Nobel Prize in Physiology or Medicine
Nobel Lecture 071214

Grid cells and the entorhinal map of space

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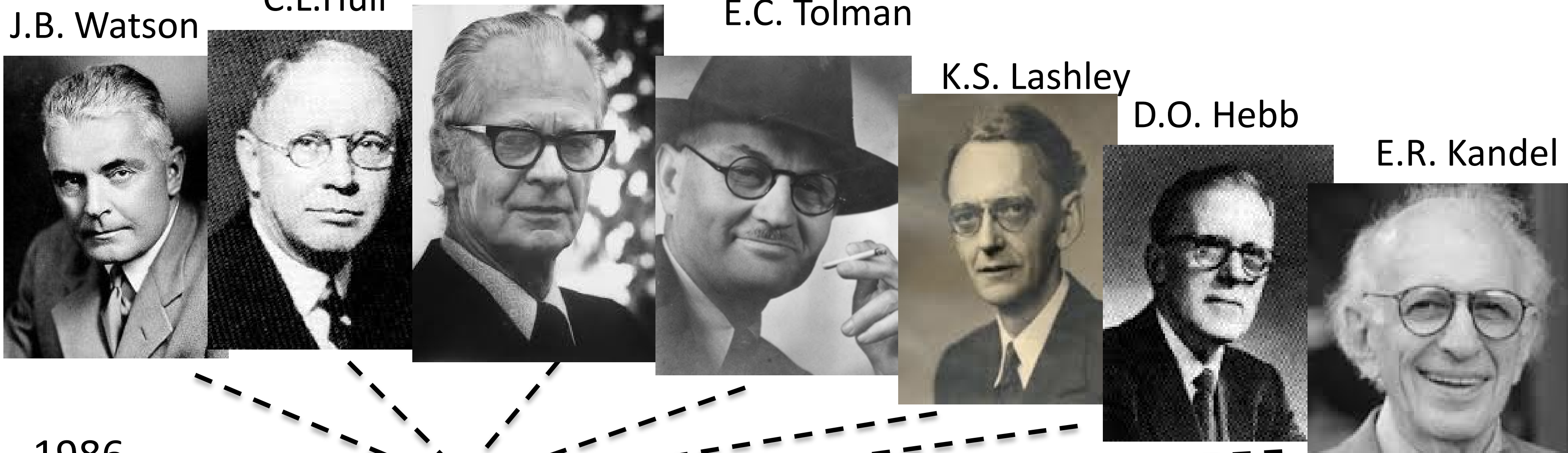
From psychology to neurophysiology - and back

J.B. Watson
C.L.Hull
B.F. Skinner
E.C. Tolman
K.S. Lashley
D.O. Hebb
E.R. Kandel



1986

Tolman writing to Hebb (1958):

"I certainly was an anti-physiologist at that time and am glad to be considered as one <u>then</u>. Today, however, I believe that this (physiologizing) is where the great new break-throughs are coming.."

Courtesy of Steve Glickman

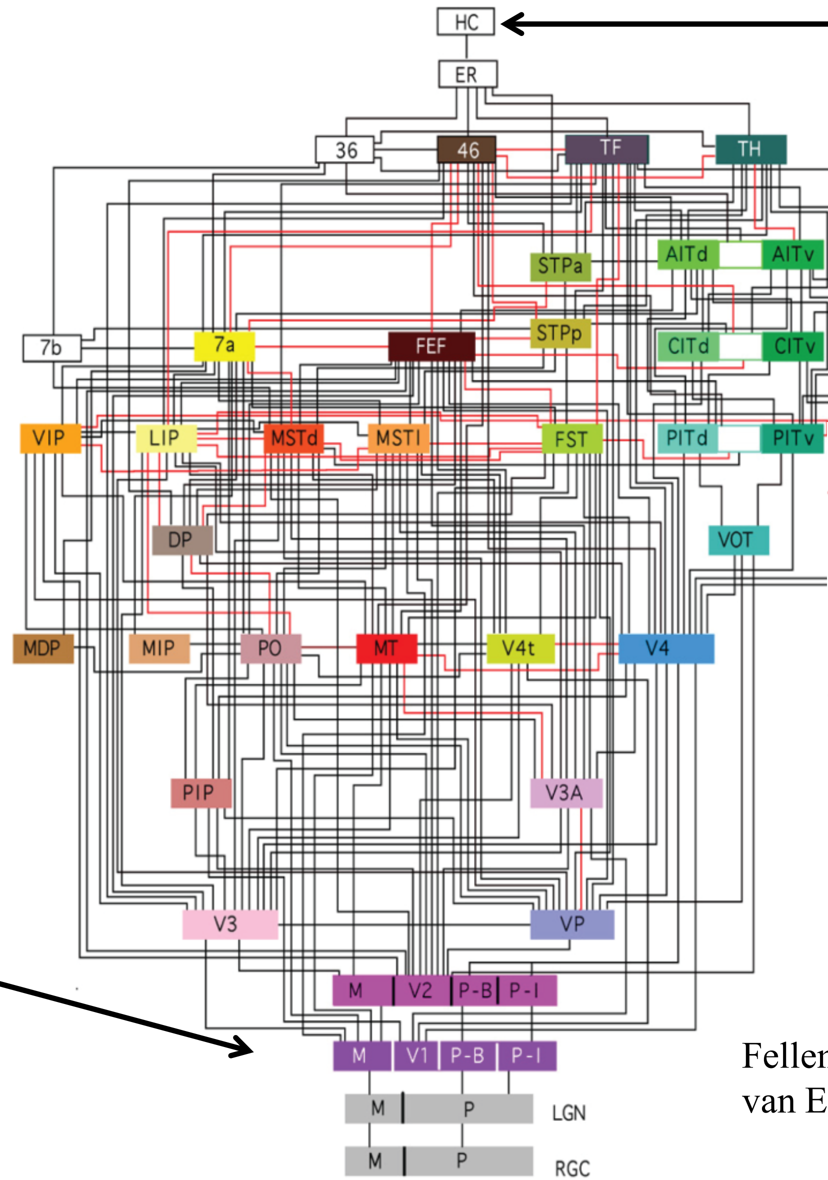
T. Sagvolden,
P.Andersen,
R.G.M. Morris,
J.O´Keefe,
C.A. Barnes,
B.L. McNaughton

1959 -:

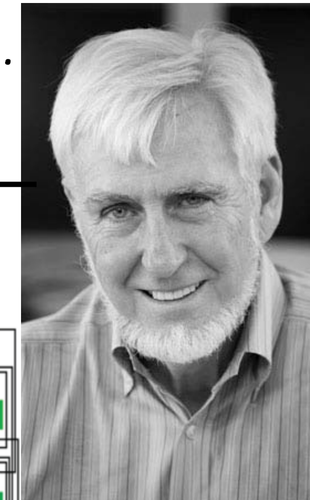
Significant progress in deciphering cortical computation was made at the 'low end' of the cortex, near the sensory receptors

D. H. Hubel and T. N. Wiesel (courtesy M. Reyes/T.N. Wiesel)

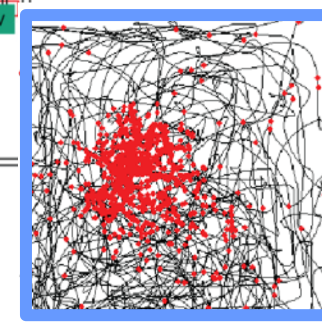
1971 -: The high end…



Felleman and van Essen, 1991

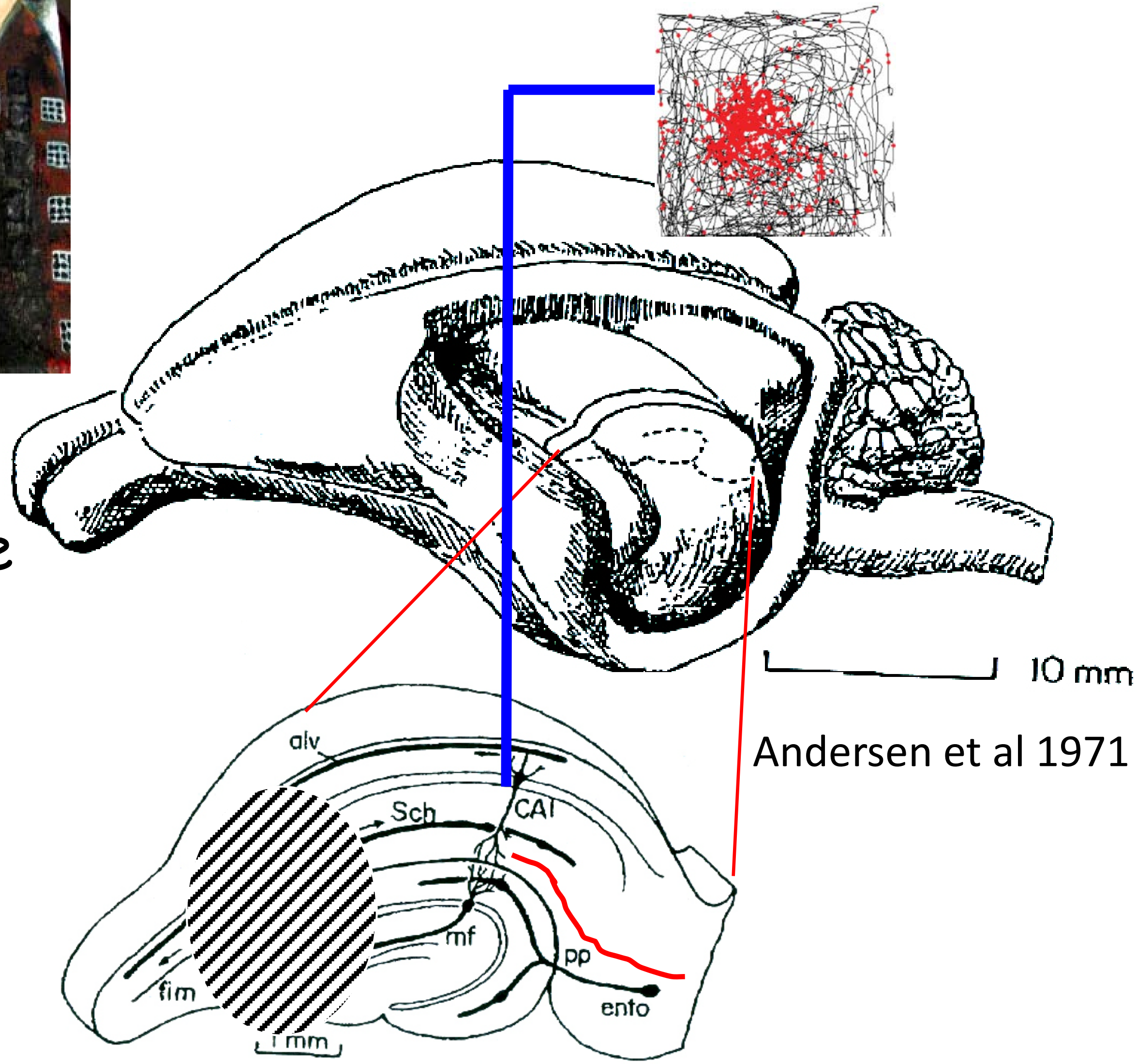


J. O´Keefe



Trondheim 1996-

Ailin Moser



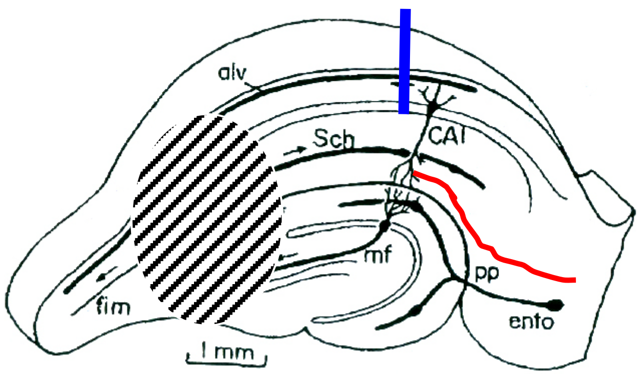
Andersen et al 1971

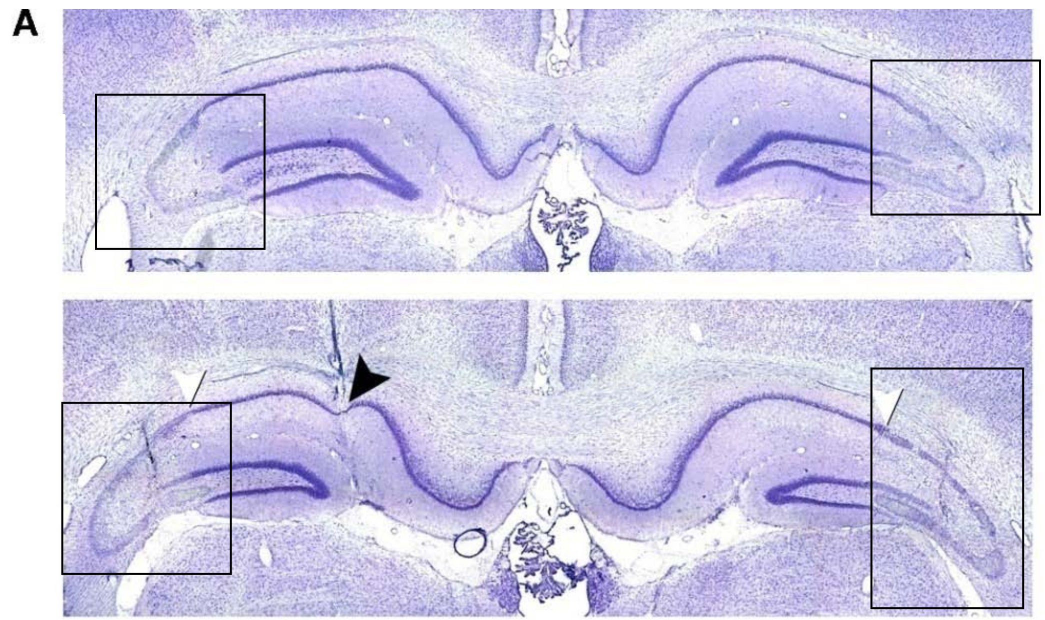
Where and how was the place signal generated?

