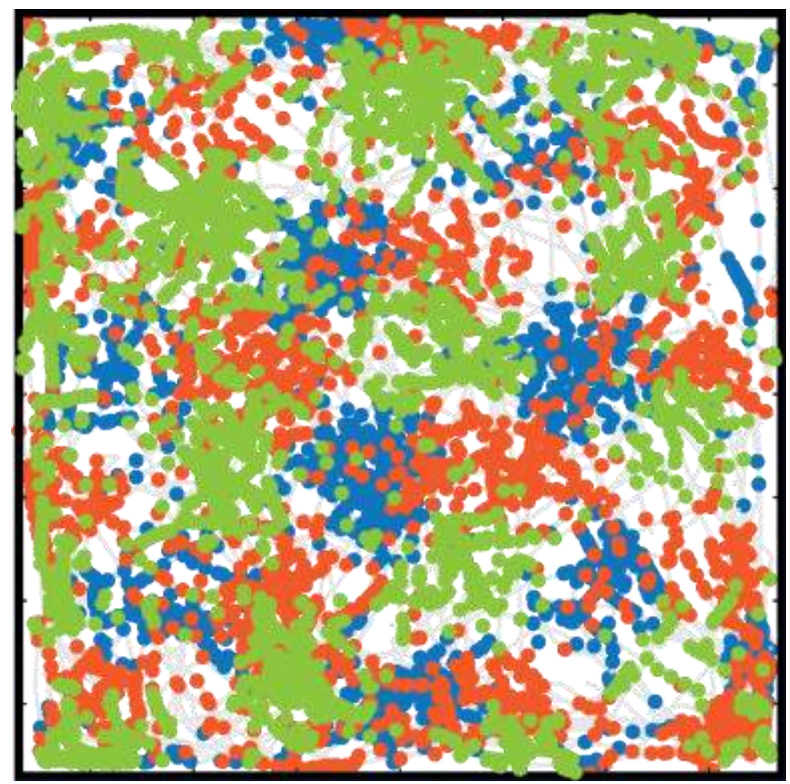
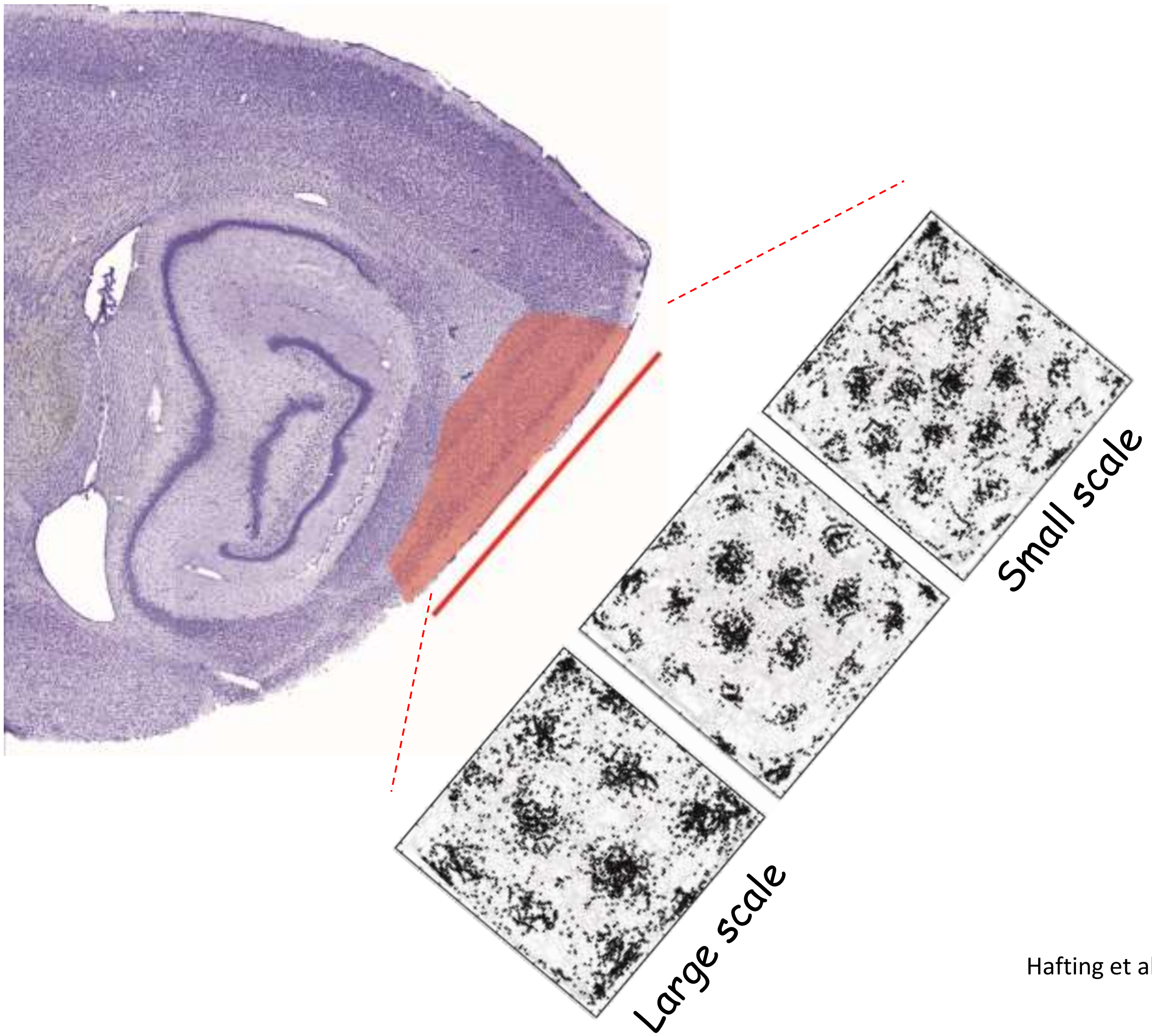




Hafting et al. (2005). *Nature* 436:801-806
(cell from Stensola et al 2012)

… similar to the salt-and-pepper organization of many other cortical representations (orientation selectivity in rodents, odours, place cells)

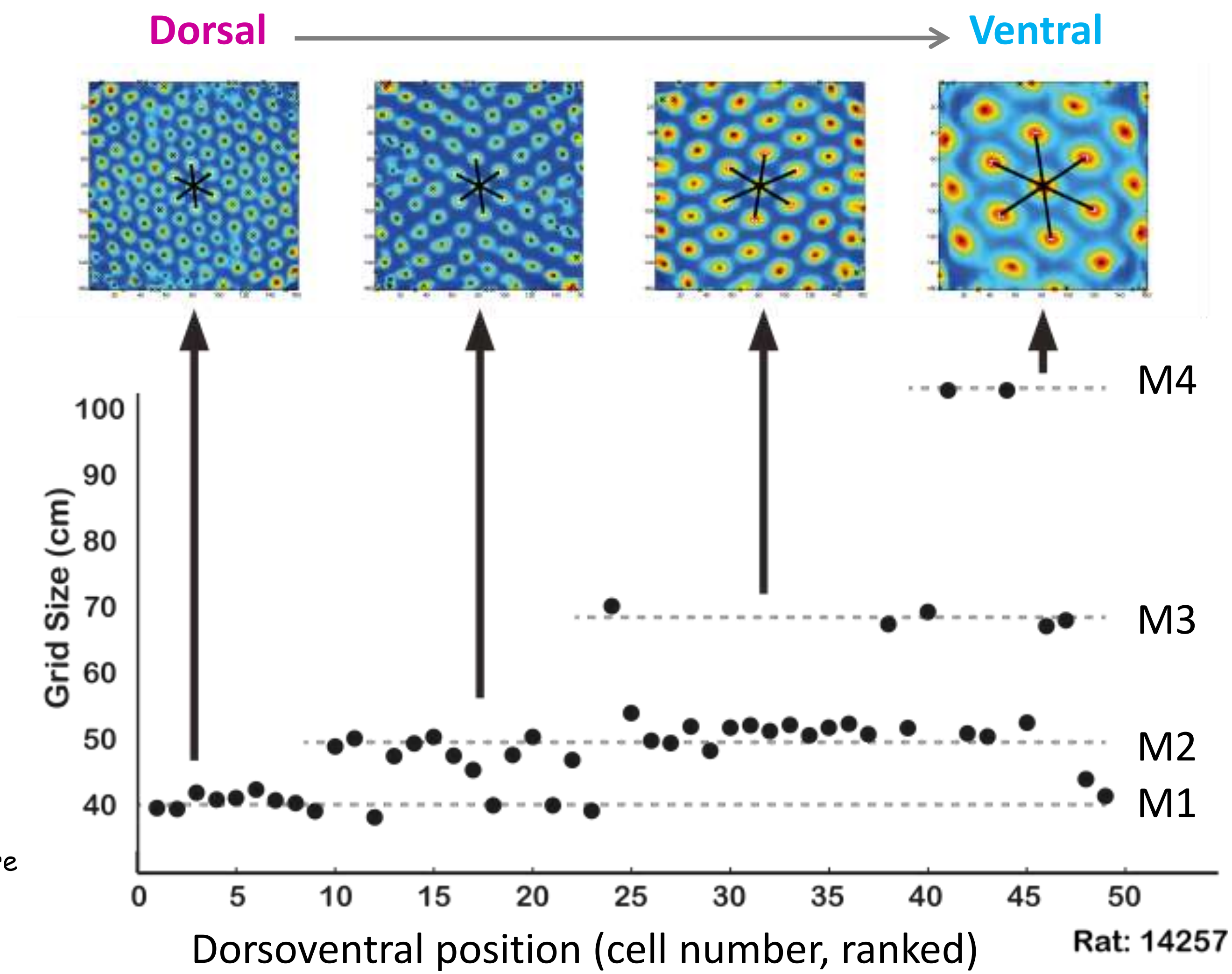
2. The scale (spacing) of the grid cells follows a dorso-ventral topograhical organization



Hafting et al. (2005). *Nature* 436:801-806

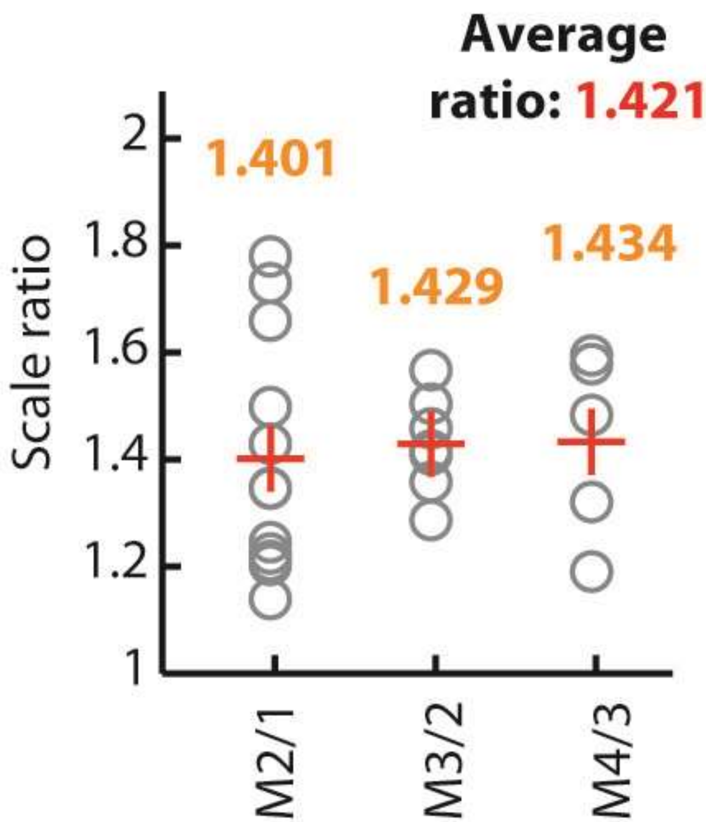
The steps in grid spacing are discrete, suggesting that grid cells are organized in modules

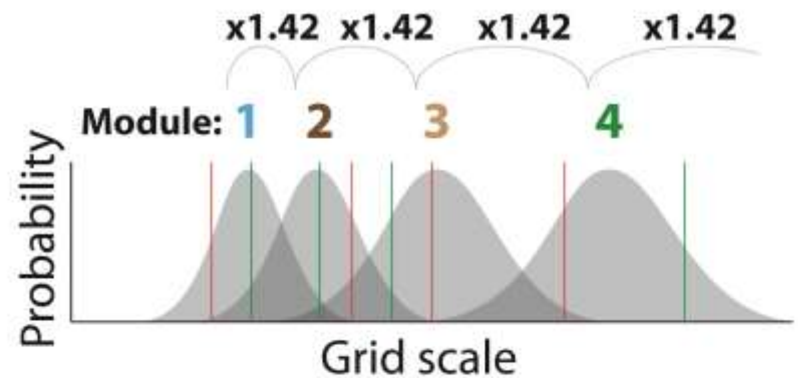
Modules were identified by a **k-means clustering** procedure



Stensola et al. *Nature*, 492, 72-78 (2012)

The average scale ratio of successive modules is constant, i.e. grid scale increases as in a geometric progression



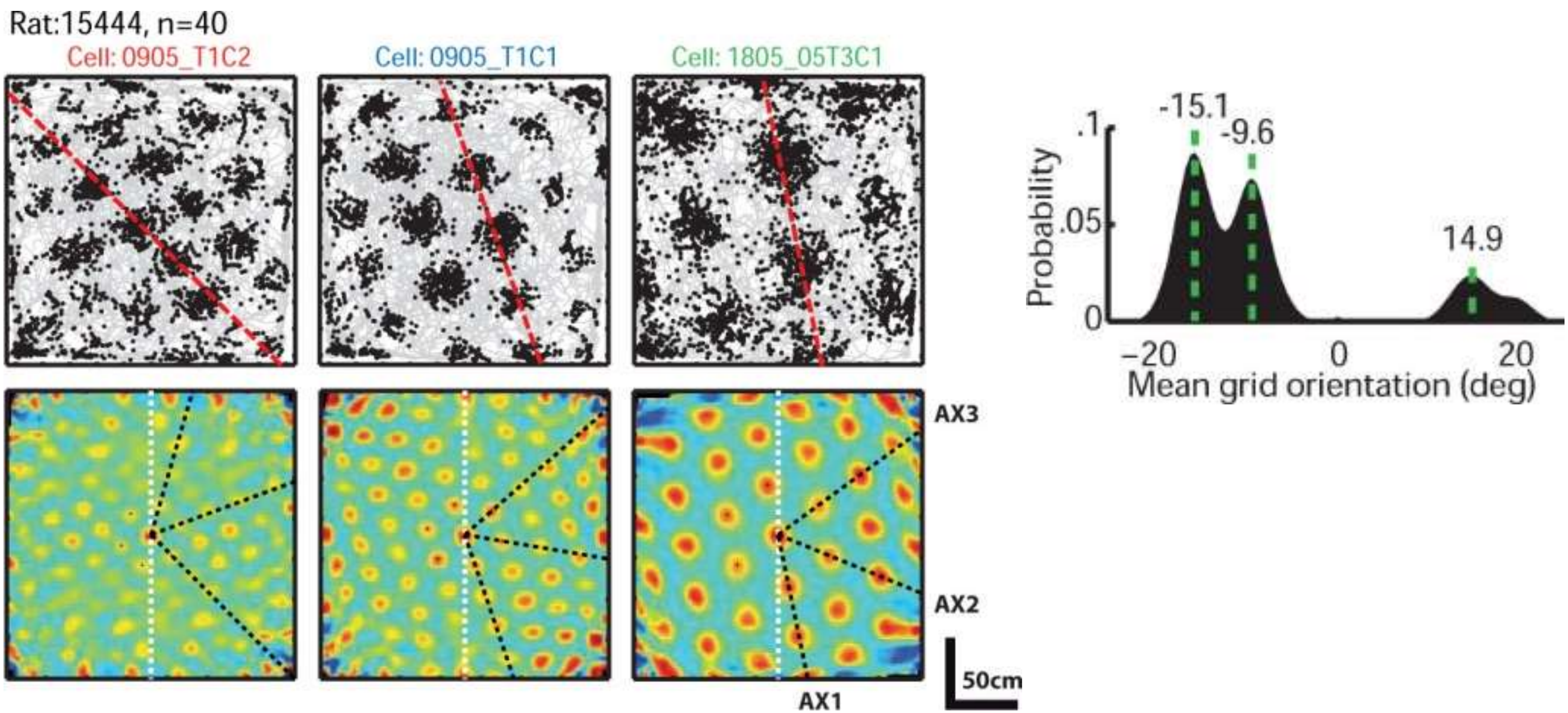


Although the set point is different for different animals, modules scale up, on average, by a factor of ~1.42 (sqrt 2).