V.H. Brun

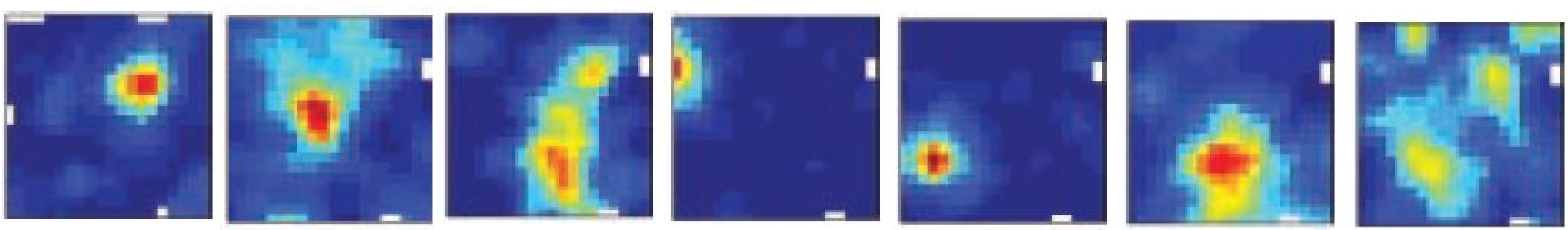
M.P. Witter

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





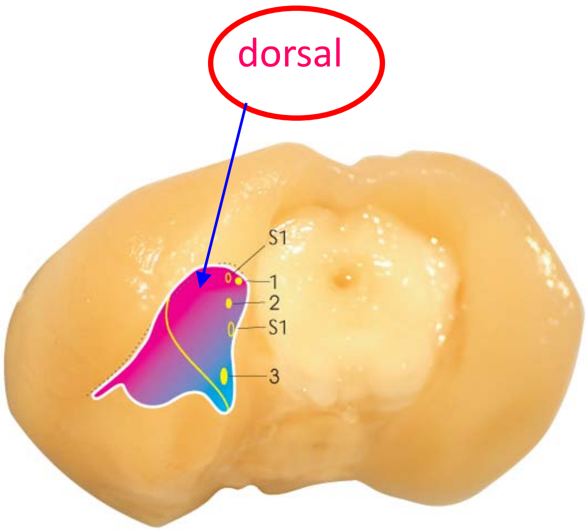
Brun et al. (2002). *Science* 296:2243-2246



Best candidate: the entorhinal cortex

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

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

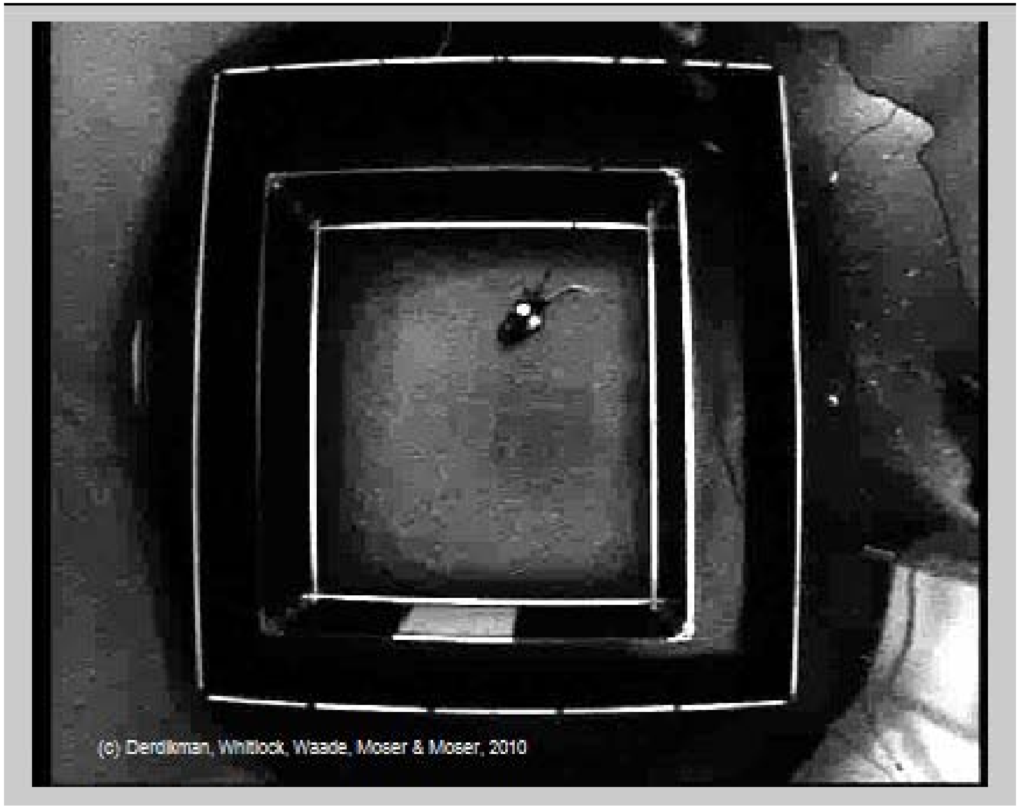


Fyhn et al. (2004). *Science* 305:1258-1264

M. Fyhn

S. Molden

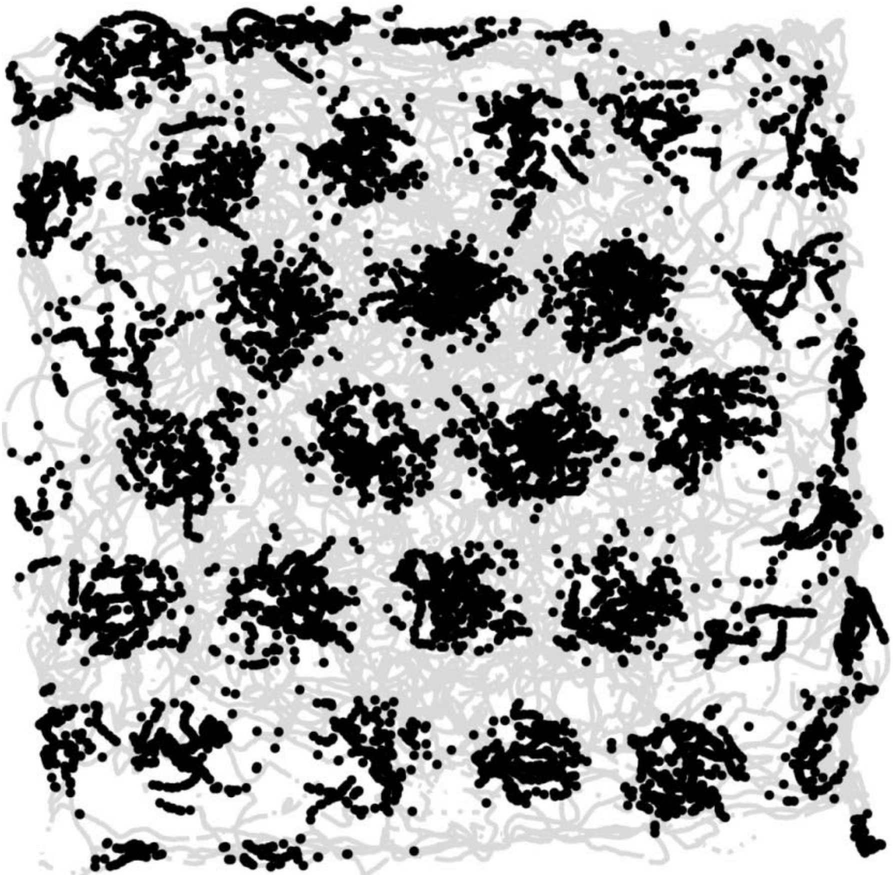
M.P. Witter



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 structure

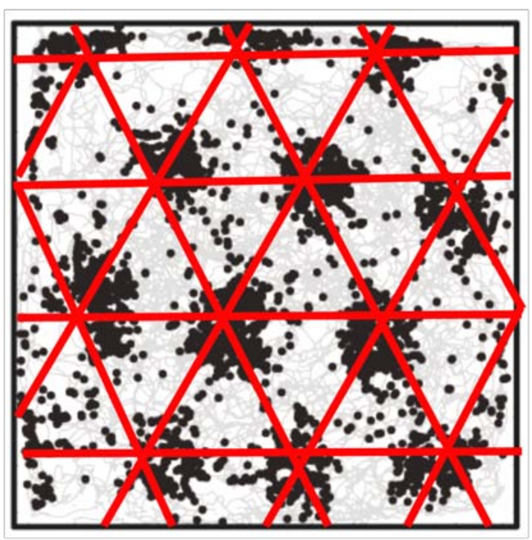
Stensola et al. *Nature*, 492, 72-78 (2012)



220 cm wide box

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

We called them grid cells



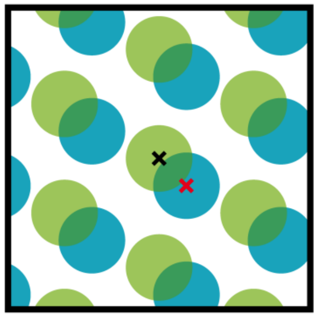
Hafting et al. (2005). *Nature* 436:801-806



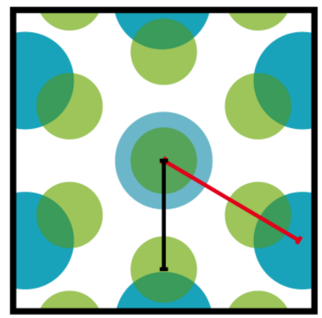
T. Hafting, M. Fyhn, S. Molden

Grid cells have at least three dimensions of variation

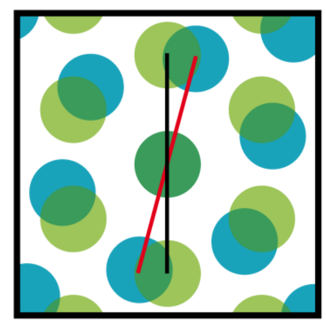
1. Phase



2. Scale

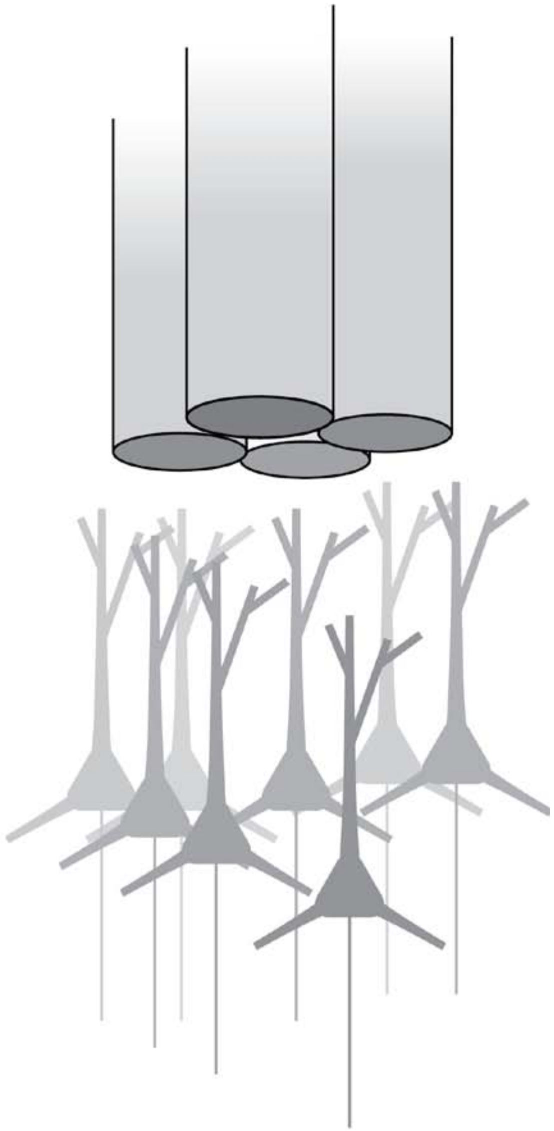


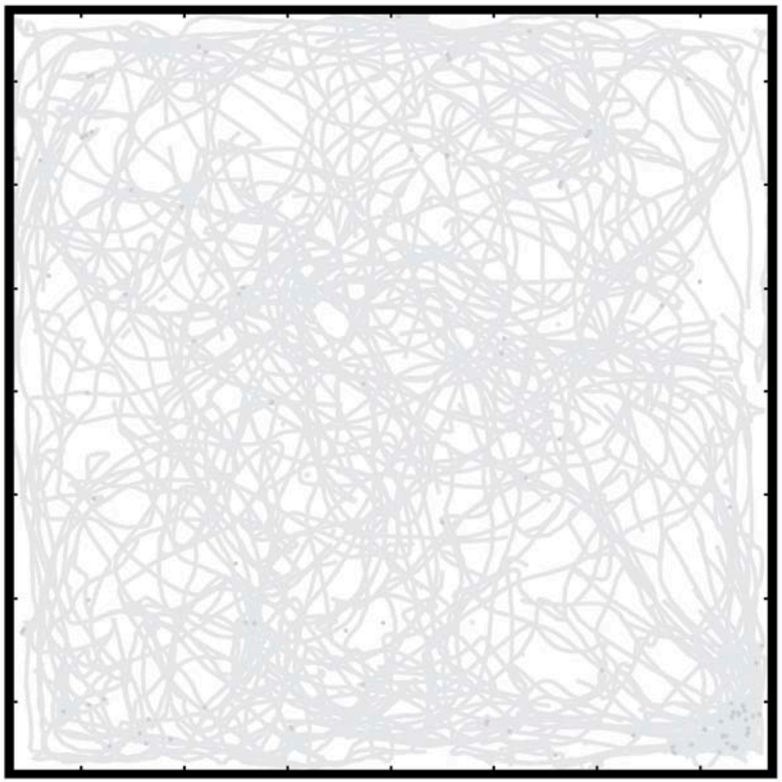
3. Orientation



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

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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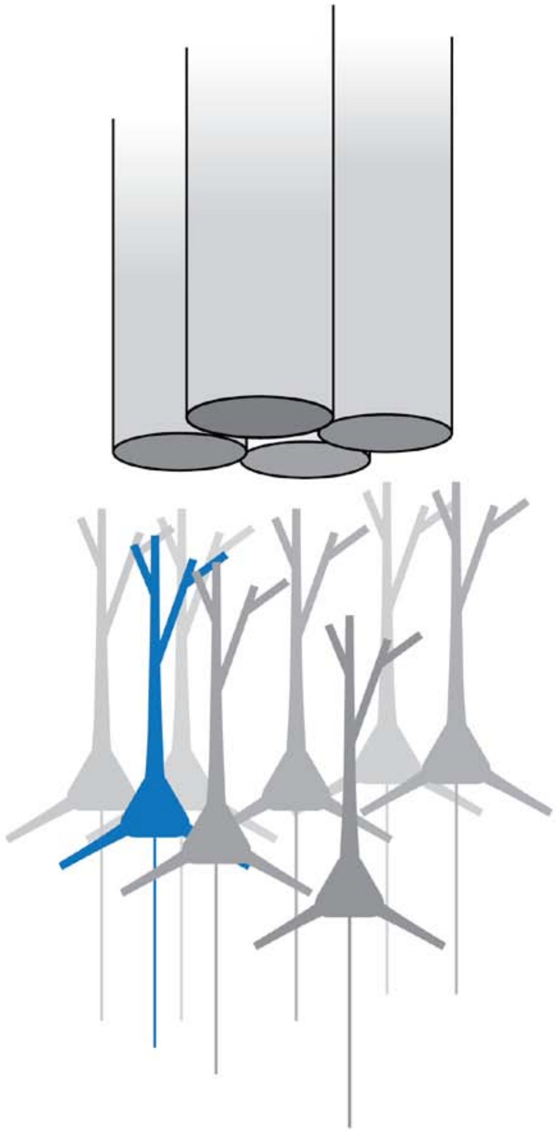