Stensola et al. *Nature*, 492, 72-78 (2012)

A geometric progression may be the optimal way to represent the environment at high resolution with a minimum number of cells (Mathis et al., 2012).

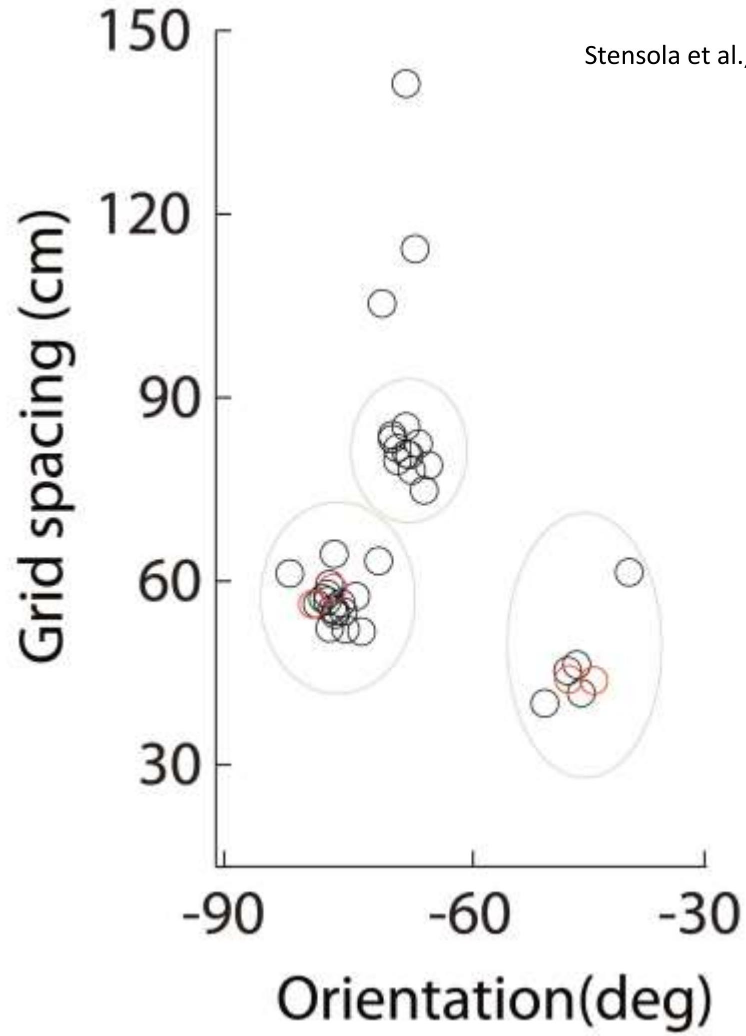
3. Multisite recordings also showed that individual animals have more than one grid orientation…



Stensola, Stensola, Solstad, Frøland, Moser, Moser, *Nature*, 492, 72-78 (2012)

… and that grid-orientation is co-modular with grid scale (i.e. scale modules and orientation modules have shared boundaries)

Example animal:

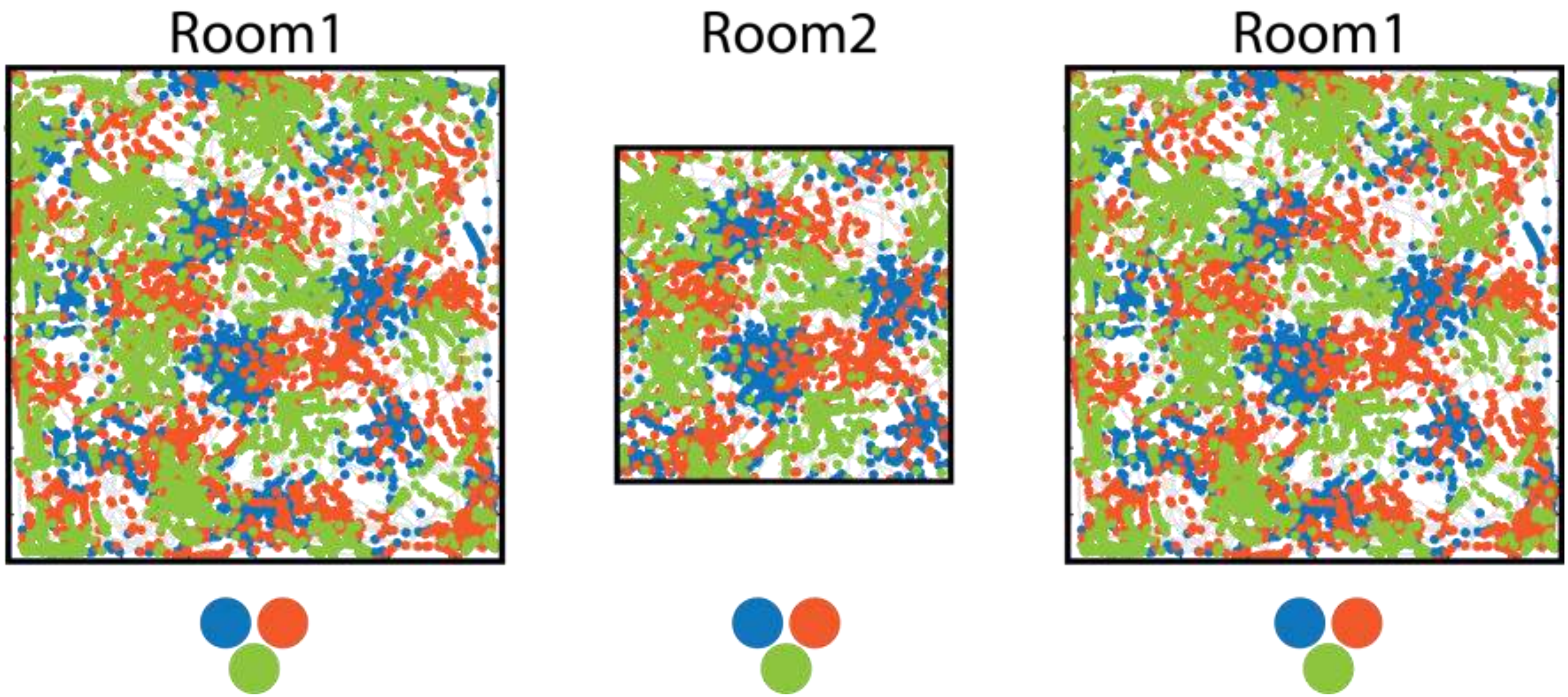


Stensola et al., *Nature*, 492, 72-78 (2012)

Grid modules responded independently to changes in the geometry of the environment.

How similar are grid maps in different environments?

Within modules, the grid map is rigid and universal:
Scale, orientation and phase relationships are preserved

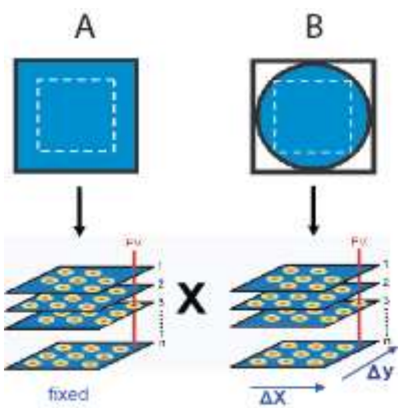


Fyhn et al (2007). *Nature* 446:190-194

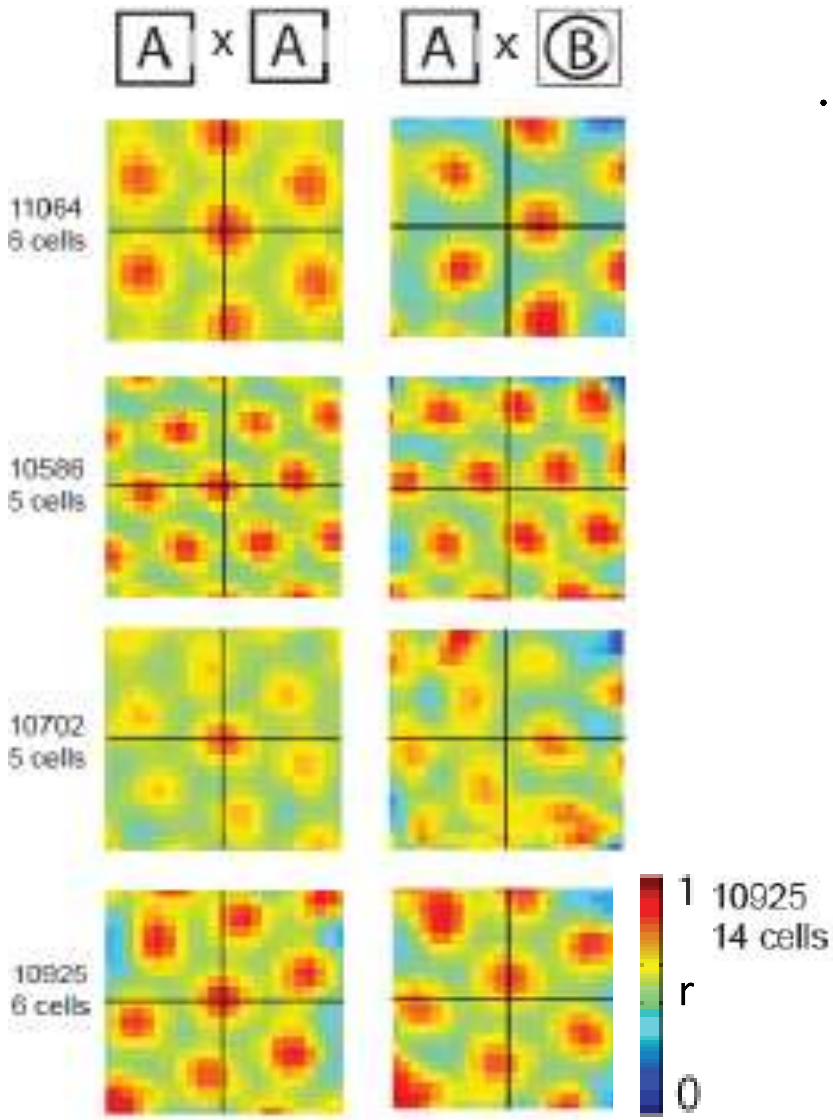
Stensola et al (2012). *Nature* 492:72-78

Grid maps: Scale, orientation and phase relationships are preserved across environments

Entorhinal cortex



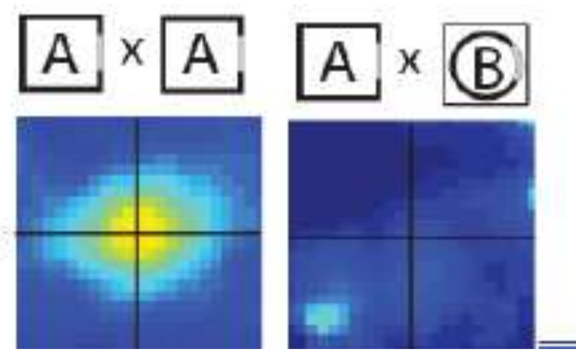
Crosscorrelation of assembly of rate maps: pattern is preserved
– just shifted



Fyhn et al. (2007). *Nature* 446:190-194.

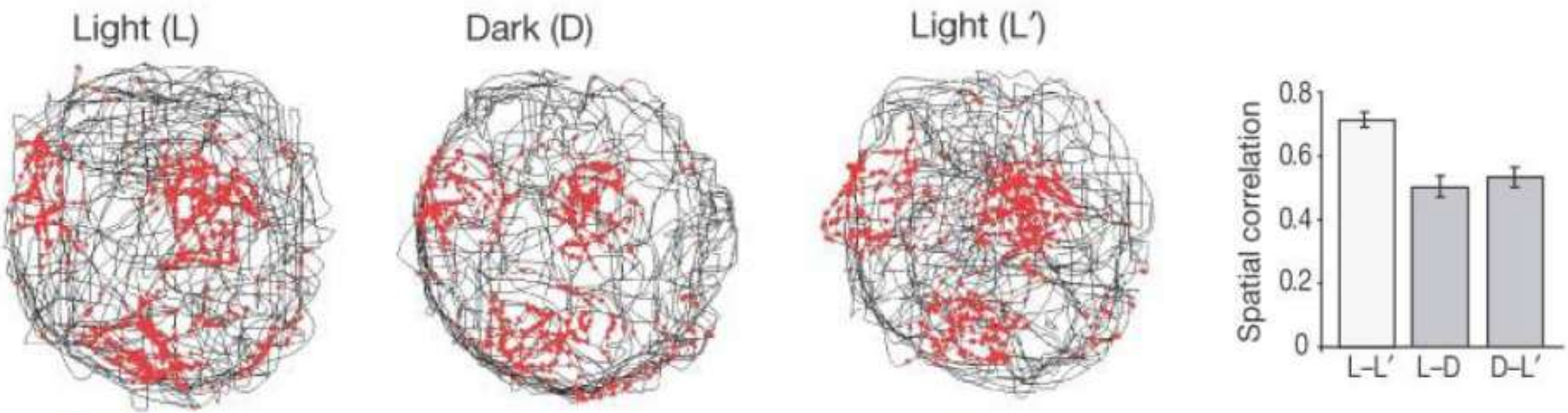
.... <u>in sharp contrast to the place-cell map</u> of the hippocampus, which can remap completely (Muller/Kubie 1987)

Hippocampus (CA3):



What determines the firing locations of a grid cell?

Grid fields persist in complete darkness…..