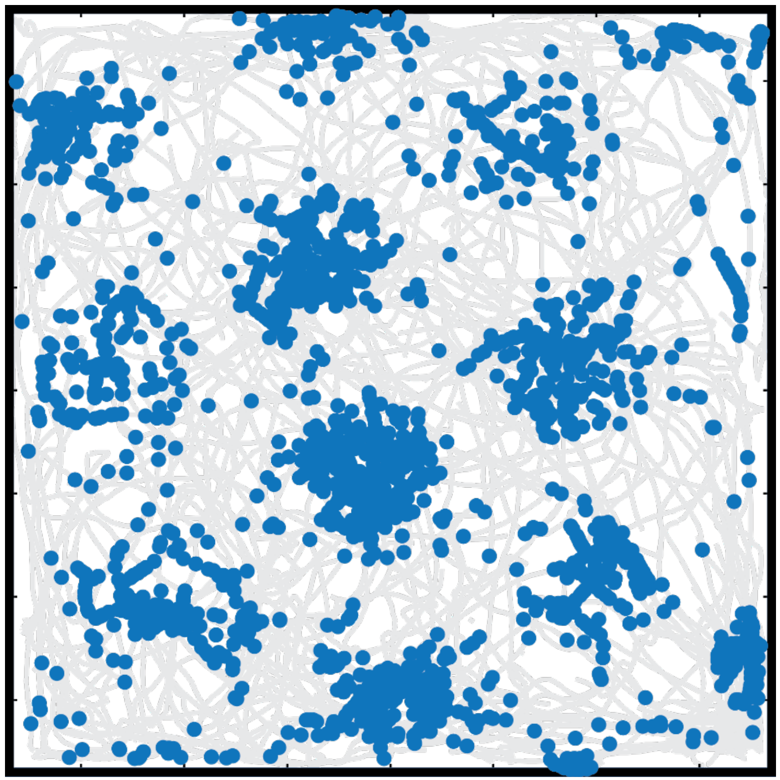

Hafting et al. (2005). *Nature* 436:801-806
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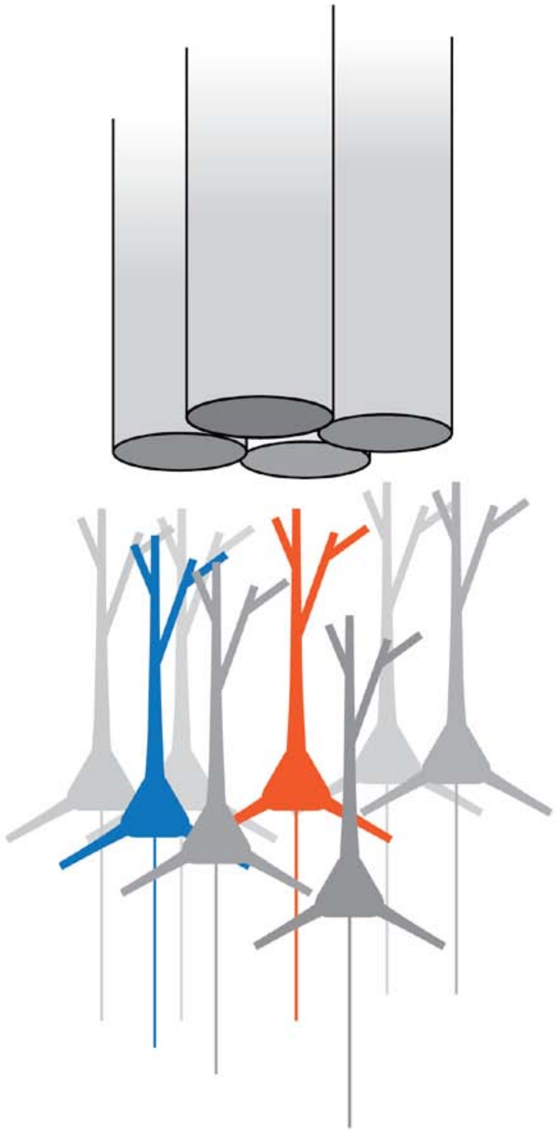

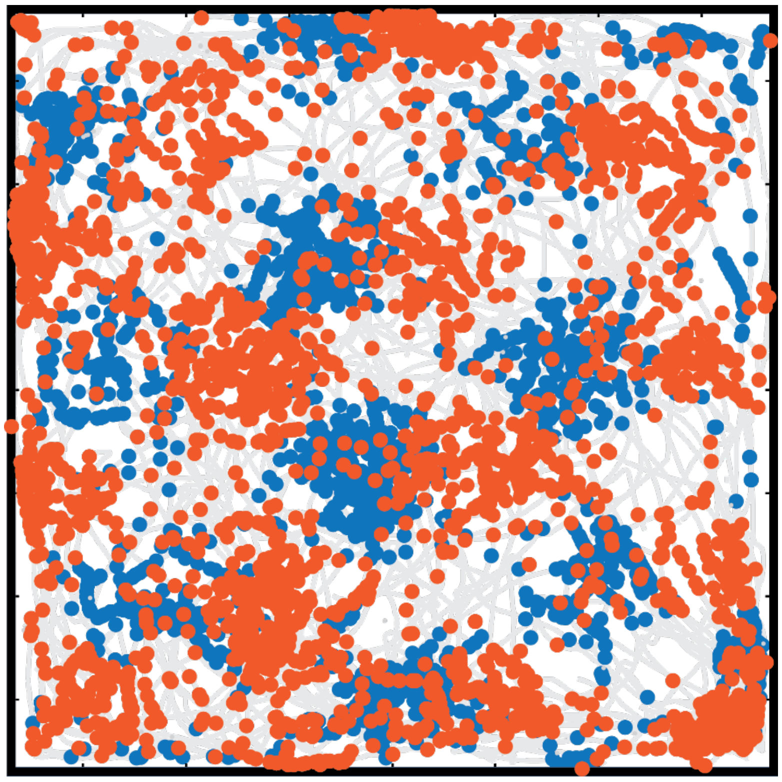

Hafting et al. (2005). *Nature* 436:801-806
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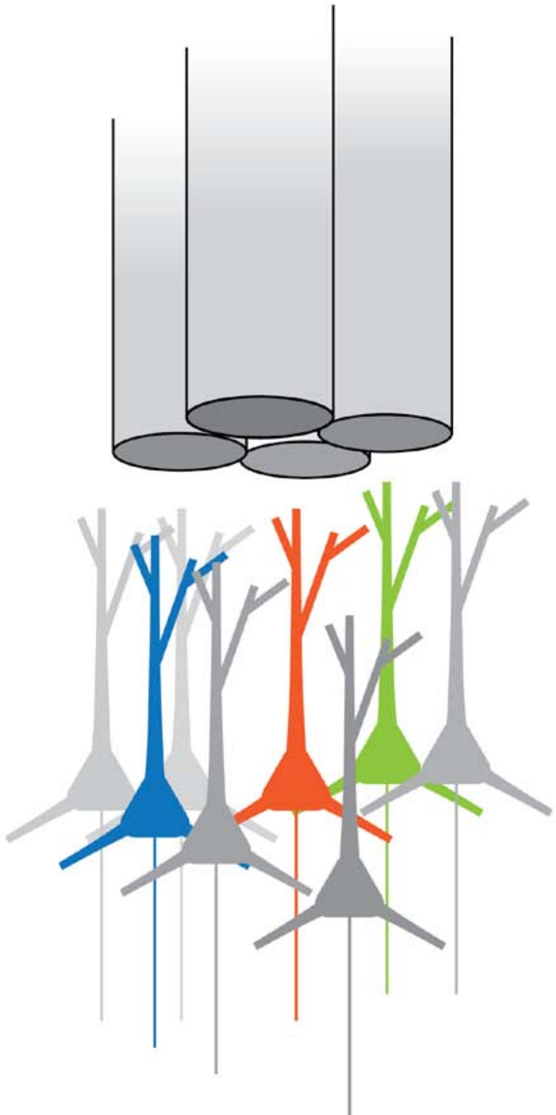
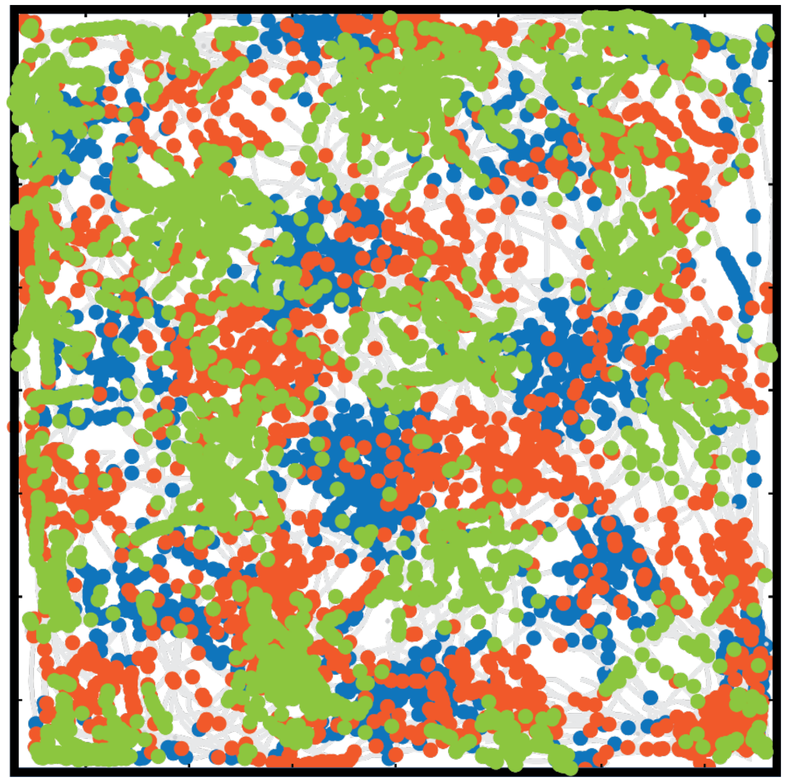
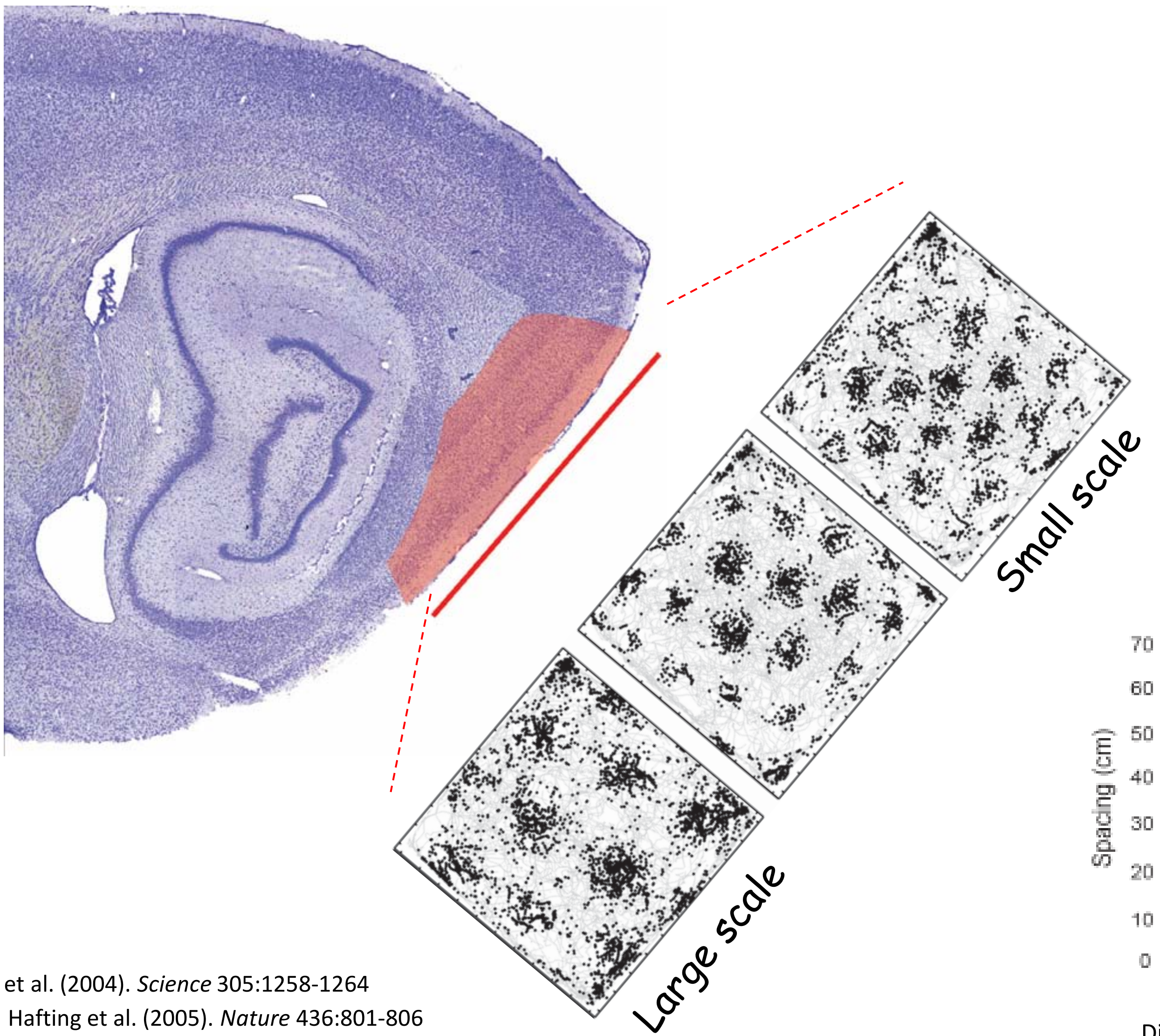


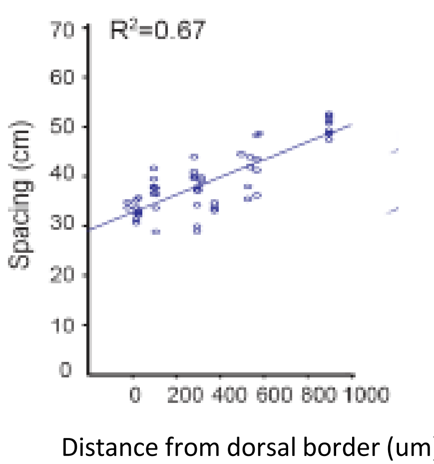


… similar to the salt-and-pepper organization of many other cortical representations (orientation selectivity in rodents, odours, place cells)

Grid scale (spacing) follows a dorso-ventral topograhical organization

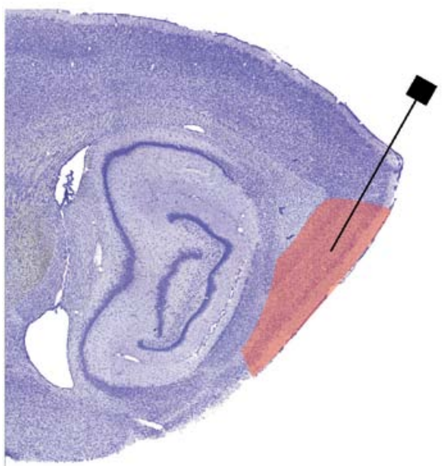


All animals:



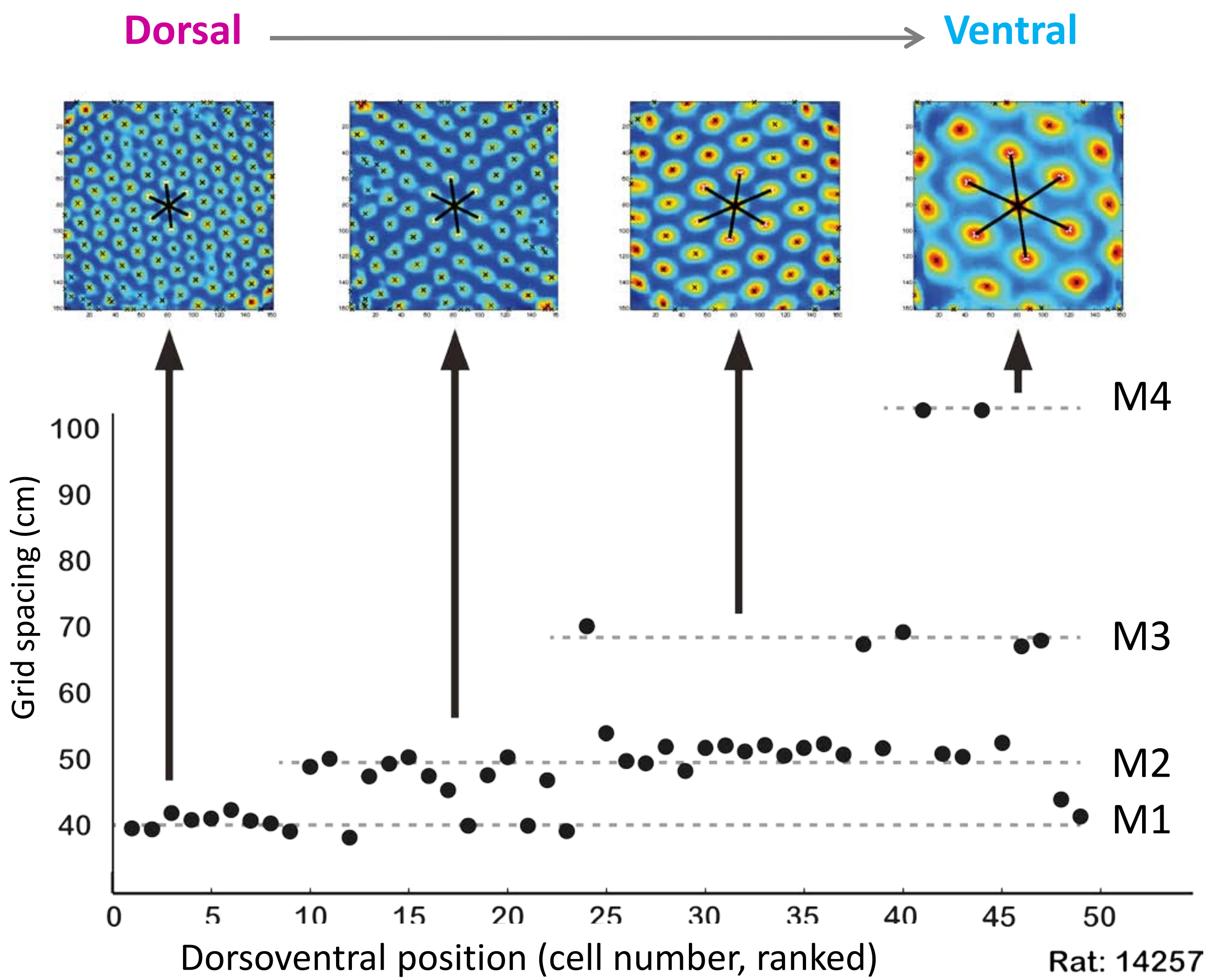
Fyhn et al. (2004). *Science* 305:1258-1264
Hafting et al. (2005). *Nature* 436:801-806
Brun et al. (2008). *Hippocampus* 18:1200-1212

But within animals, the steps in grid spacing are discrete, suggesting that grid cells are organized in modules



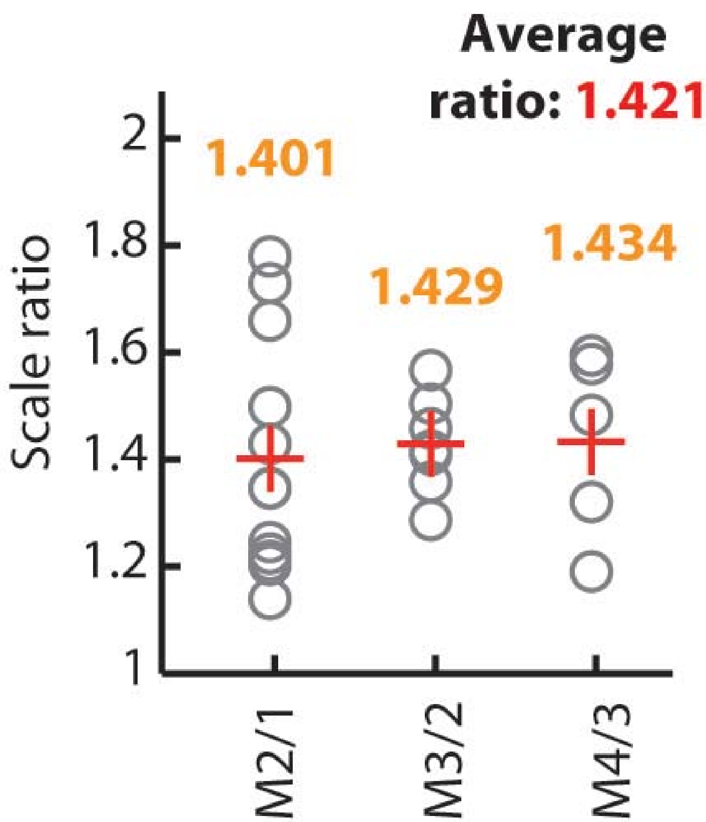
Tor & Hanne Stensola

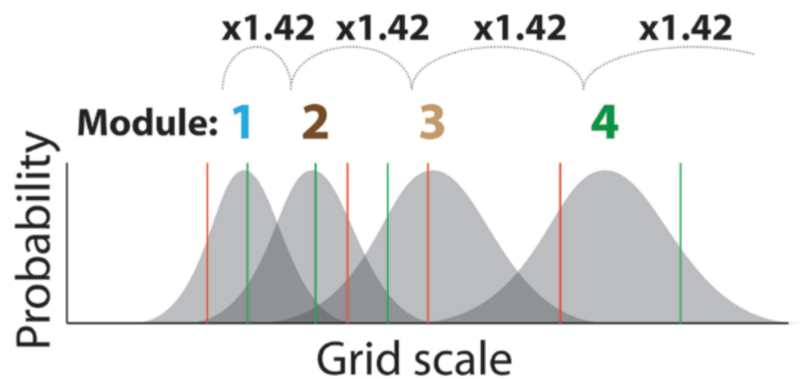
Trygve Solstad
Kristian Frøland



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



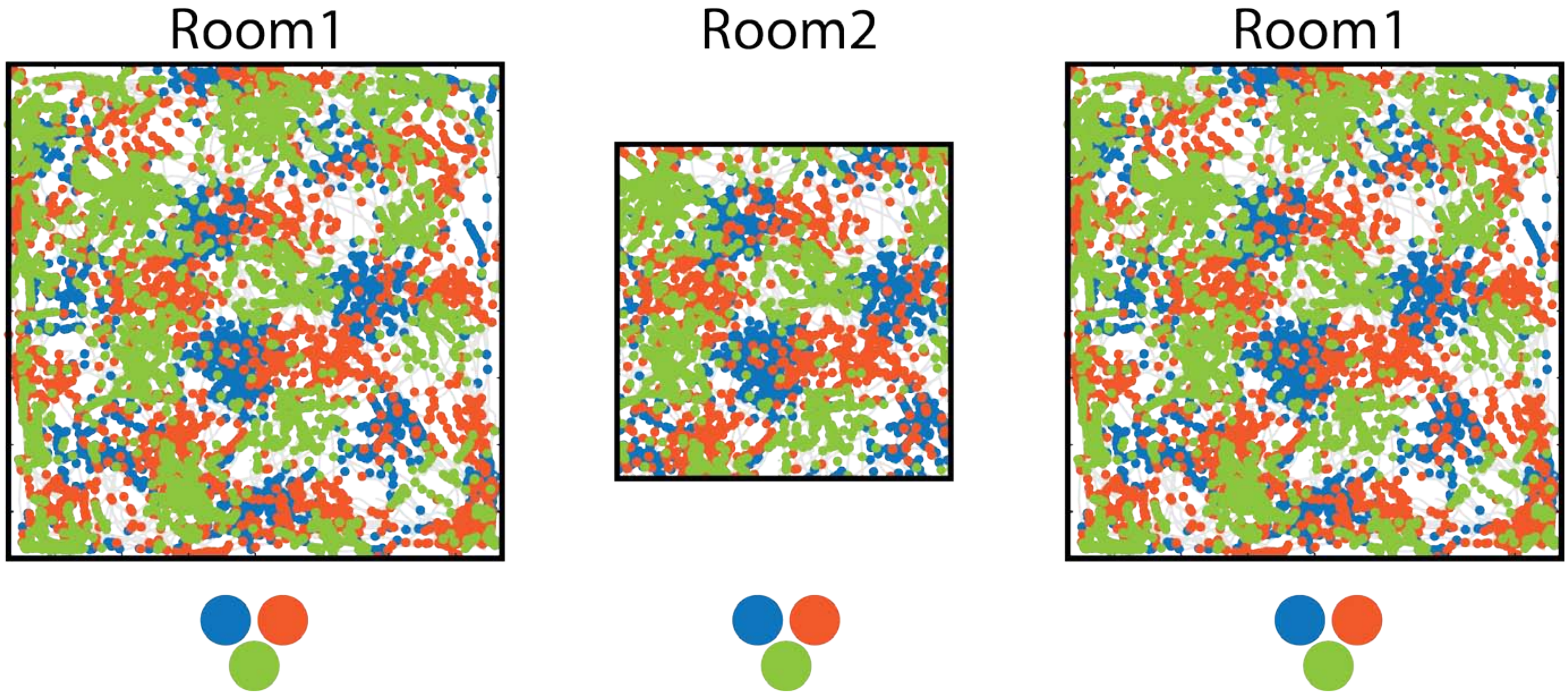


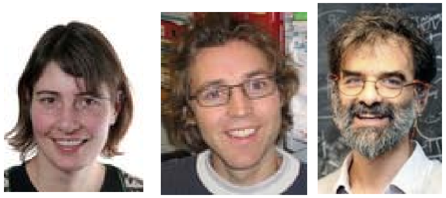
Although the set point is different for different animals, modules scale up, on average, by a factor of ~1.42 (sqrt 2).