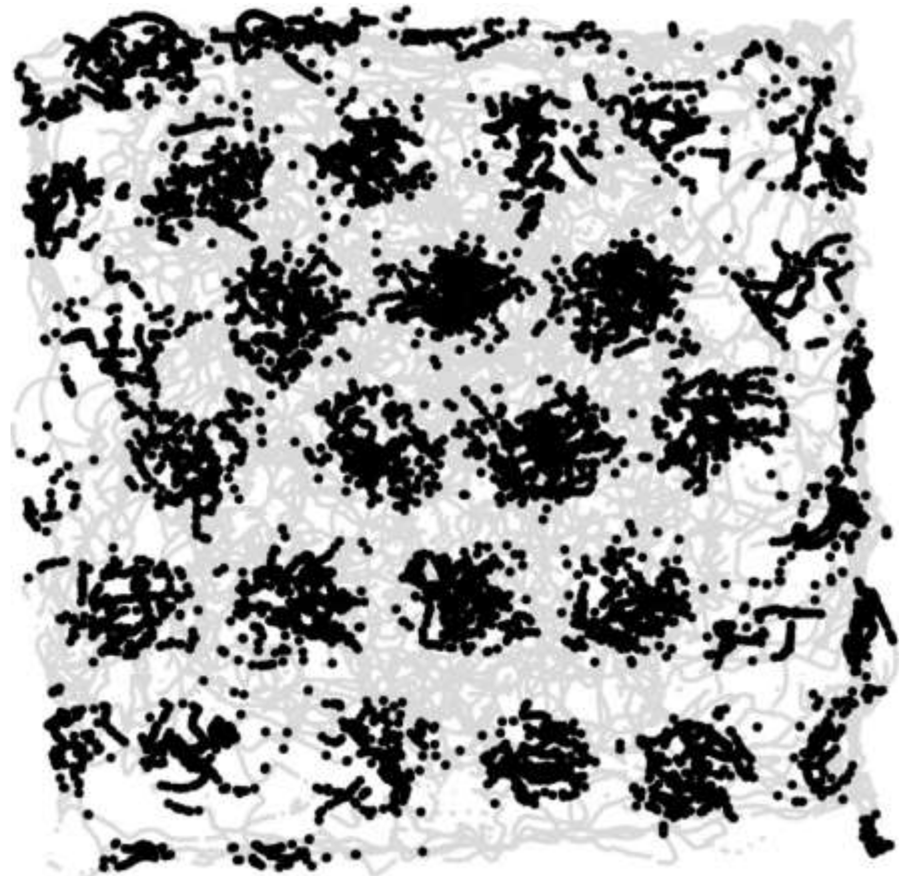
Hafting et al. (2005). *Nature* 436:801-806

… ruling out visual inputs as a necessary contributor to the grid pattern

The hexagonal firing pattern is maintained despite continuous changes in speed and direction

Grid cells are thought to be part of a path integration system where distance is computed from changes in speed and direction over time,

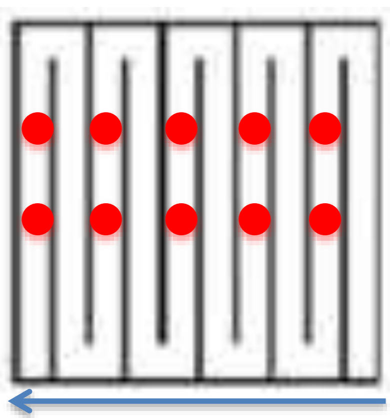
i.e. a key sensory input is thought to be proprioceptive (perception of self-motion).

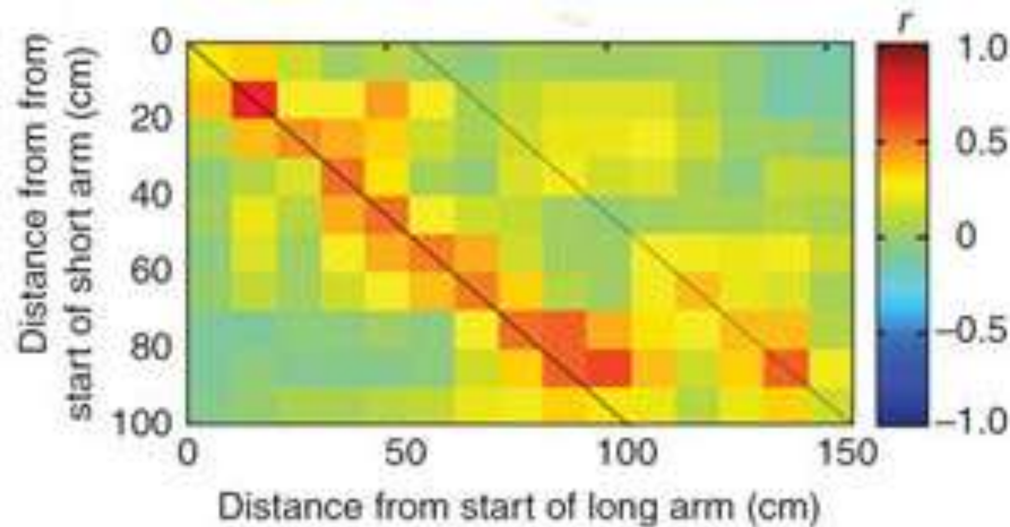


Evidence for path integration: Grid fields are determined by the distance walked from key landmarks rather than the position of the landmarks themselves

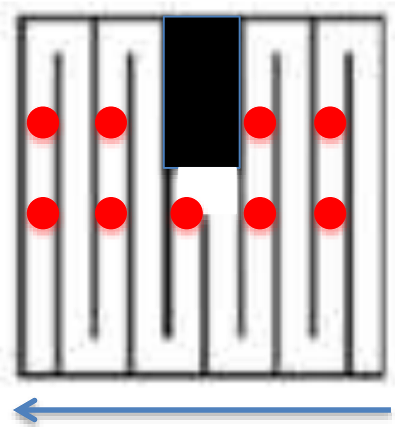
Hairpin maze:

Derdikman et al., (2009). Nature Neurosci. 12, 1325-1332

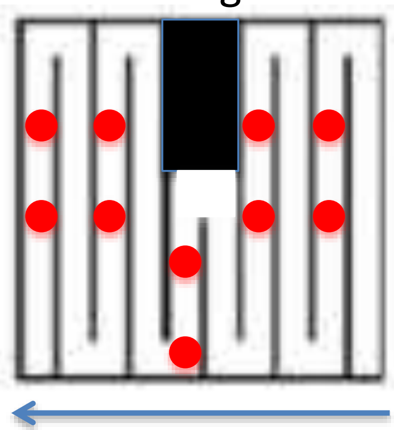


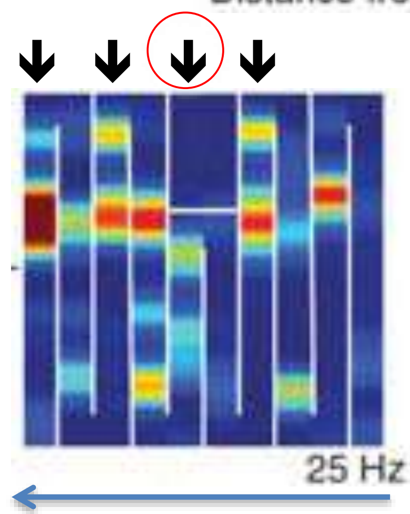


Distal landmarks



Path integration

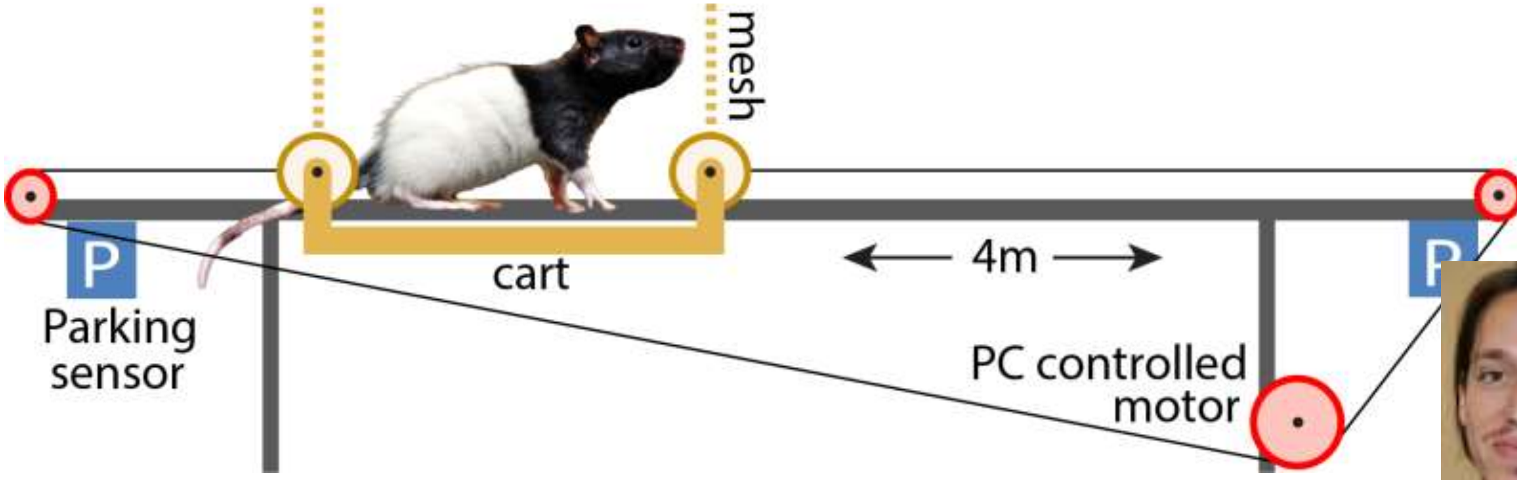




But: Path integration <u>requires accurate (preferrably linear) representation of instantaneous running speed</u>. Not found so far..

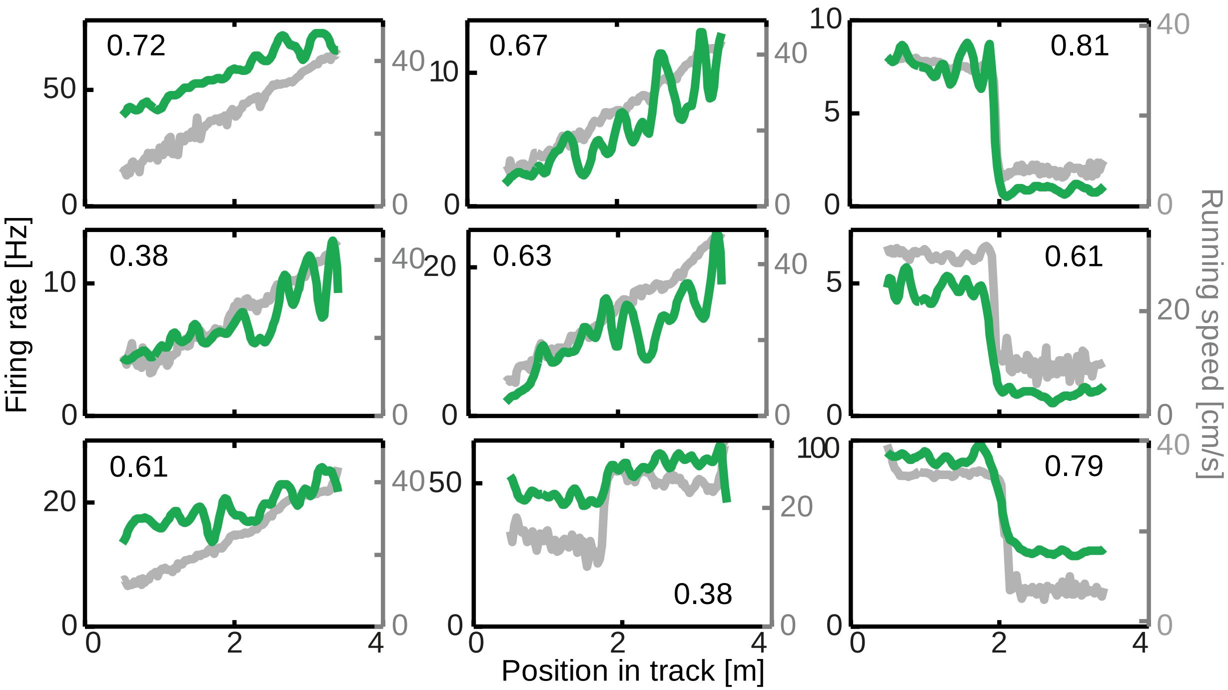
So is there a speed signal in the grid-cell network?

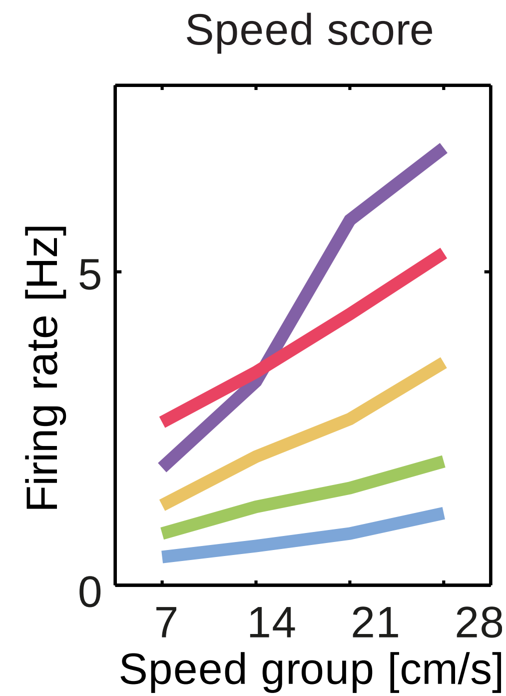
To search for speed cells, we made a Flintstone car to enable control of the rat's running speed.

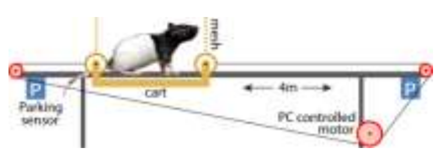


Emilio Kropff et al., unpublished

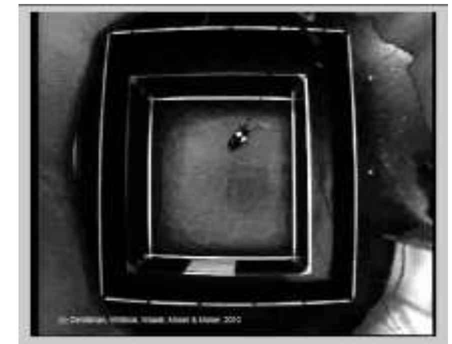
Grid cells were found to intermingle with a separate population of speed cells – cells with firing rates that linearly followed the animal's running speed