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; Wei et al. 2013).

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



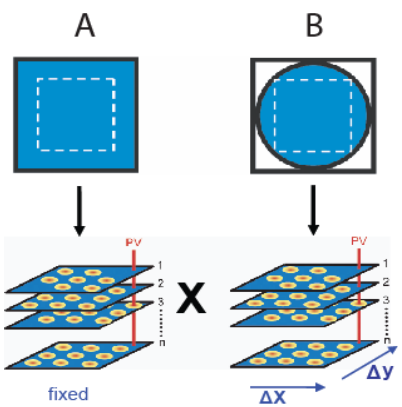


M. Fyhn T. Hafting A. Treves
Fyhn et al (2007). *Nature* 446:190-194

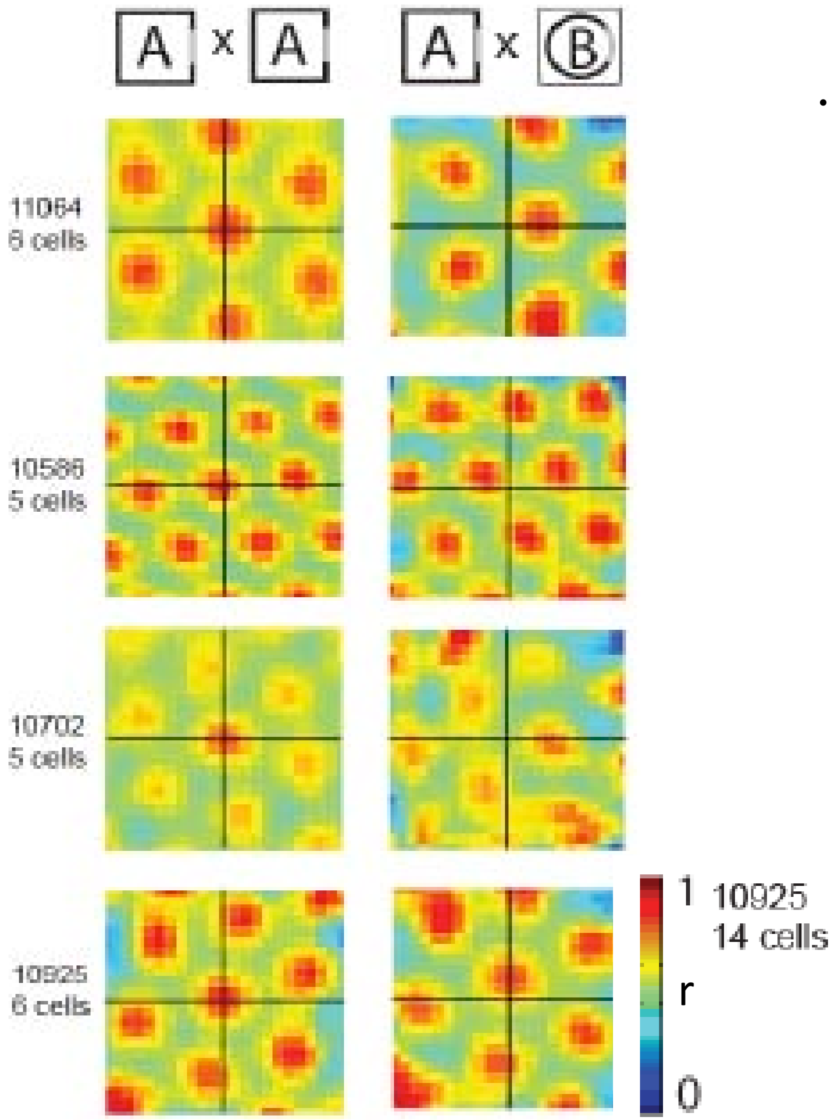
Tor & Hanne Stensola
Stensola et al (2012). *Nature* 492:72-78

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

Entorhinal cortex



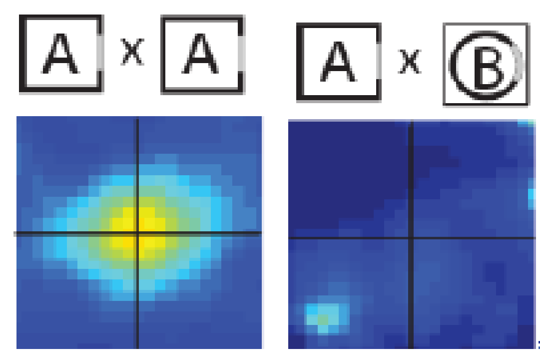
Crosscorrelation of assembly of rate maps: pattern is preserved
– just shifted



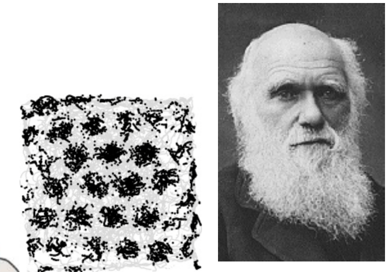
Fyhn et al. (2007). *Nature* 446:190-194.

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

Hippocampus (CA3):

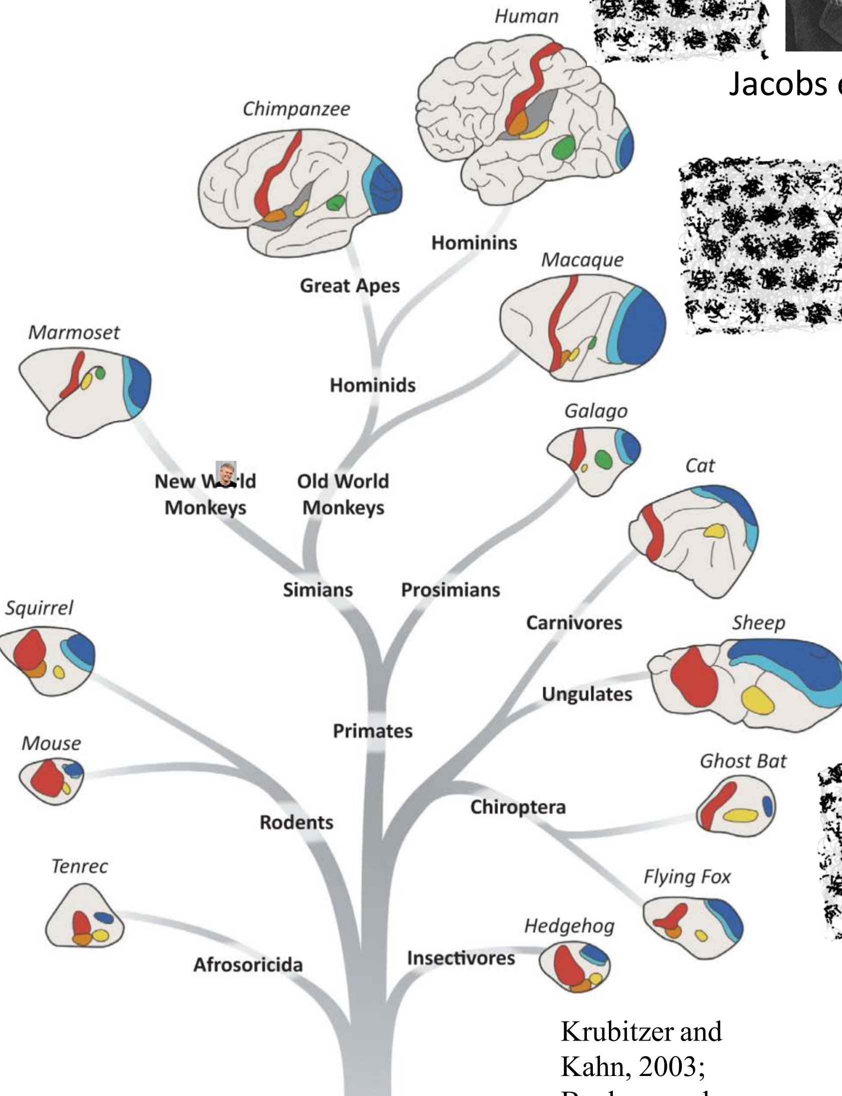


Grid-like cells have since been reported in bats, monkeys and humans, suggesting they originated early in mammalian evolution

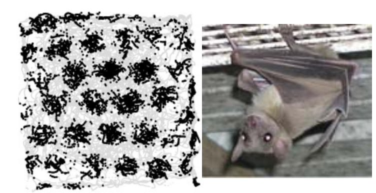


Jacobs et al., 2013

Killian et al., 2012



Krubitzer and Kahn, 2003; Buckner and Krienen, 2013



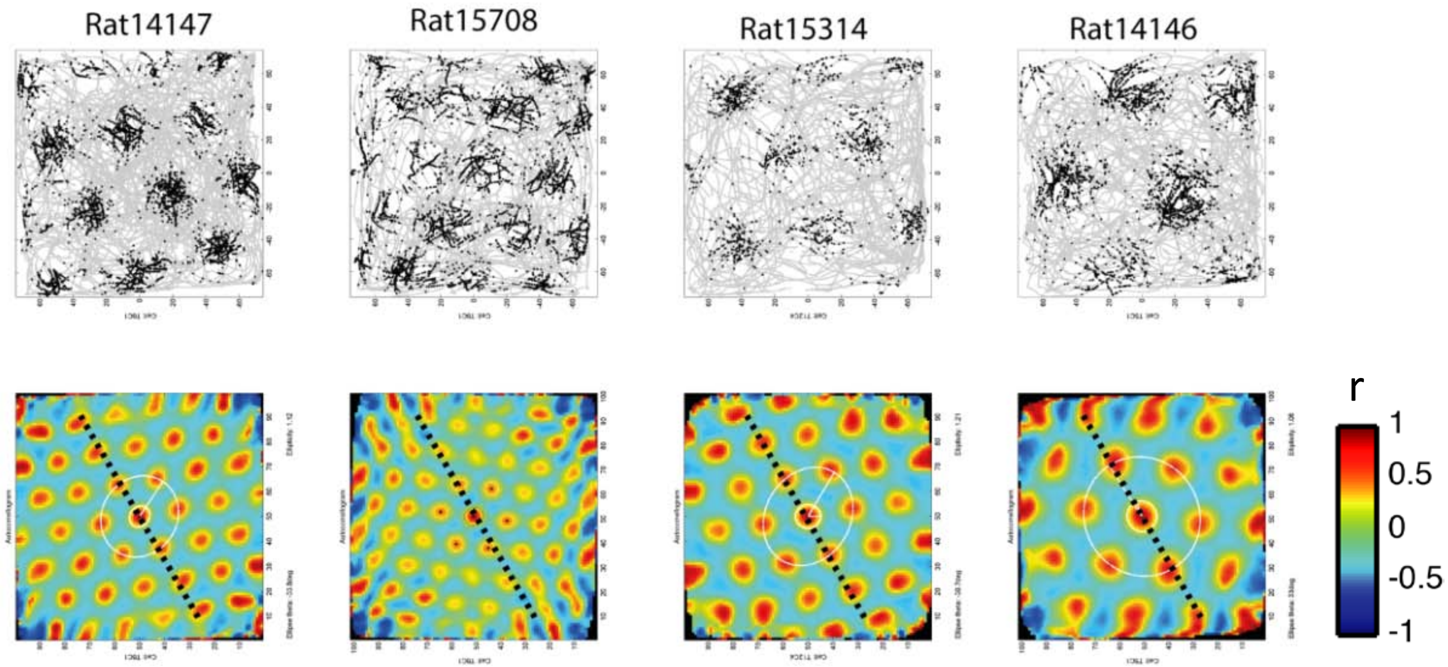
Yartsev et al 2011

Fyhn et al 2008

1. Mechanism for geometric alignment

To be useful for navigation, grid cells cannot only respond to self-motion cues. They must also anchor to external reference frames. How?

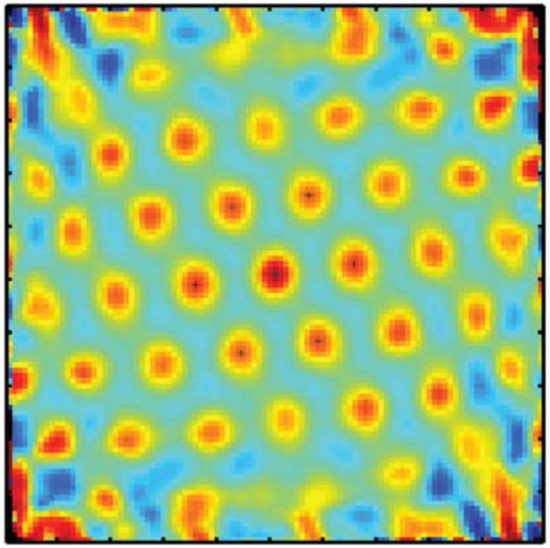
Grid orientation is remarkably similar across animals. The same few orientation solutions are expressed in different animals….

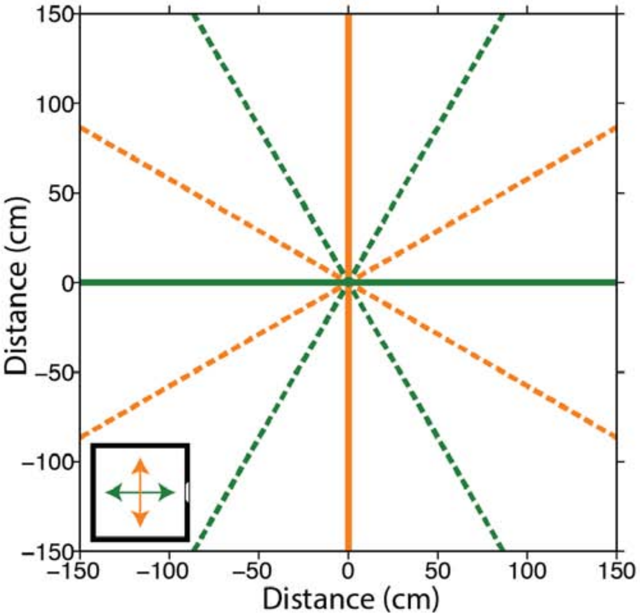


What are then the factors that determine orientation?

Tor & Hanne Stensola

Grid orientation is determined by the cardinal axes of the local environment





Stensola et al. (2015).
Nature, in press

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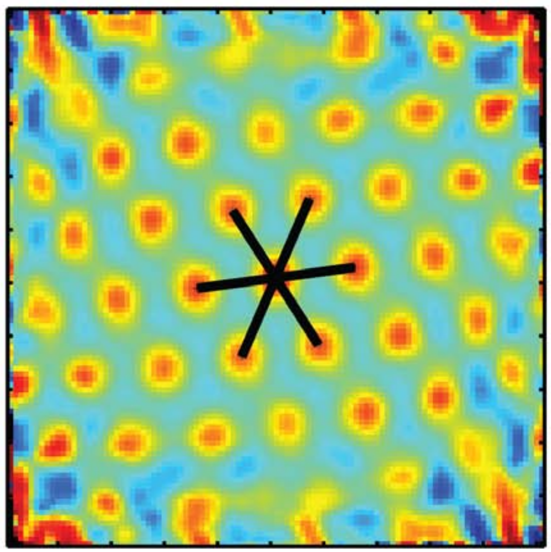

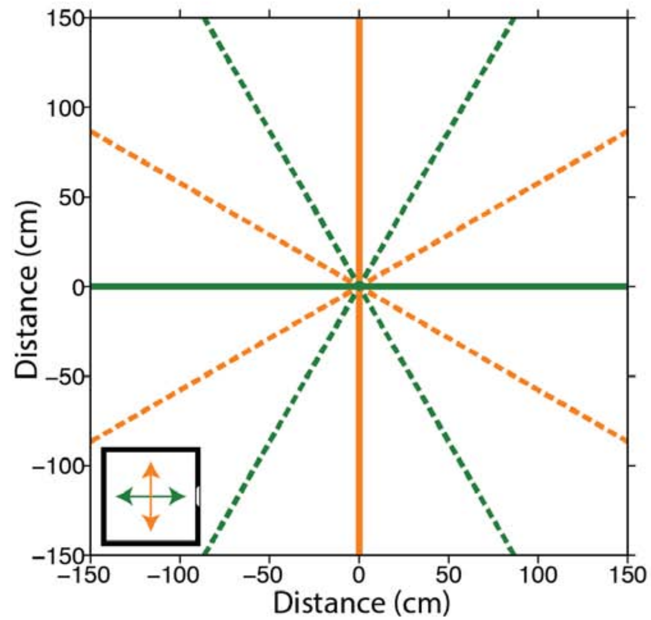

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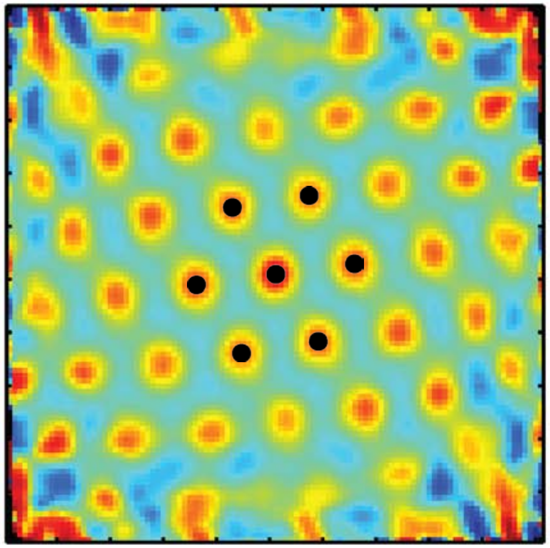

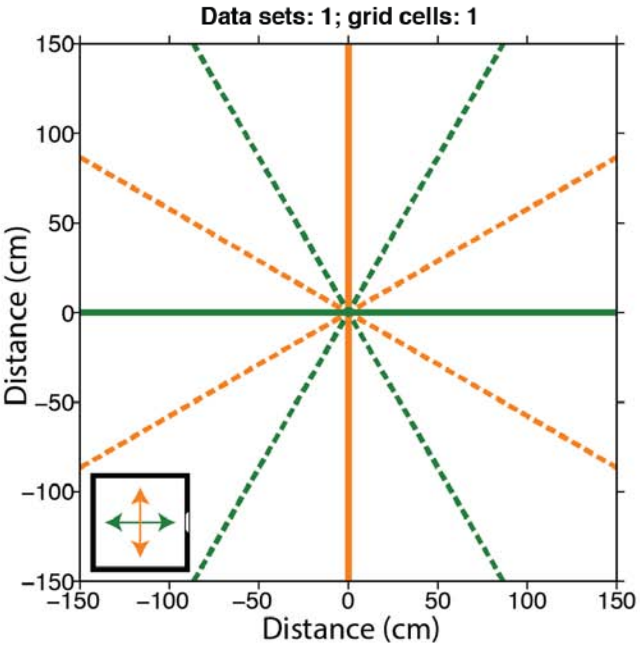

Stensola et al. (2015).
Nature, in press

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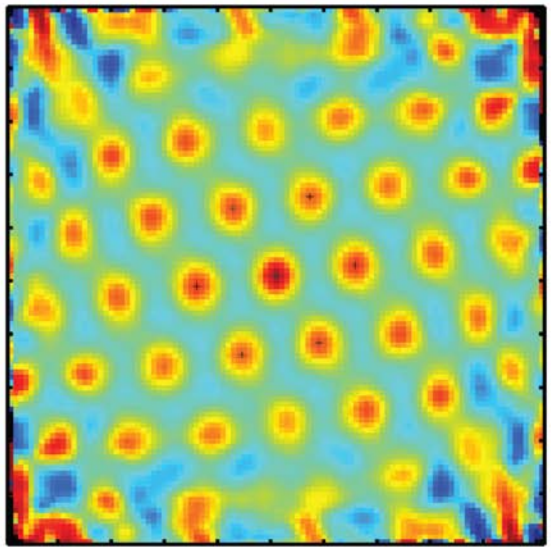

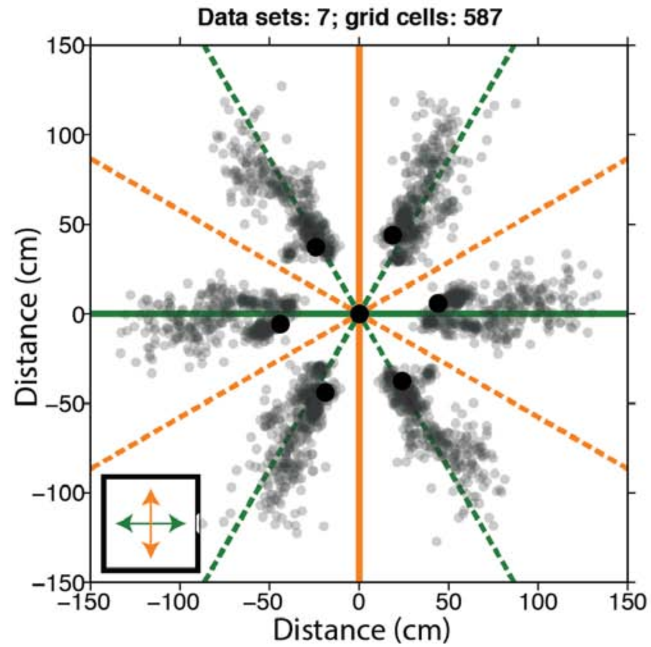

Stensola et al. (2015).
Nature, in press

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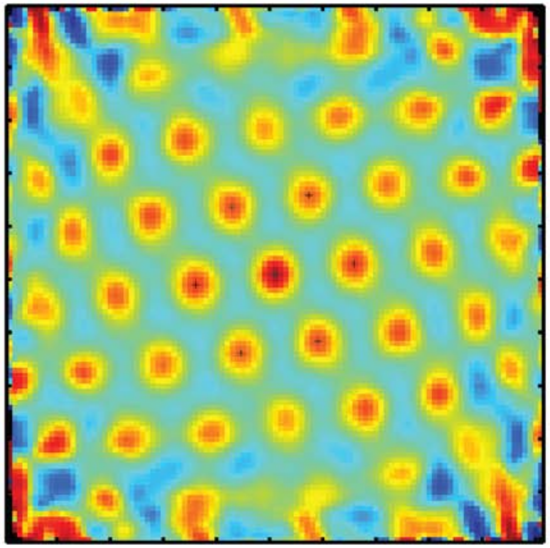
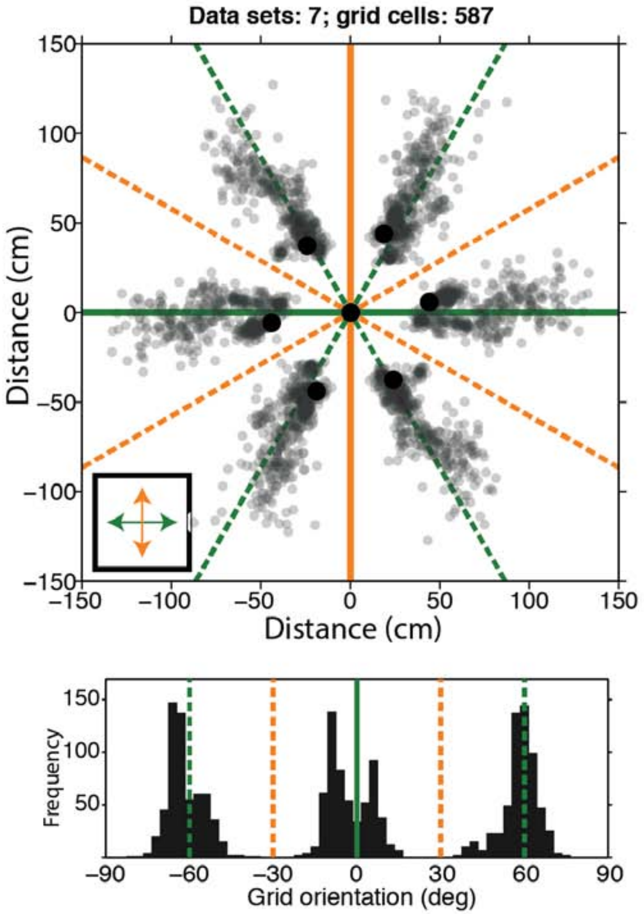
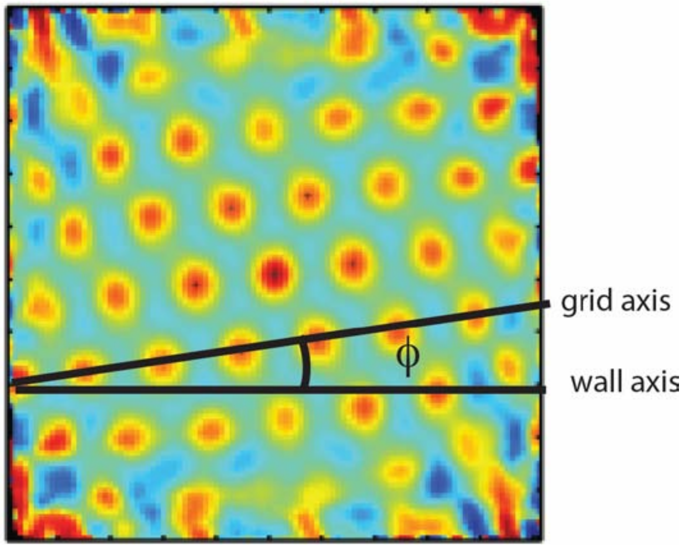
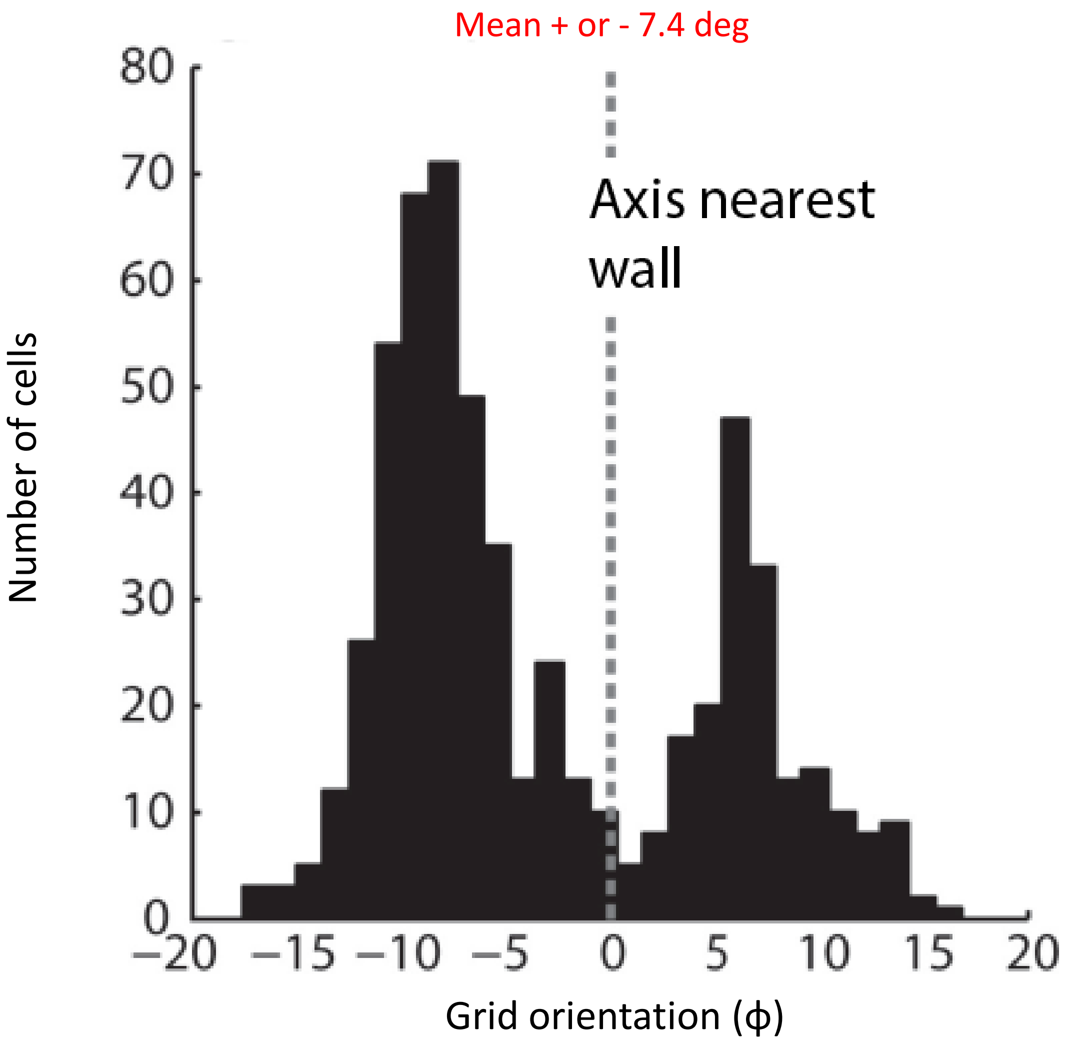