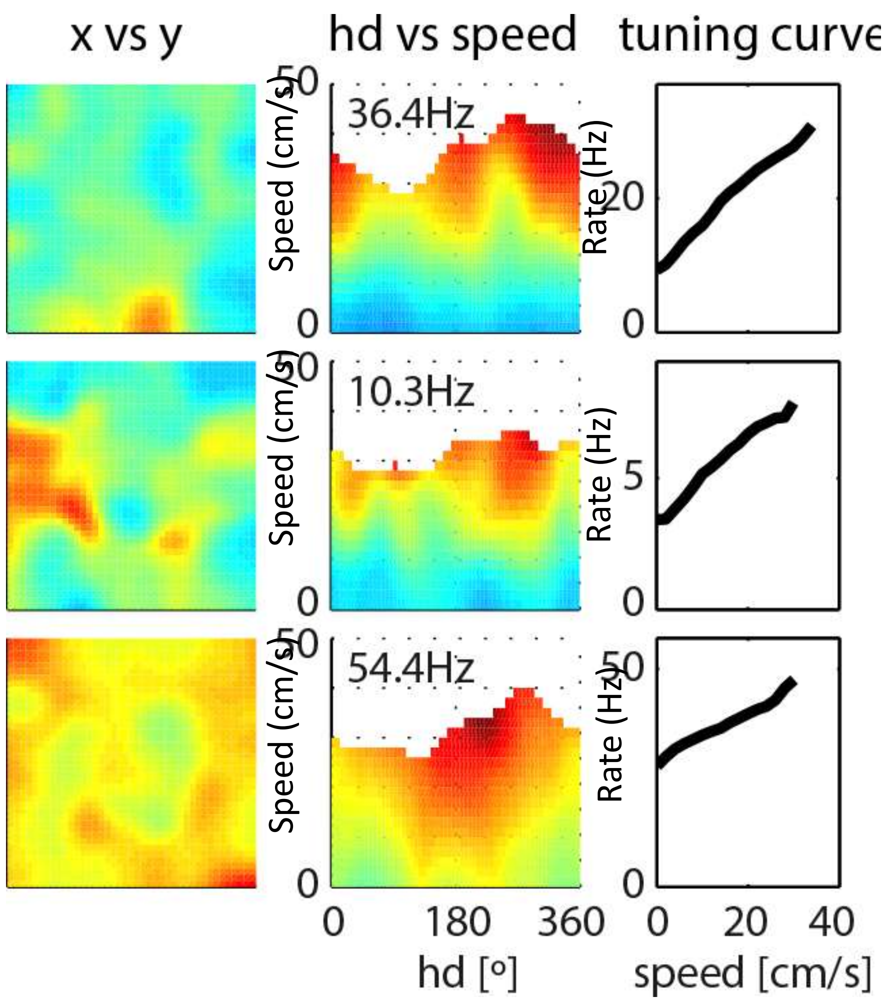




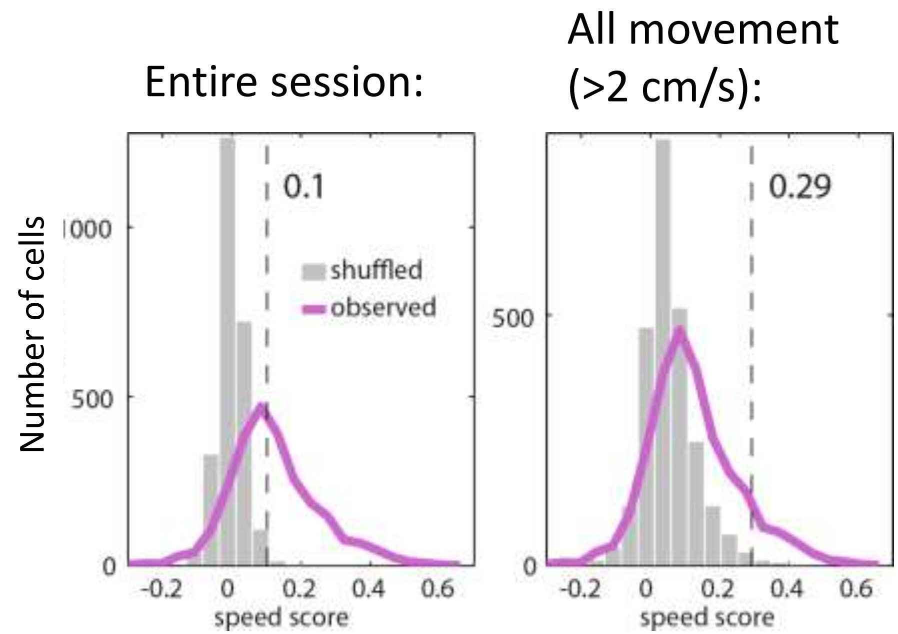


Speed cells were abundant also in standard open environments.
Speed cells fired throughout the environment.
Speed-rate relationships were linear.





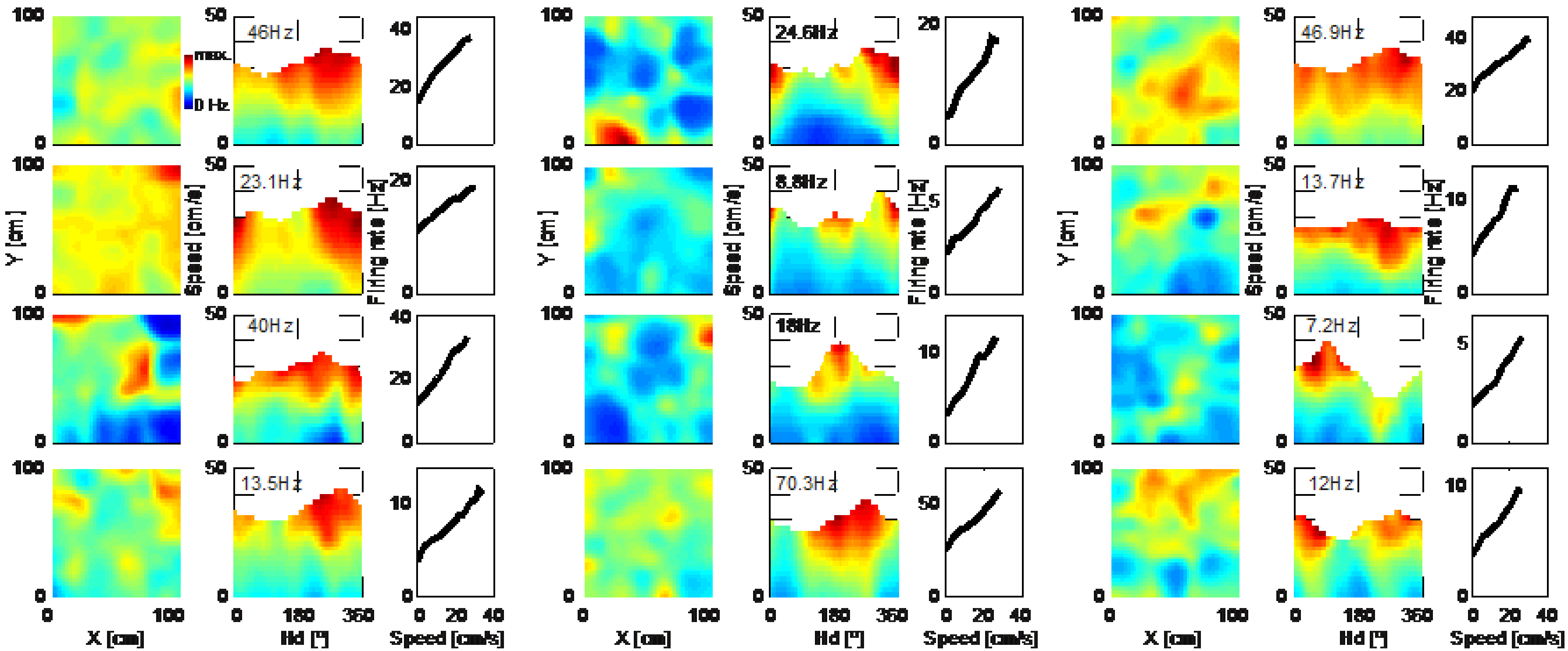
Firing rate is color-coded



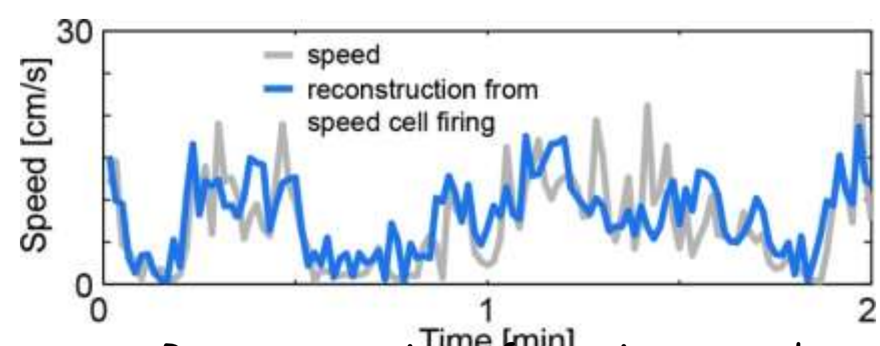
Correlation between instantaneous rate and speed

Kropff et al., unpublished.

256 neurons in the open environment passed the 99th percentile speed cell threshold with the strictest shuffling procedure

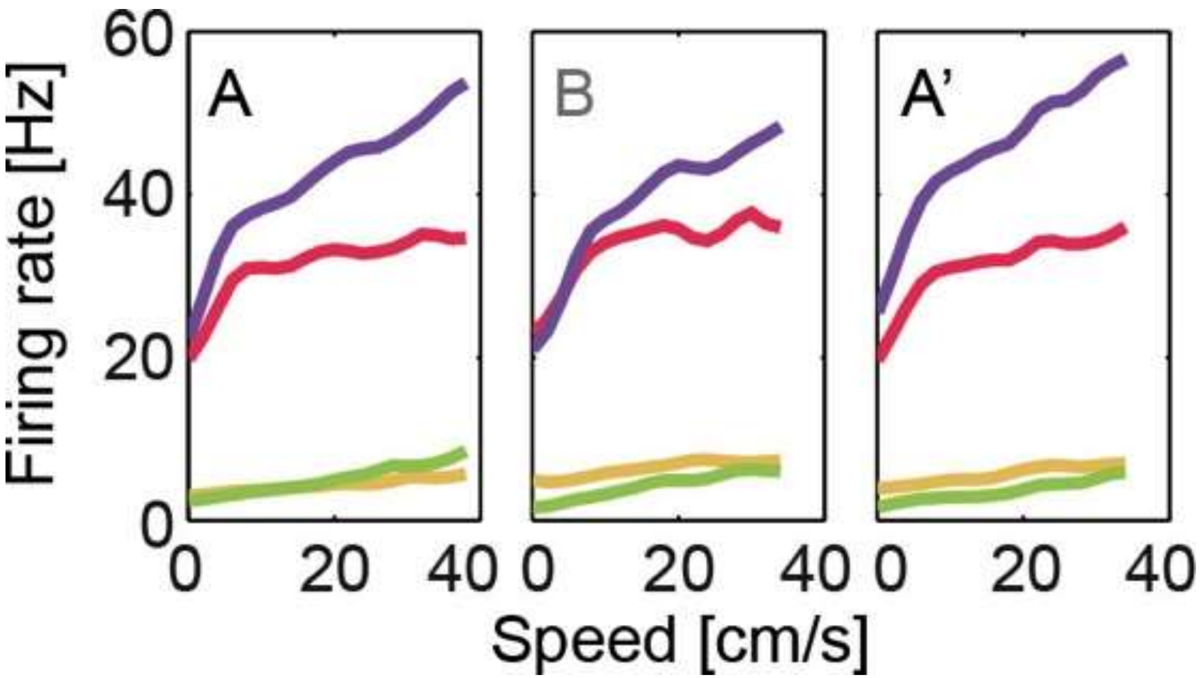


All of these cells had a linear speed-rate relationship

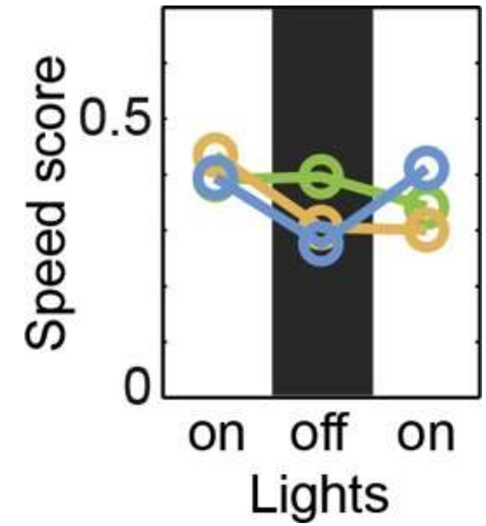


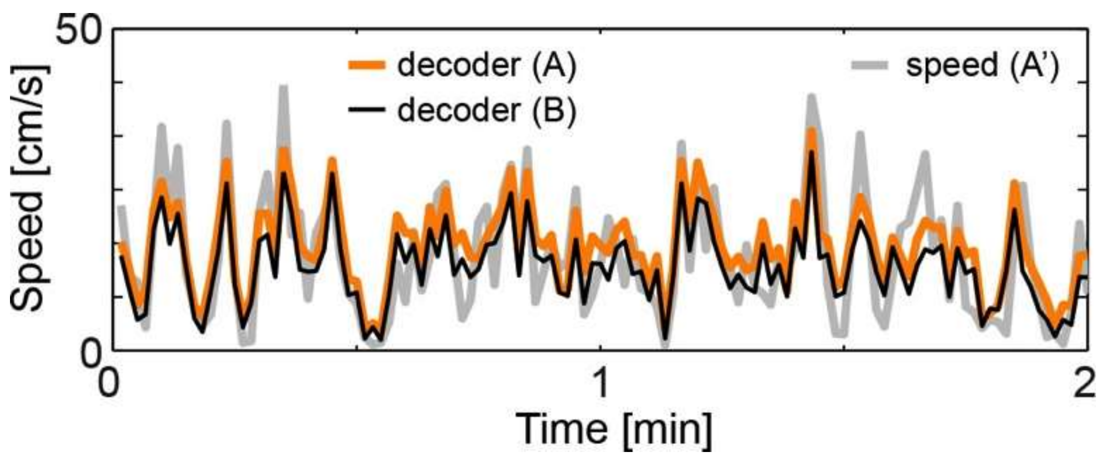
Reconstruction of running speed from speed-cell rates

Speed cells maintain their identity across environments



... including total darkness

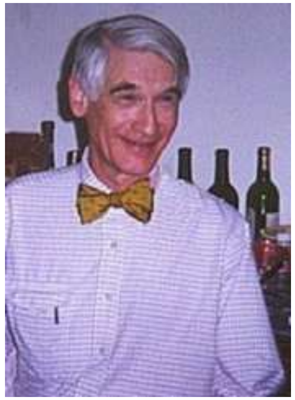




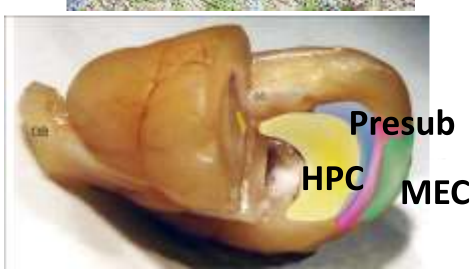
The existence of local speed cells is consistent with a role for self-motion information in translating activity across grid cells in moving animals.

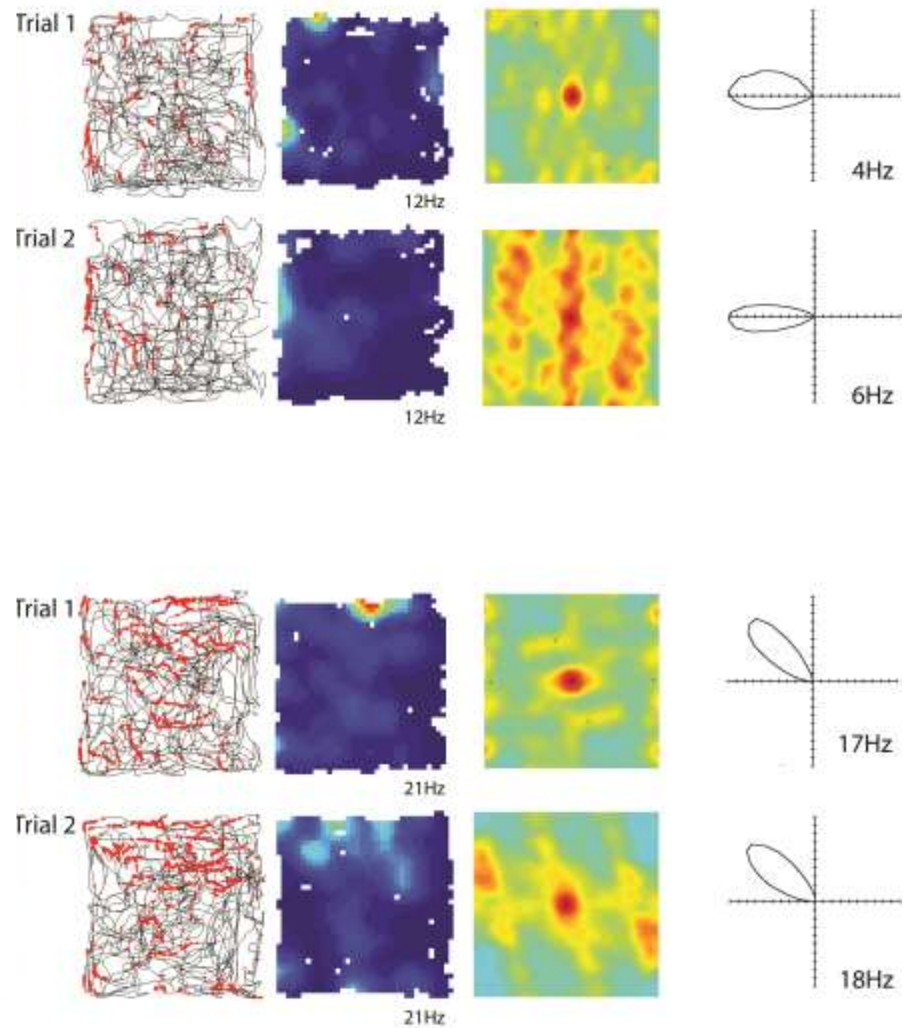
The entorhinal cortex has more than grid cells..

Grid cells are not alone :
they coexist with entorhinal head-direction cells (2006)…



An inner compass
Ranck, 1985



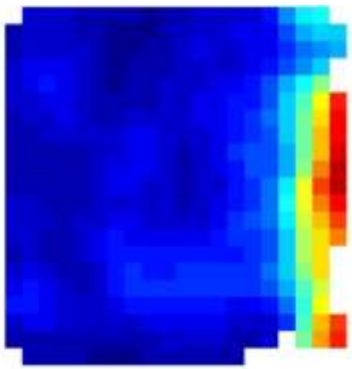


Sargolini et al. (2006), *Science*

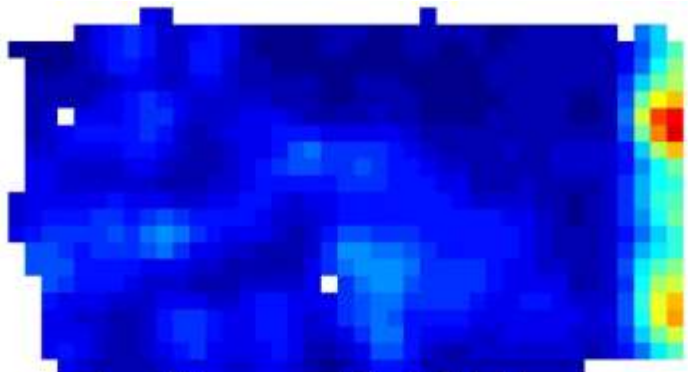
…and with **border cells** that fire specifically along local borders (2008)…

The firing fields of the border cells follow the walls of the box when the box is stretched…

….in the *x* direction:

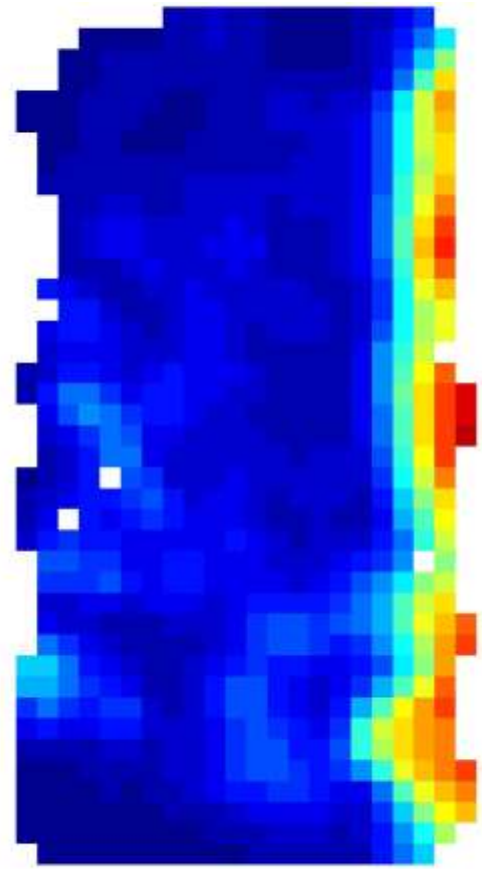


13Hz



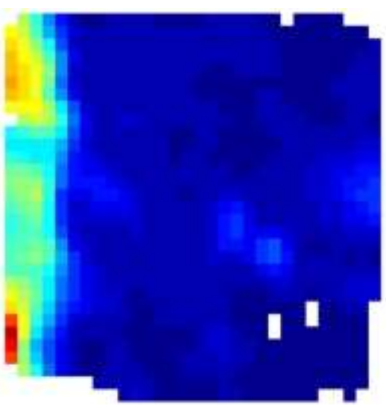
11Hz

….and in the *y* direction:

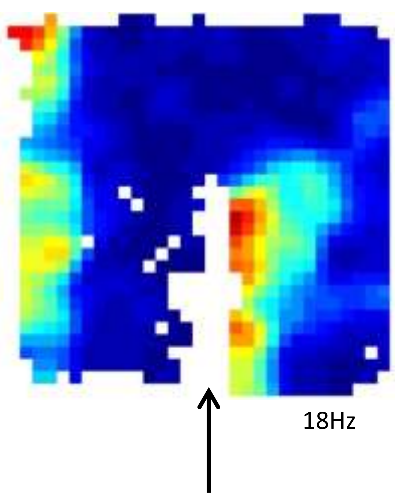


9Hz

Introducing a barrier duplicates the firing field:



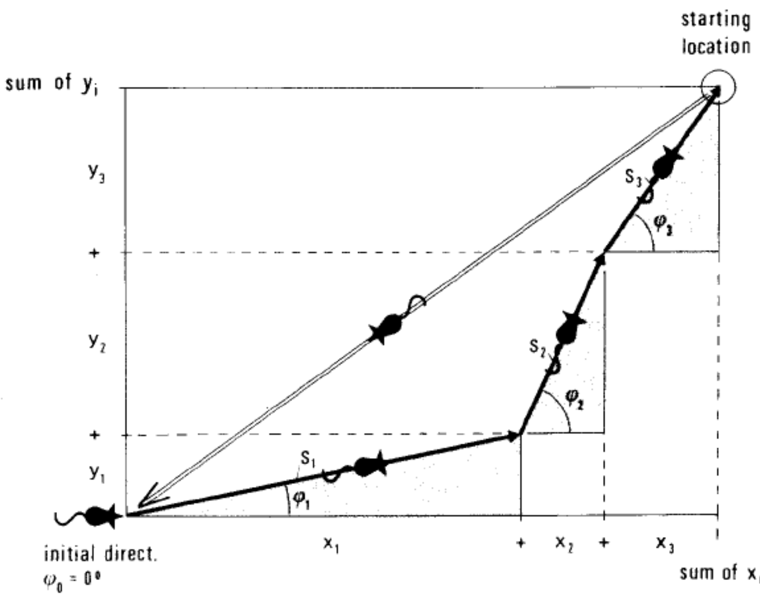
24Hz

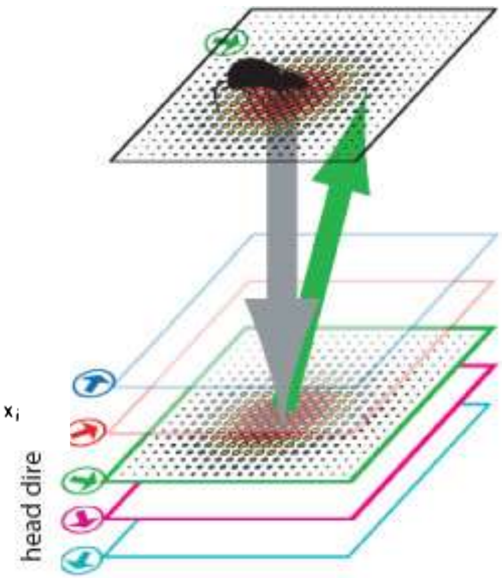


18Hz

Solstad et al. (2008), *Science*

Grid cells, place cells, head direction cells, border cells and speed cells may be components of a Tolmanian internal map of space





The internplay between these cells creates a dynamic neural representation of where you are, representations that also are stored in memory

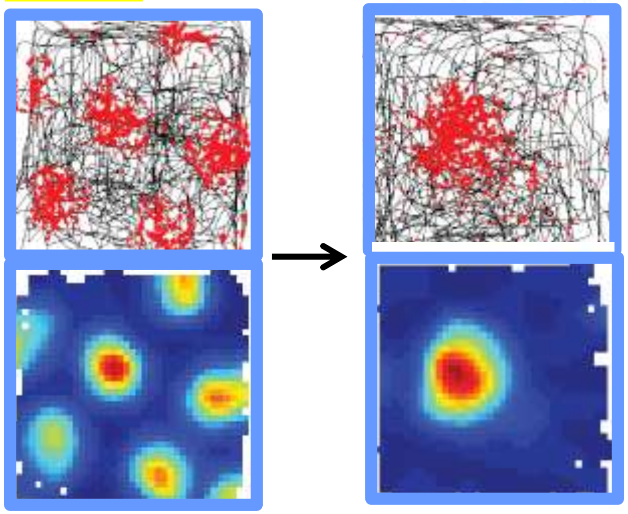
E.C. Tolman (1886-1959)

Are place cells made from any of these multiple entorhinal cell types ?

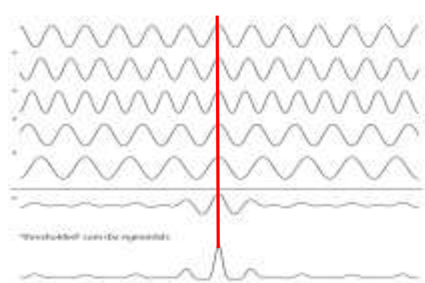
If so, what is the mechanism for the entorhinal-hippocampal spatial transformation?

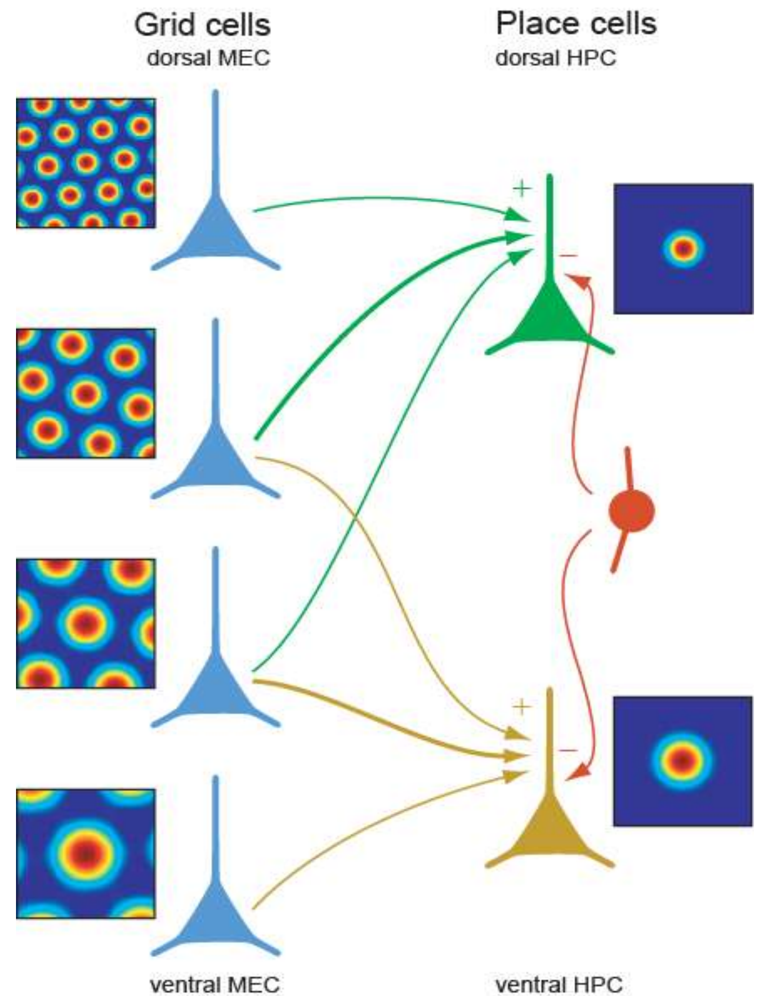
2006:

GRID PLACE



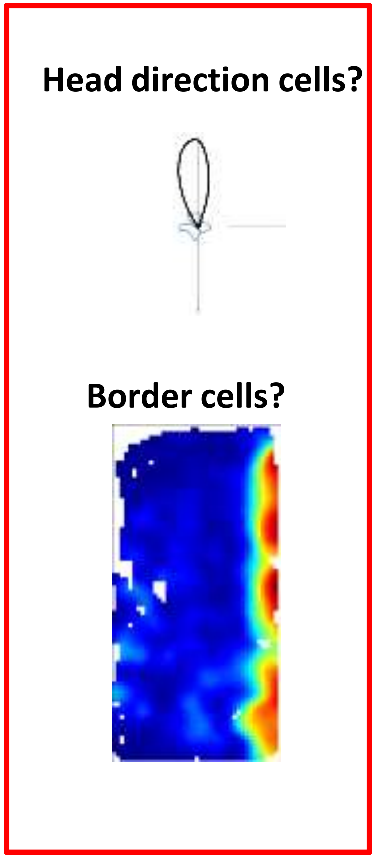
Linear Σ

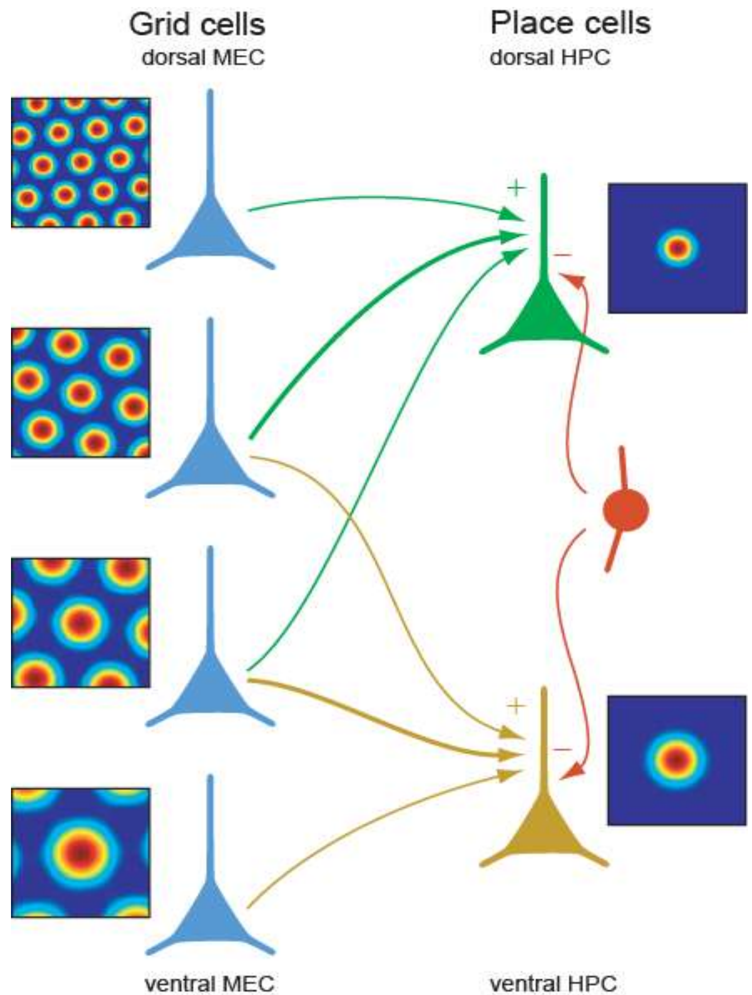




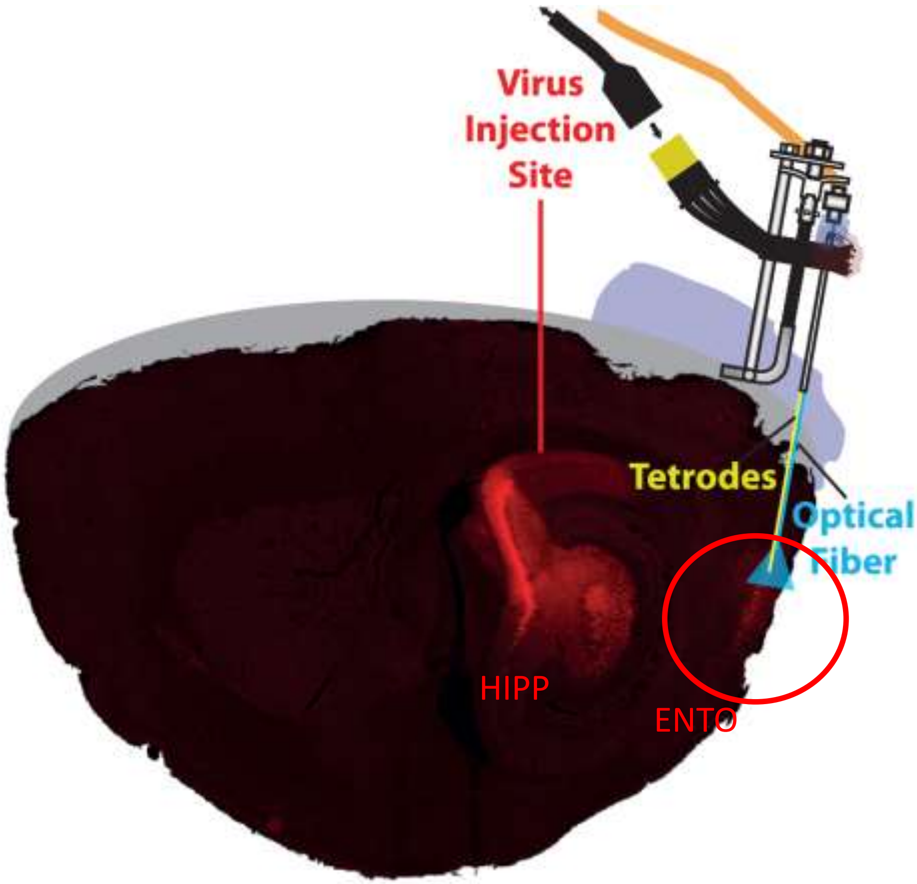
Solstad et al. (2006). *Hippocampus* 16:1026-1031

But are grid cells the *only* spatial input to place cells?