Stensola et al. (2015).
Nature, in press

But the alignment is not perfect. After normalization to the nearest wall, grid orientations peak not at 0° but at ±7.5°



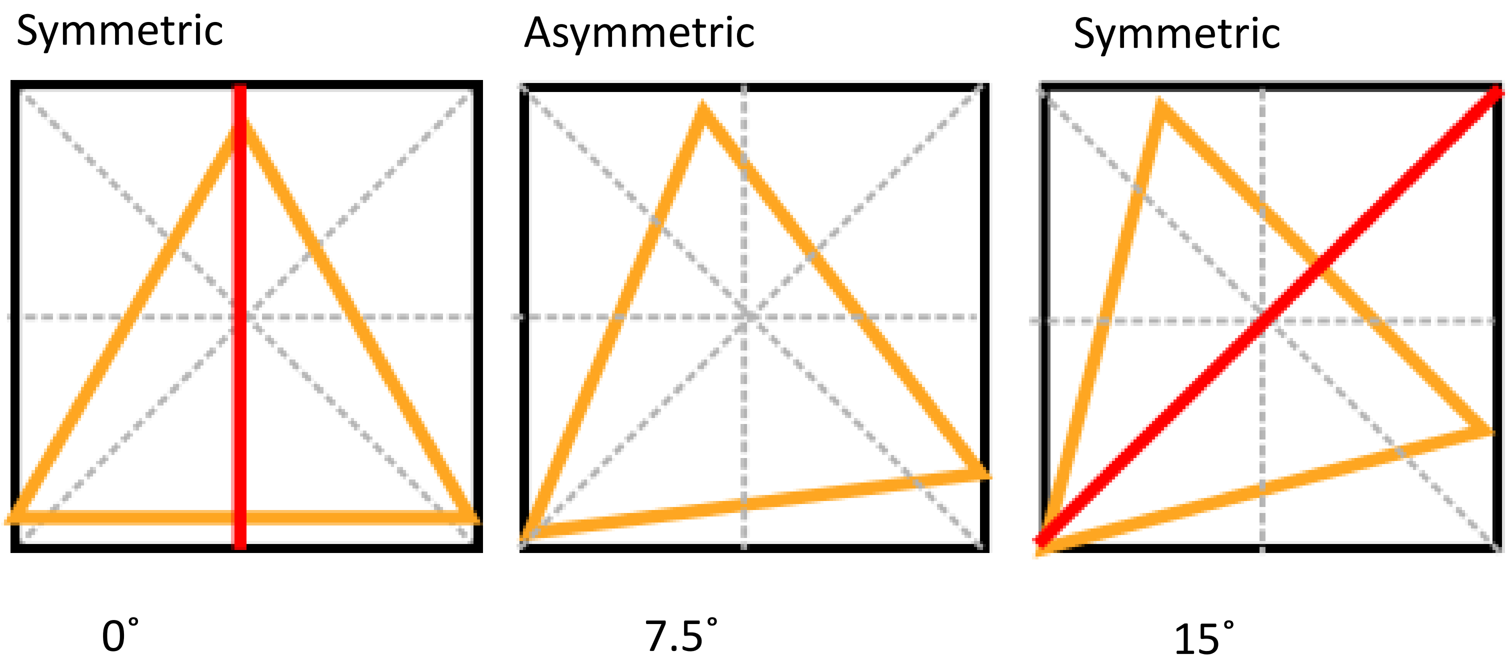


Orientations shy away from both 0° and ±15° !

Stensola et al. (2015). *Nature*, in press

What is special about 7.5°?

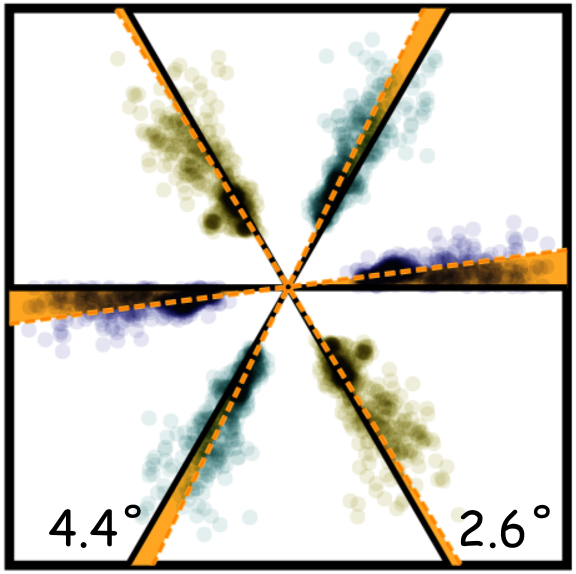
<u>7.5° minimizes symmetries</u> with the axes of the environment

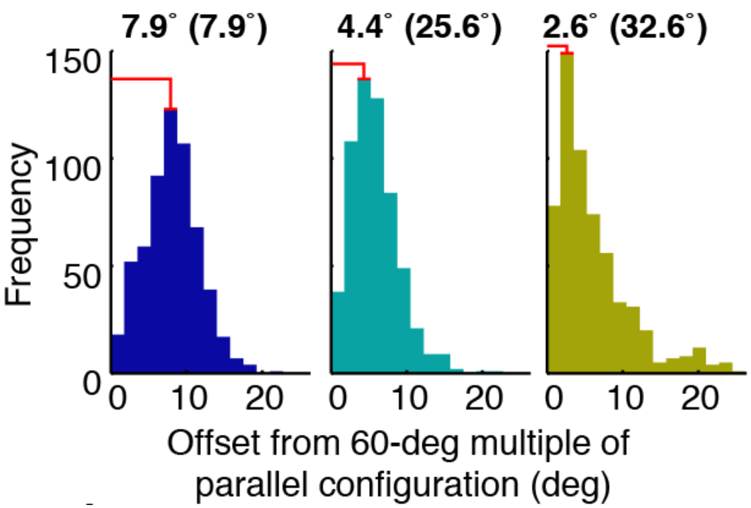


Helpful to disambiguate geometrically similar segments of the environment?

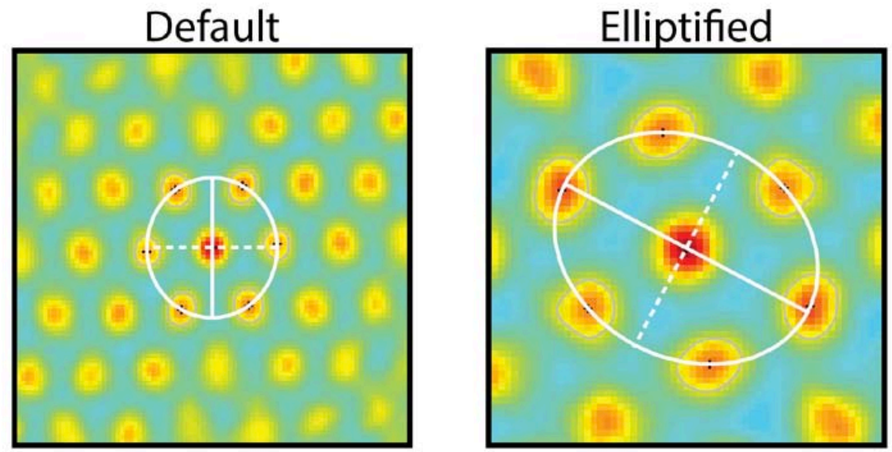
What is the mechanism behind the 7.5° offset?

The rotation differed between the 3 grid axes…

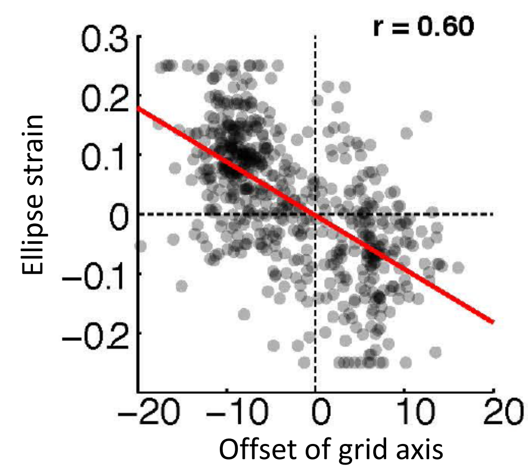




Differential rotation of the grid axes implies elliptification of the grid pattern:

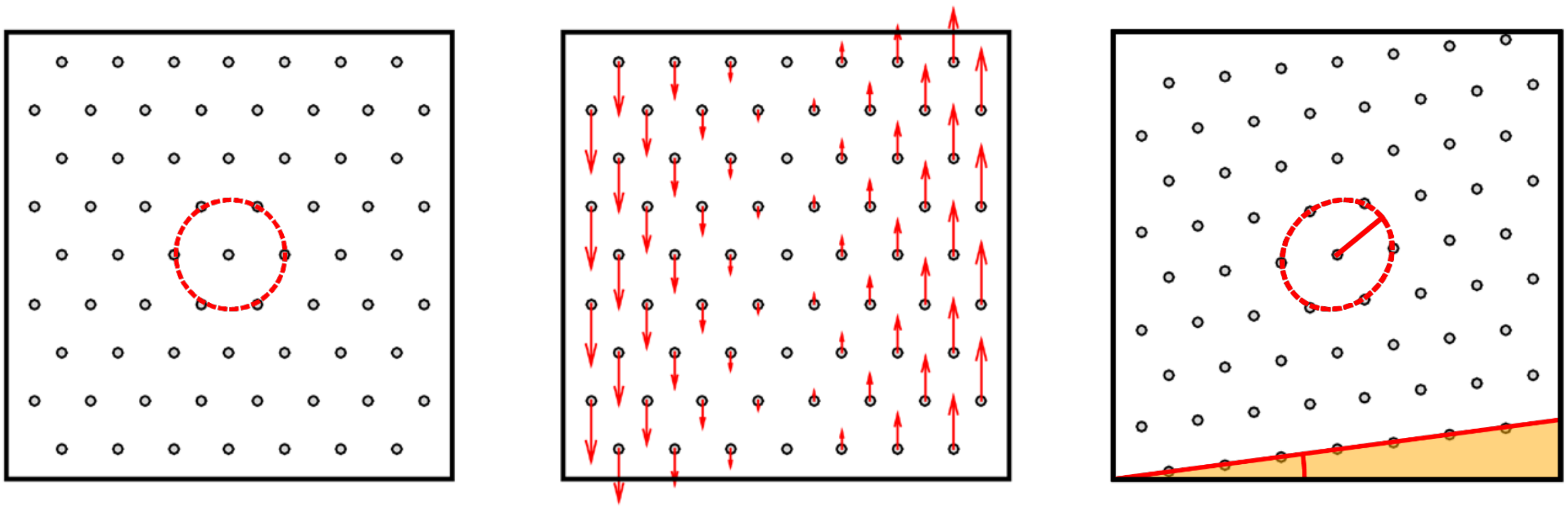


Rotational offset and elliptic deformation were correlated:



Stensola et al. (2015). *Nature*, in press

Elliptification and axis rotation may thus be common end products of shearing forces from the borders of the environment

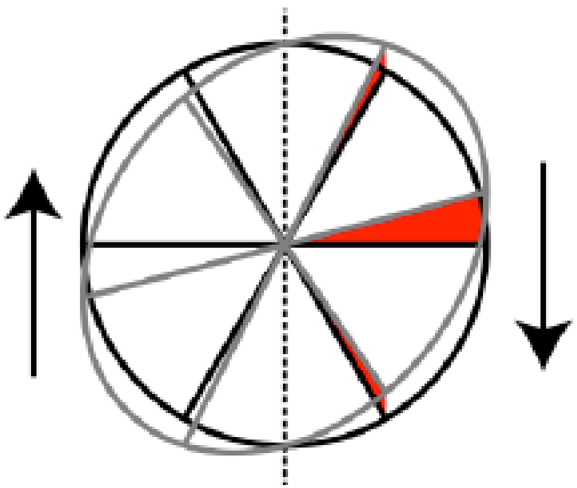


Stensola et al. (2015).
Nature, in press

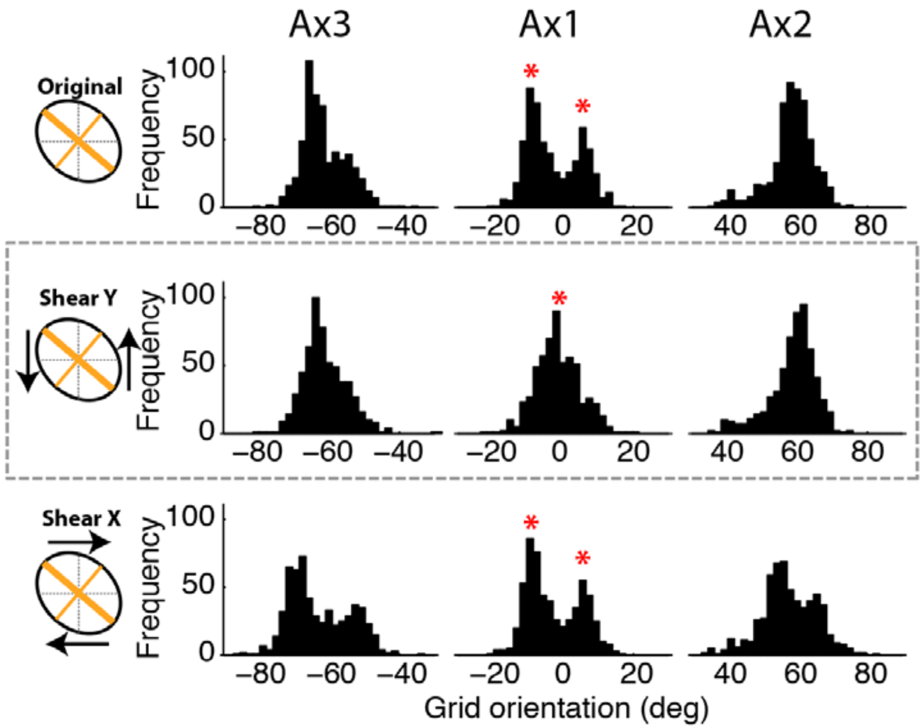
$$f(x,y) = \begin{bmatrix} x + \gamma_1 y \\ y + \gamma_2 x \end{bmatrix}$$

elliptification
non-coaxial rotation

Minimizing ellipticity along one wall axis (by analytically reversing the shearing) completely removed the bimodality in the offset distribution, for all axes…