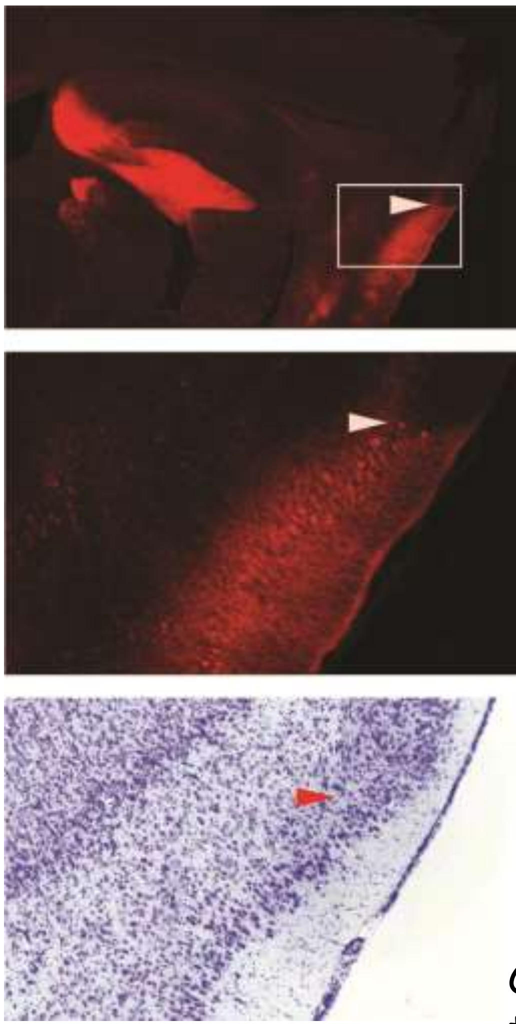
Optogenetic identification of hippocampus-projecting cells in medial entorhinal cortex

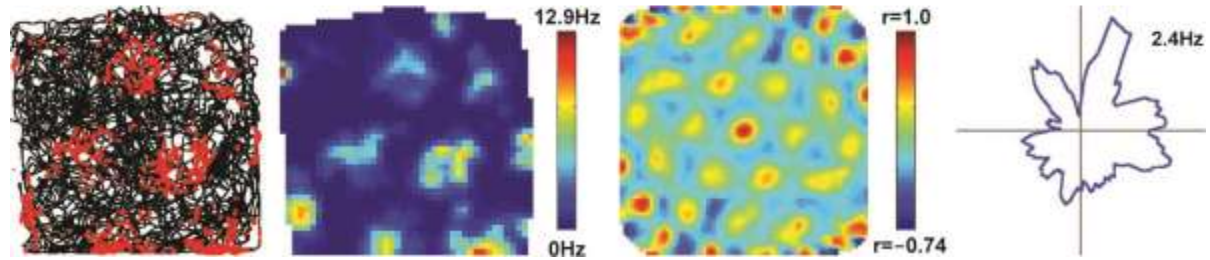


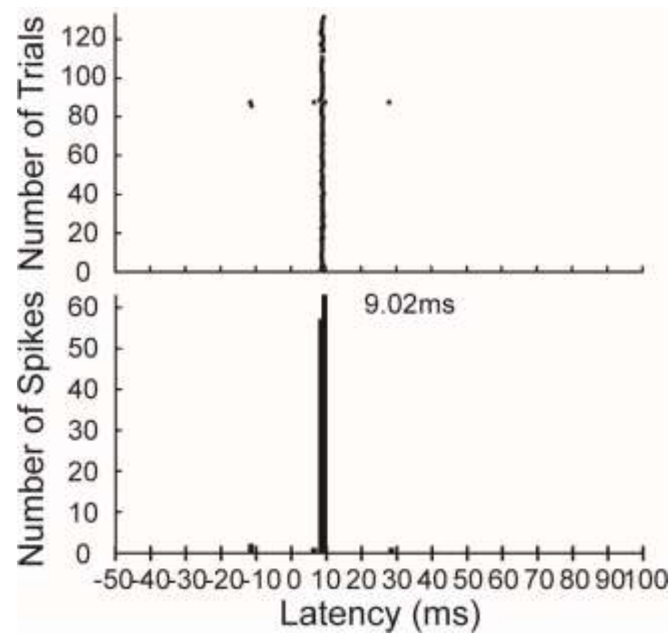
- We infused traffic-improved rAAV virus into the hippocampus: Retrograde transport from axon to soma
- rAAV carries gene for channel-rhodopsin2 (ChR2) as well as FLAG (which encodes a peptide sequence that can be identified by fluorescent antibodies)
- Transfected neurons are labelled (red): Both hippocampus and entorhinal cortex
- Combined fiber-tetrode array was implanted in medial entorhinal cortex
- Hippocampus-projecting entorhinal cells were identified as those that responded instantaneously (smallest latency) to local light pulses

A photoresponsive grid cell

Hippocampus-projecting entorhinal cells infected with ChR2 (rAAV-ChR2-FLAG) were identified as those that fired directly, at minimum latency in response to photostimulation



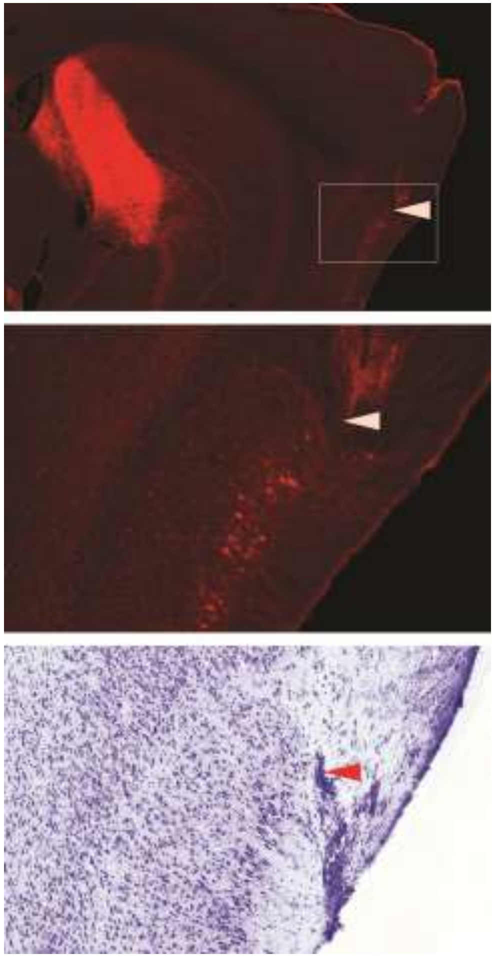


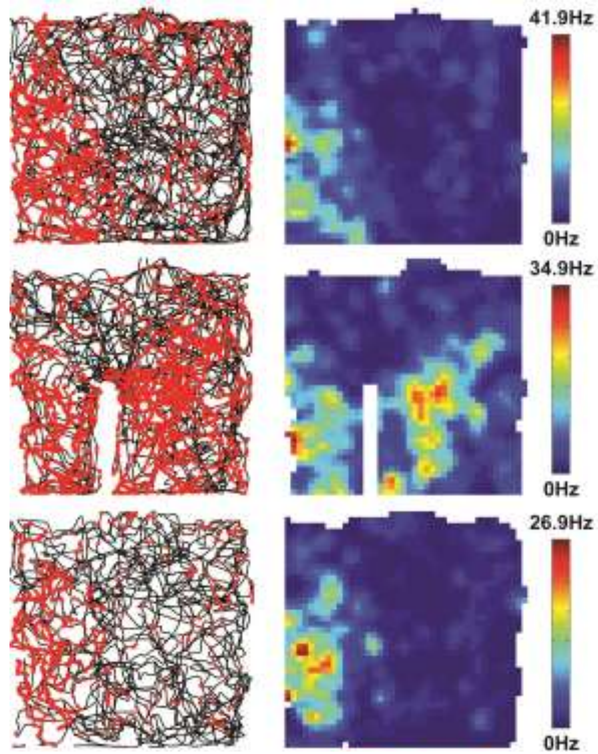


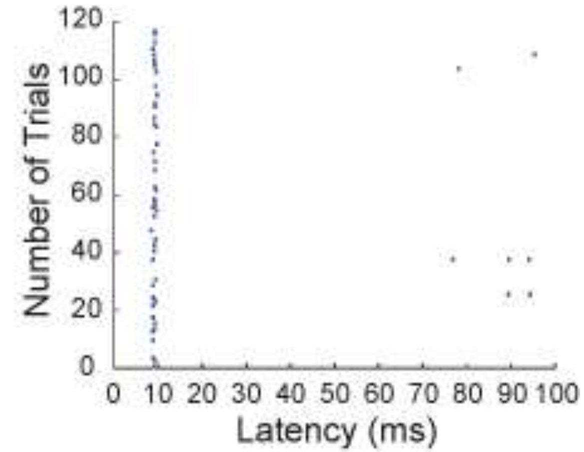
Constant short-latency firing suggests that grid cells project to the hippocampus

Zhang et al. (2013). Science 340:1232627

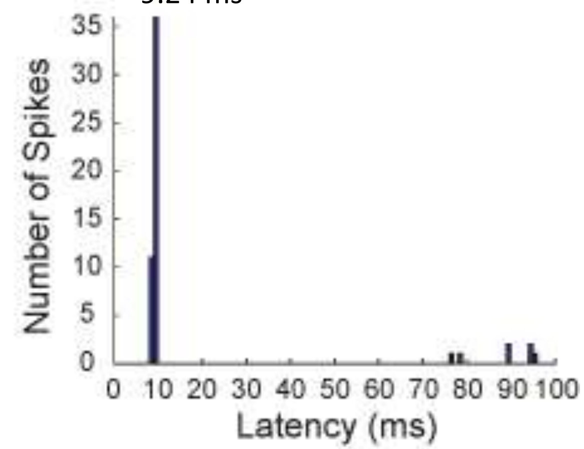
A photoresponsive border cell





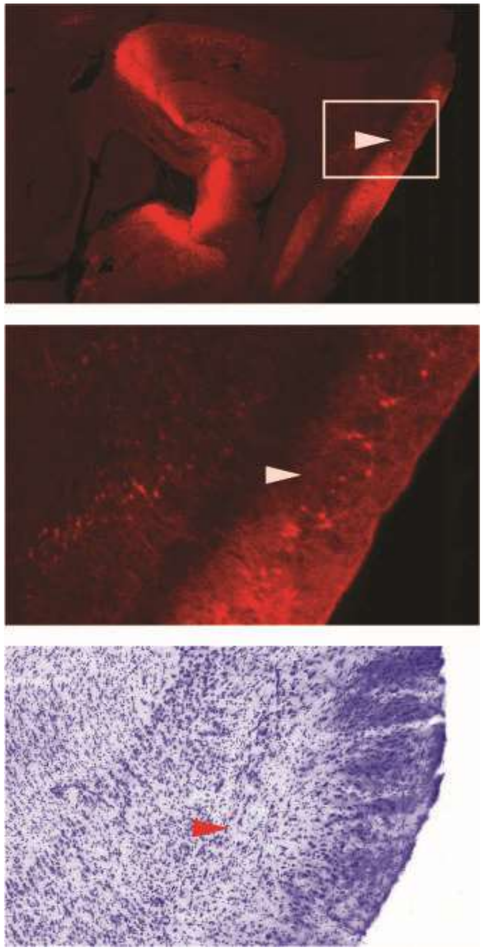


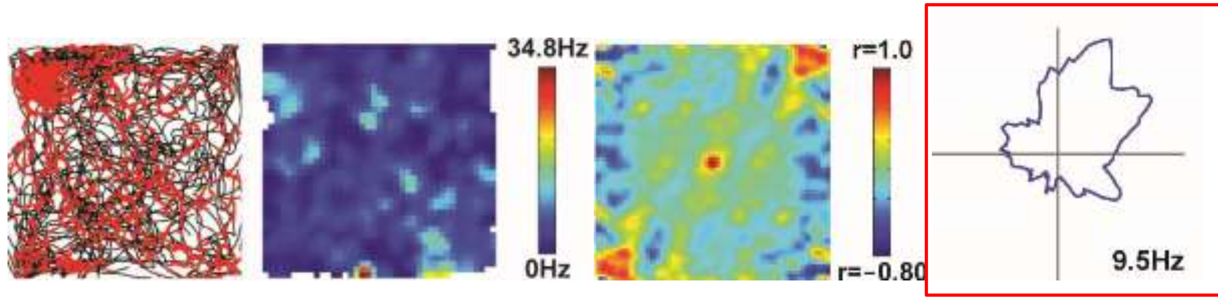
9.24 ms

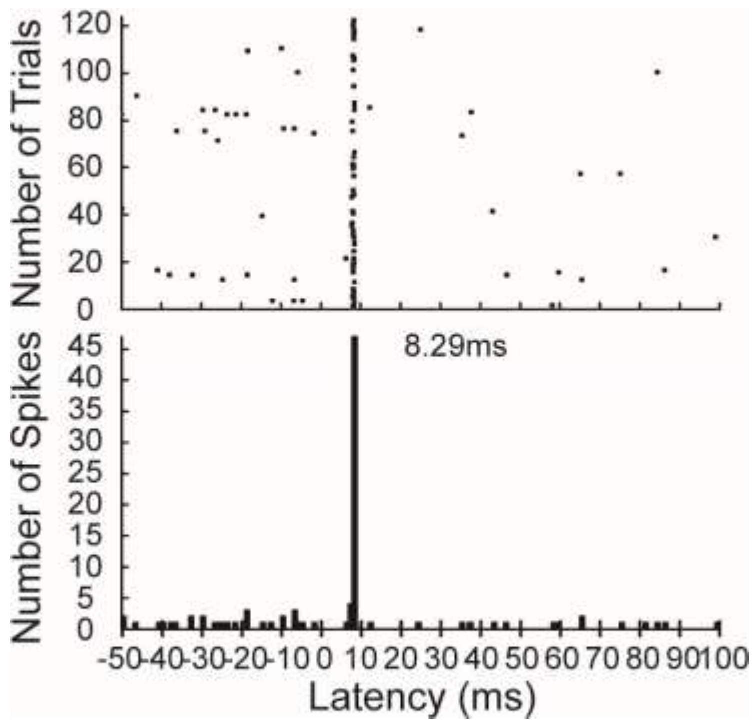


Constant short-latency firing suggests that also border cells project to the hippocampus

A photoresponsive head direction cell

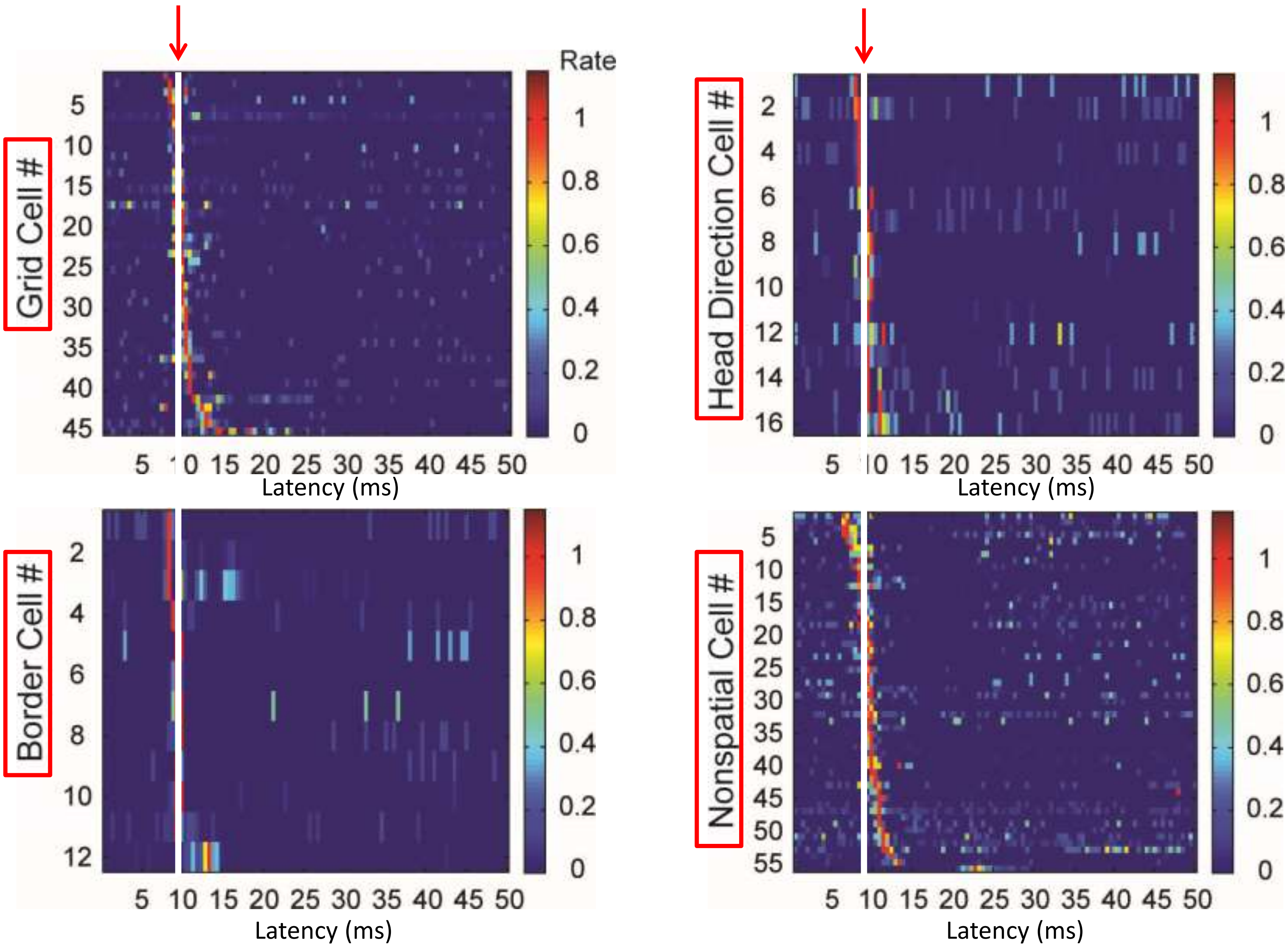






Constant short-latency firing suggests that also head direction cells project to the hippocampus

Within each cell class, spikes were evoked at nearly constant and minimal latencies (~9 ms, s.d. 0.5-1.0 ms), as expected if cells were activated directly

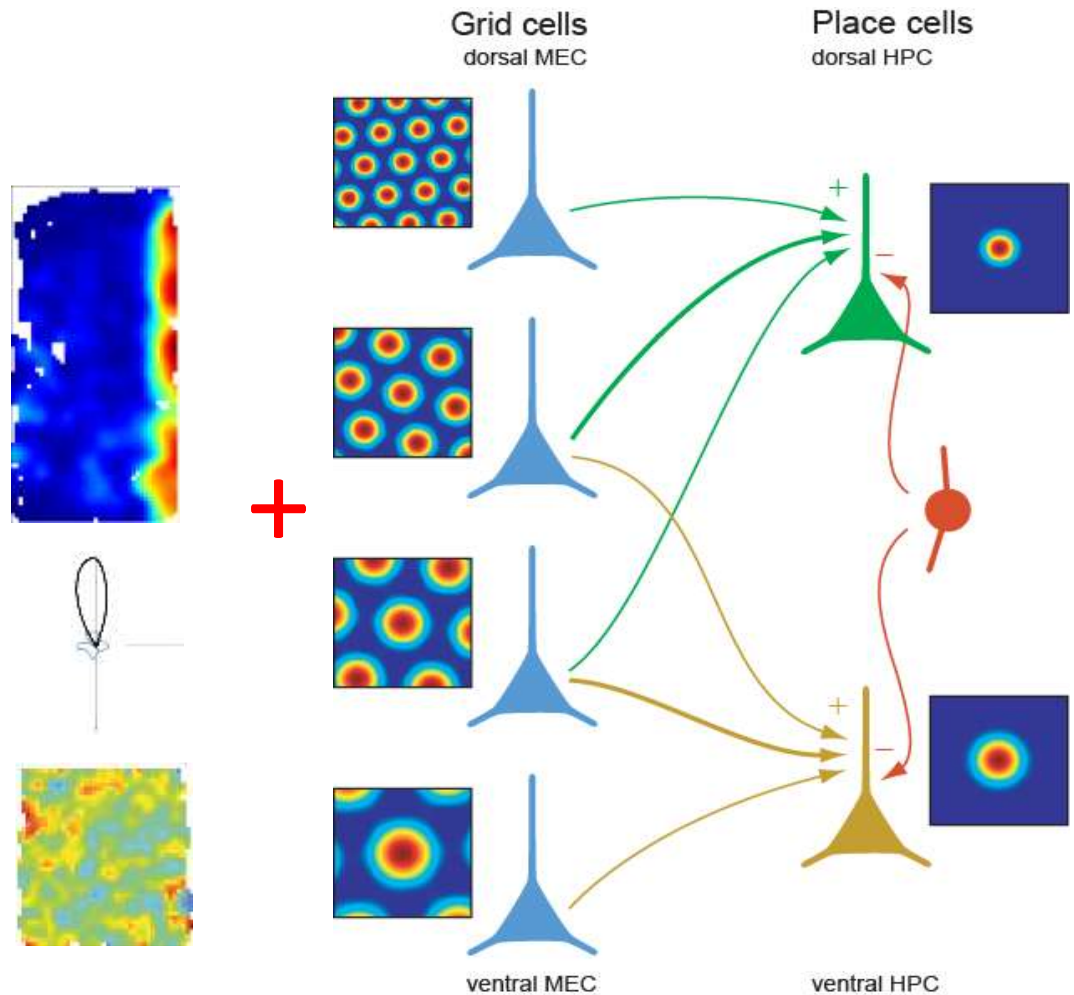


Zhang et al. (2013). Science 340:1232627

What are then the entorhinal inputs that give rise to hippocampal place signals?

The data identify grid cells as the major spatial input to the hippocampus but also suggest that border cells and head direction cells have strong hippocampal projections.

Thus place cells may reflect convergence of grid and border inputs from the entorhinal cortex, possibly with grid cells providing <u>path-integration</u> self-motion input and border cells providing <u>geometrical</u> information.

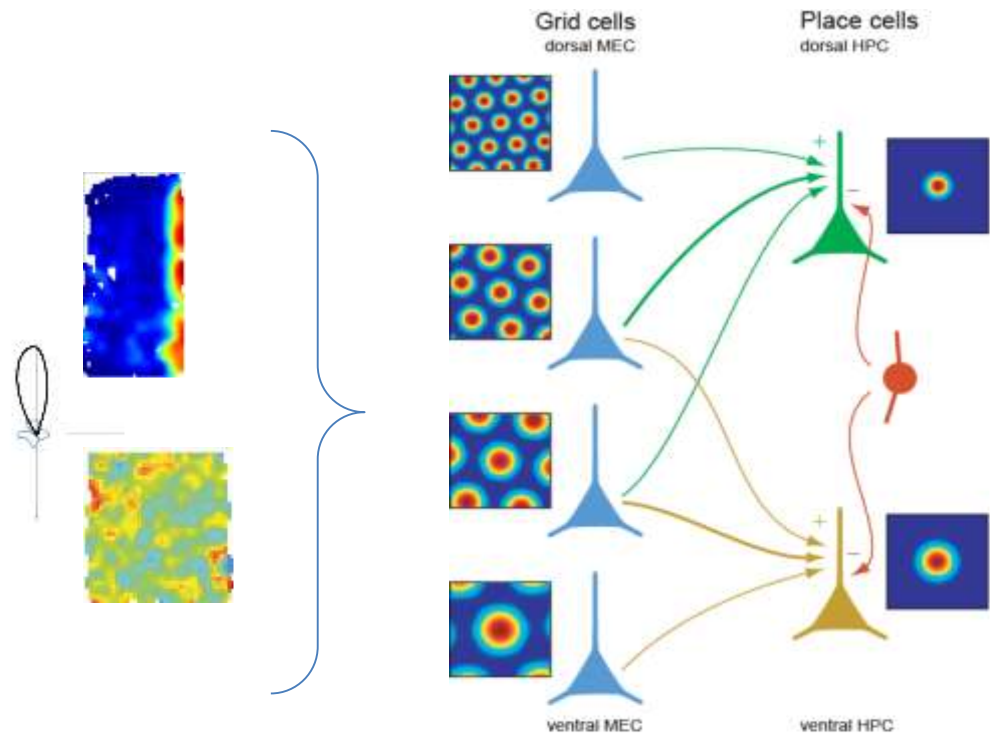


Does the hippocampus have intrinsic mechanisms for gating selected spatial inputs?

Hippocampal cells receive input from a broad spectrum of medial entorhinal cell types.

With such a variety of inputs, the local circuit of place cells may have mechanisms for gating certain signals, <u>much like orientation-selective cells</u> in V1 generate orientation-specific output despite <u>multiple</u> orientations in their inputs (Jia et al., 2010).

Convergent input from a broad spectrum of cell types may enable a place cell to respond more dynamically, favouring different inputs under different conditions.



What network mechanisms could possibly create the grid pattern?

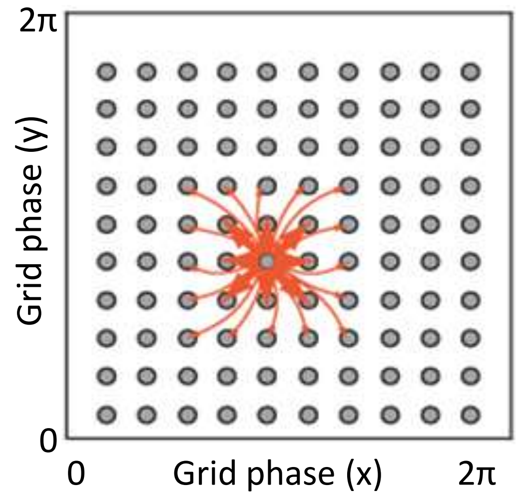
Computational models

Most network models for grid cells involve continuous attractors...

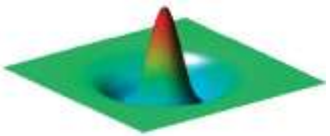
…where

- localized firing may be generated by mutual excitation between cells with similar grid phase

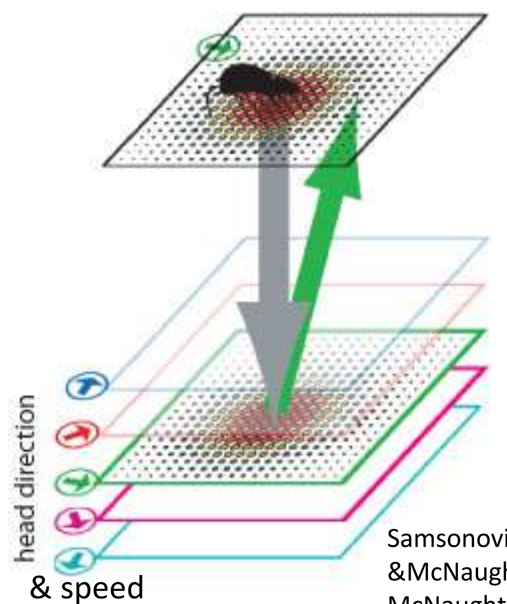
- and such activity is translated across the sheet in accordance with the animal's movement in the environment (e.g. as expressed in speed cells)



BRAIN SURFACE: Grid cells arranged according to grid phase (xy positions). Cells with similar fields mutually excite each other. (with an inhibitory surround).



Mexican hat

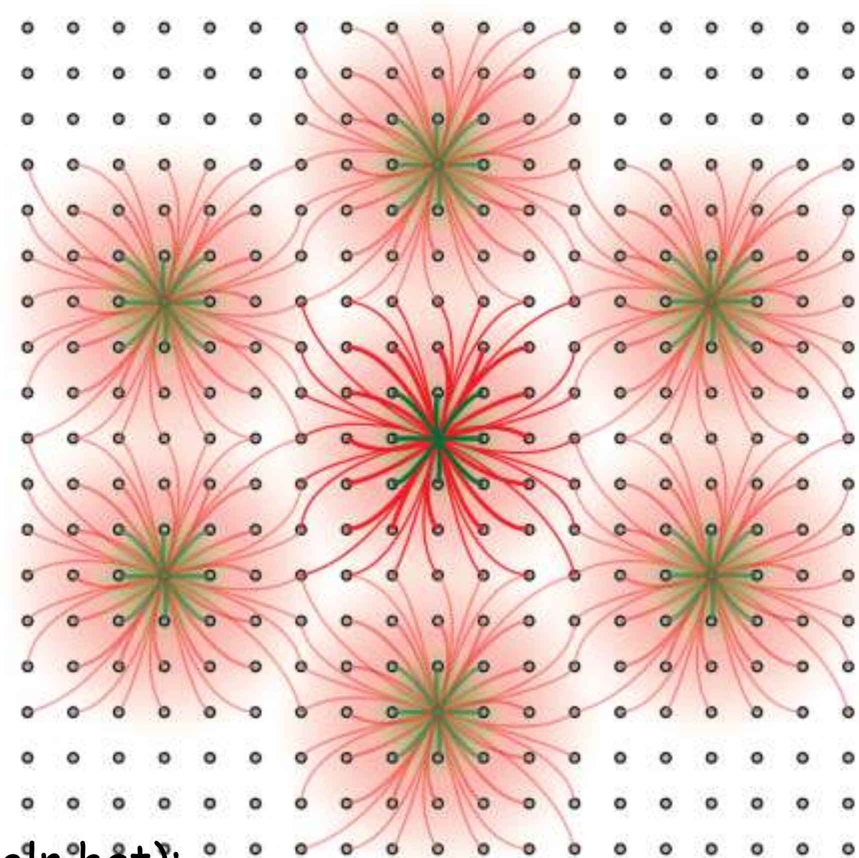


Samsonovitch &McNaughton 1997; McNaughton et al. 2006

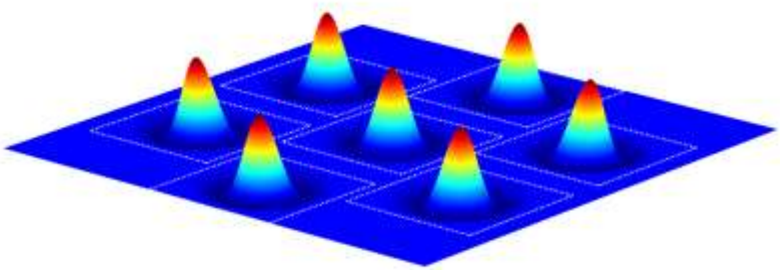
THIS EXPLAINS LOCALIZED FIRING BUT WHERE DOES THE HEXAGONAL PATTERN COME FROM?

Origin of hexagonal structure

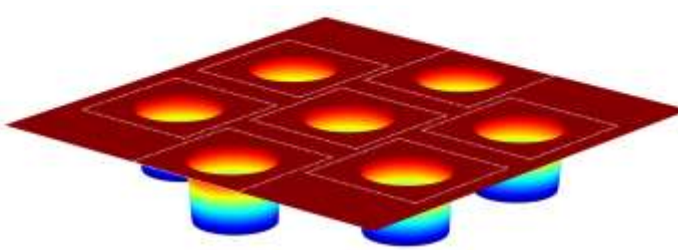
Fuhs & Touretzky, 2006; McNaughton et al. 2006; Burak & Fiete, 2009; Couey et al., 2013



Competition between self-exciting blobs with inhibitory surrounds may cause the network to self-organize into a hexagonal pattern, in which distances between blobs are maximized.



Similar self-organization may occur with purely inhibitory surrounds (inverted Lincoln hat):

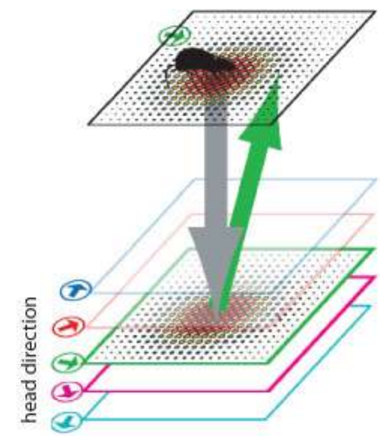


Y. Roudi

Self-organization of *grid* network in a continuous attractor model

Roudi group: Couey et al., 2013;
Bonnevie et al 2013

Y. Roudi
(and Benjamin Dunn
and Aree Witoelaar)



& speed

Then, when the activity bumps are translated across the network in accordance with the animal's movement, using speed and direction signals, it will yield grid fields in individual cells.

Conclusions

1. The firing fields of a grid cell define a hexagonal array that tessellates the entire local space.
2. Grid cells cluster into a small number of modules that are discontinuous in grid scale, grid orientation, and other properties.
3. Grid cells intermingle with head direction cells and border cells as well as a large population of speed cells whose firing rates increase linearly with running speed throughout the environment.
4. Speed cells form a distinct cell population not overlapping with grid, head direction or border cells.
5. Linear speed signals are required for path integration-based position updating of grid cells.
6. Place cells may be created through a transformation of inputs from grid cells, border cells and other spatial signals.
7. The grid pattern may be generated by attractor network mechanisms.

All work:
May-Britt Moser

Entorhinal maps:
Vegard Brun
Marianne Fyhn
Torkel Hafting
Sturla Molden
Francesca Sargolini
Trygve Solstad
Charlotte Boccara
Emilio Kropff
Dori Derdikman
Jonathan Whitlock

Alessandro Treves
Bruce McNaughton
Menno Witter

Attractor model::
Yasser Roudi
Benjamin Dunn
Aree Witoelaar

Money:
NTNU,
The Kavli Foundation,
The Norwegian Research Council Centre of Excellence Scheme,
European Commission's 7th Framework Progr.,
ERC Advanced Investigator Grant scheme,
Louis Jeantet Foundation

Speed cells:
Emilio Kropff
Eric Carmichael

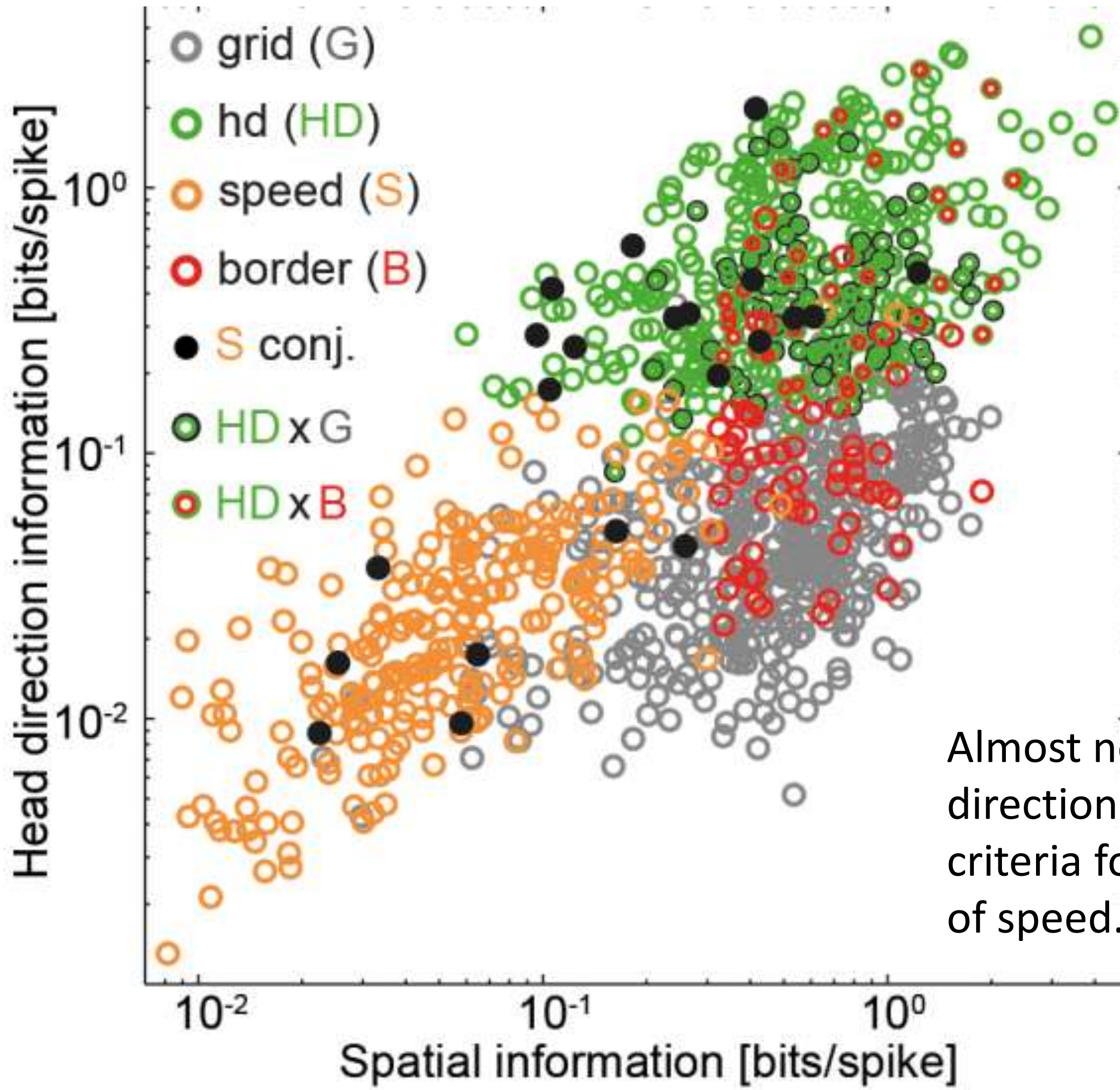
Grid modules:
Tor Stensola
Hanne Stensola
Kristian Frøland
Trygve Solstad

Grid-to-place::
Sheng—Jia Zhang
Jing Ye
Chenglin Miao
Albert Tsao
Ignas Cerniauskas
Debora Ledergerber

So can we understand how neural activity gives rise to behavior?

Yes

Speed cells formed a population of their own, distinct from grid cells, border cells and head direction cells…

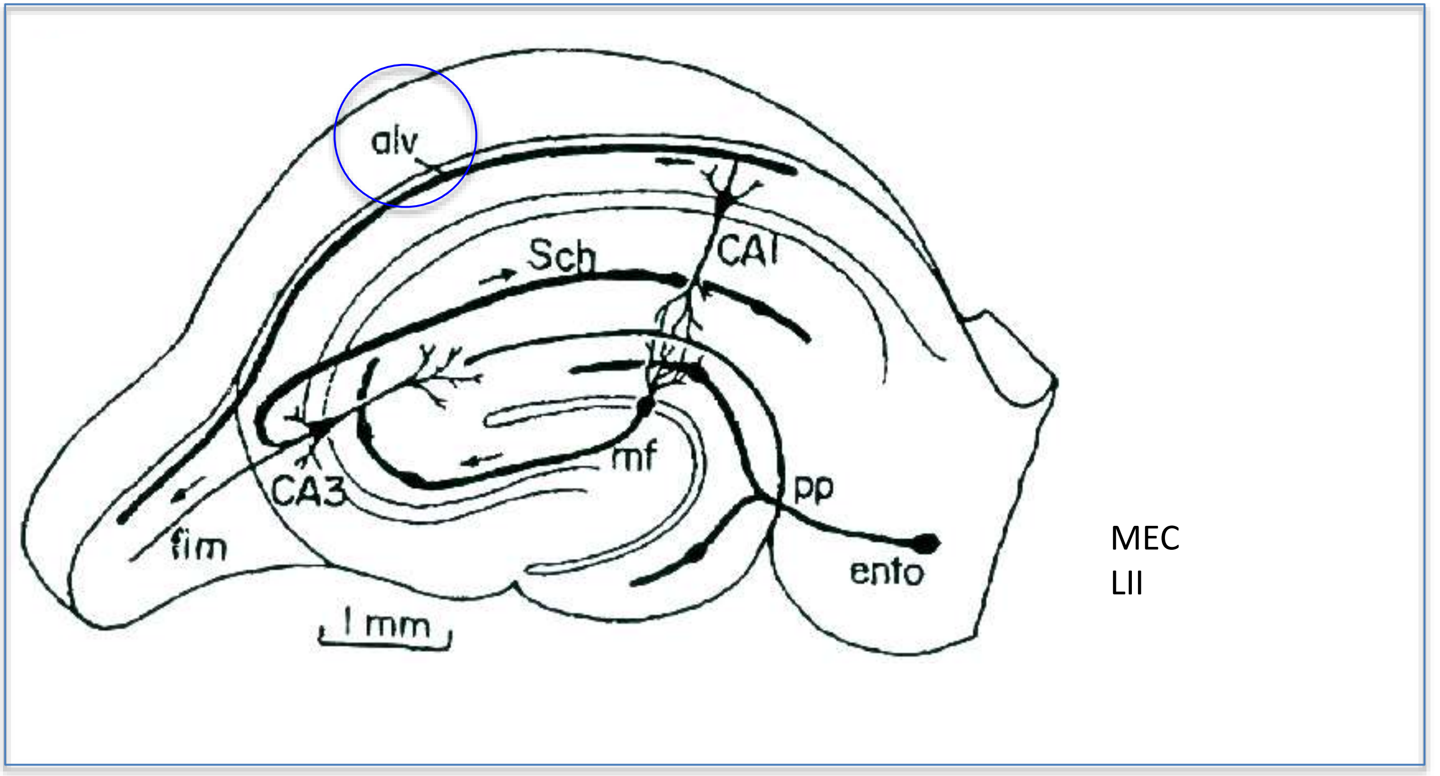


Almost no grid or head direction cells passed criteria for linear encoding of speed.

Kropff et al., unpublished.

But maybe the cells were activated synaptically?

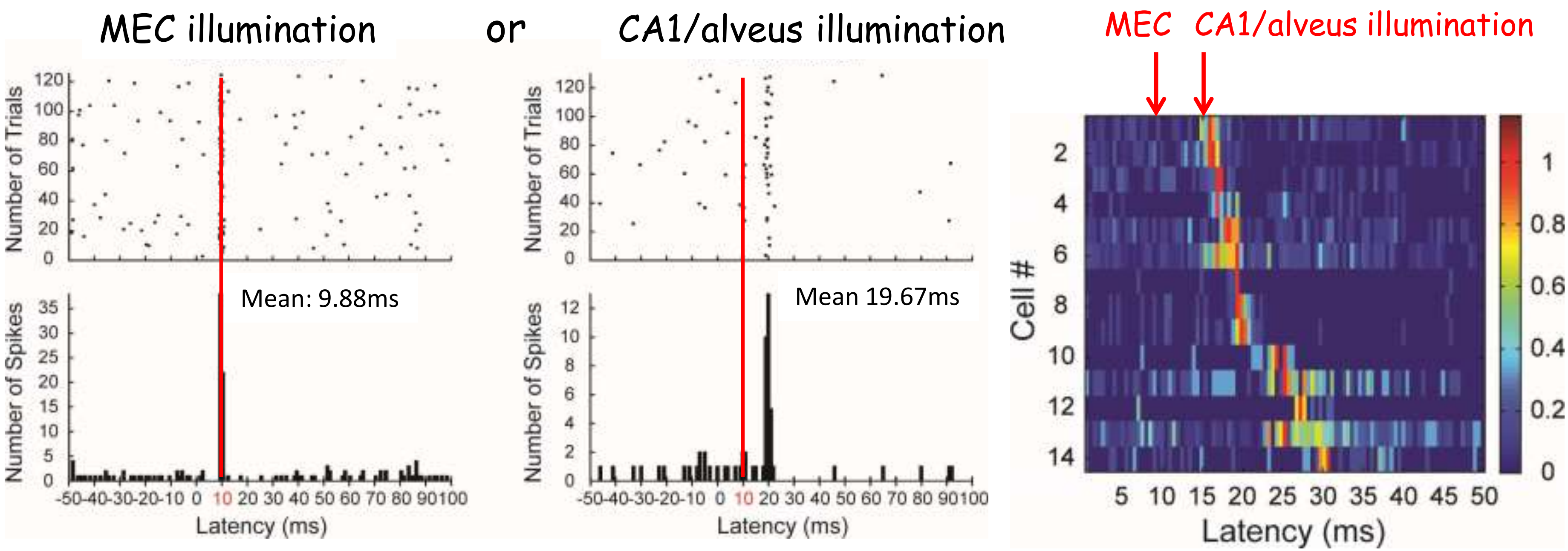
We tested this by photostimulating axons from hippocampus to entorhinal cortex in the alveus



Photostimulation in the alveus resulted in consistently longer firing latencies (>15-20 ms), suggesting that in this case the activation was synaptic

Same MEC cell with:

All MEC cells with:



Zhang et al. (2013). Science 340:1232627