De-shearing

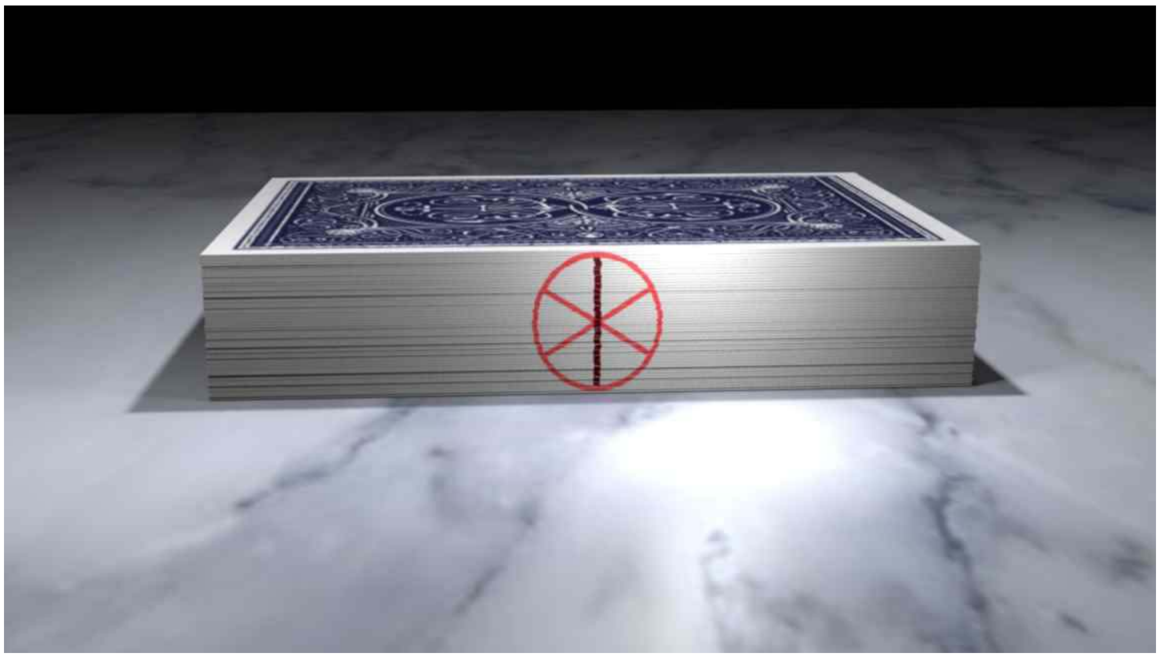


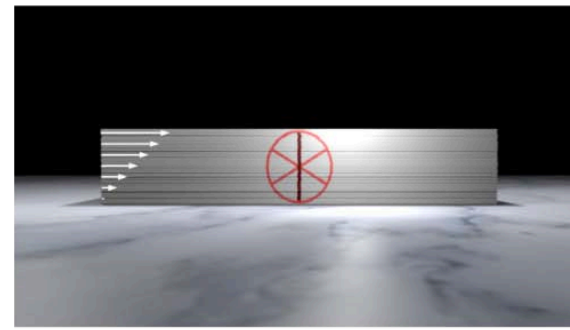
… implying that grid patterns are anchored – and distorted – in an axis-dependent manner by shear forces from specific boundaries of the environment

Stensola et al. (2015). *Nature*, in press

Shear forces along the walls cause elliptification and axis-dependent grid rotation

AXIS ORTHOGONAL TO SHEAR FORCES:





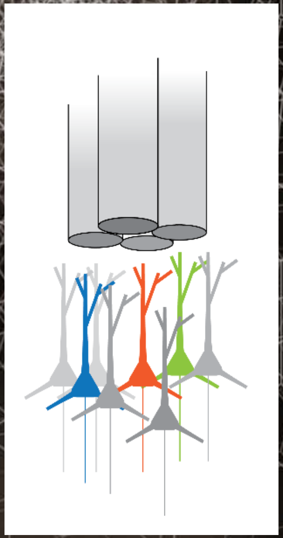
The data point to shearing as the mechanism for grid distorition and rotation and imply that local boundaries exert distance-dependent effects on the grid

Animation by T. Stensola

2. Fine-scala functional anatomy

To understand how grid patterns are generated, and how grid cells interact with other cell types, we need to determine **how the network is wired together**.

But tetrode recordings are not sufficient for this purpose.



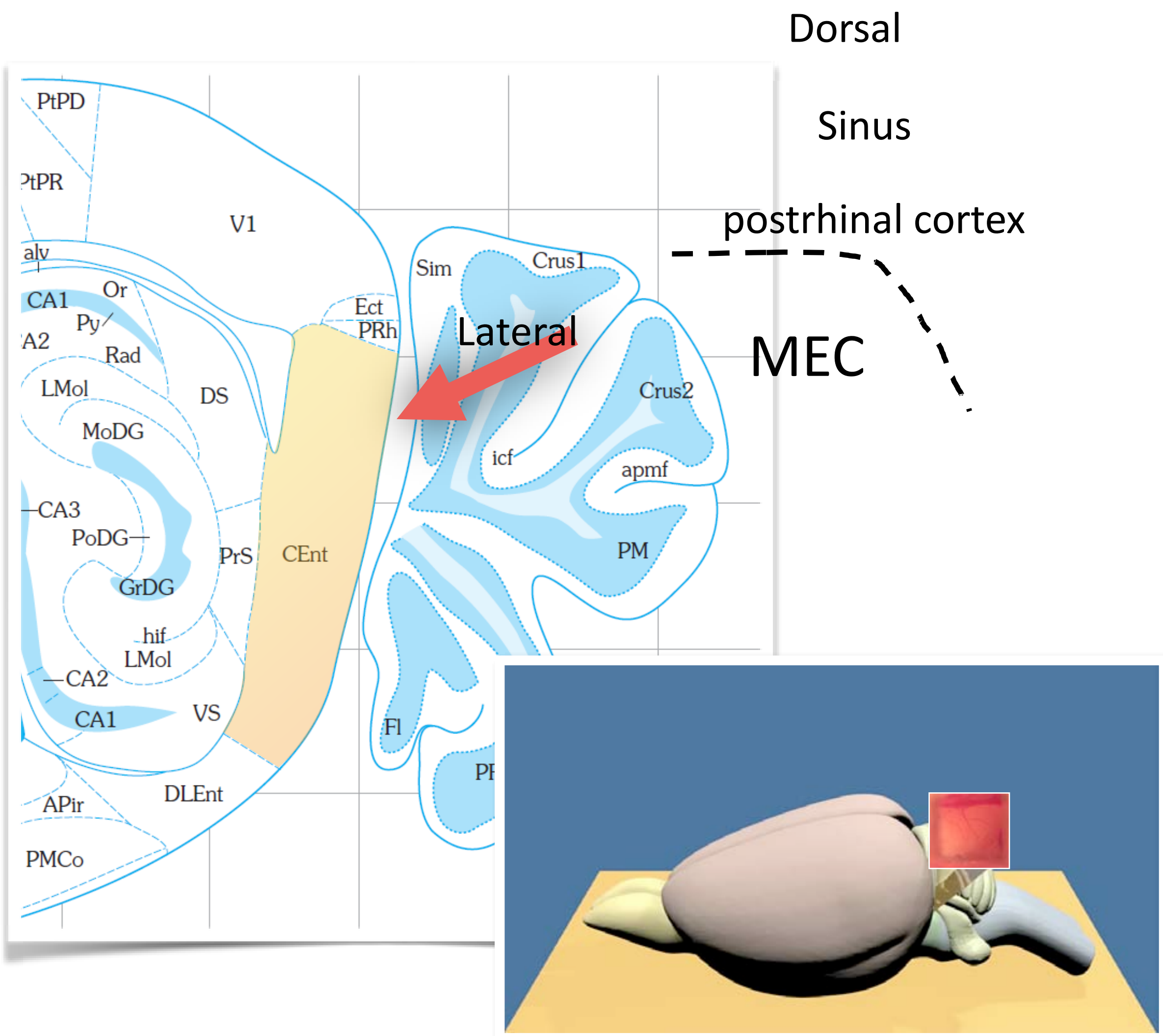
Determining the fine-scale functional topography of the entorhinal space network:

Optical imaging with a fluorescent calcium indicator would improve the spatial resolution beyond that of tetrodes...

But access to the medial entorhinal cortex is a challenge..

Albert Tsao

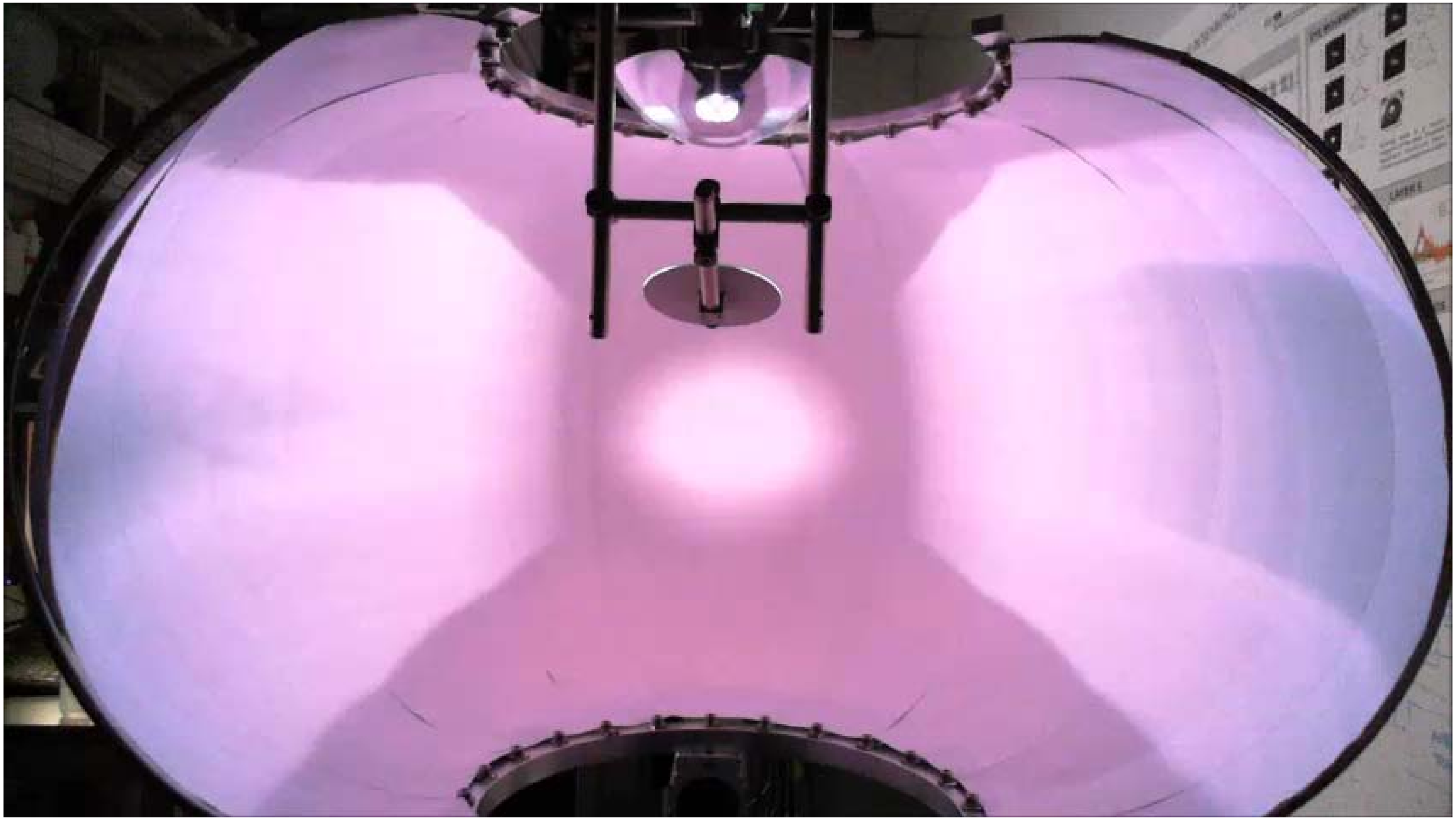
Tobias Bonhoeffer

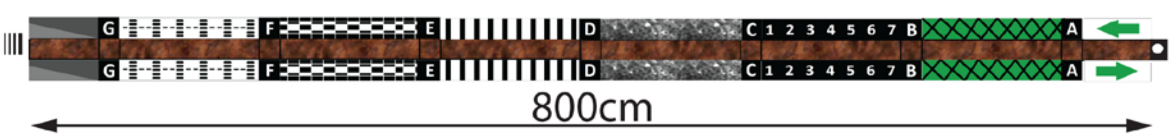


Possible solution: Accessing the entorhinal surface through a prism

Tsao et al., unpublished;
See Heys et al, Neuron, Dec 2014, for a similar approach

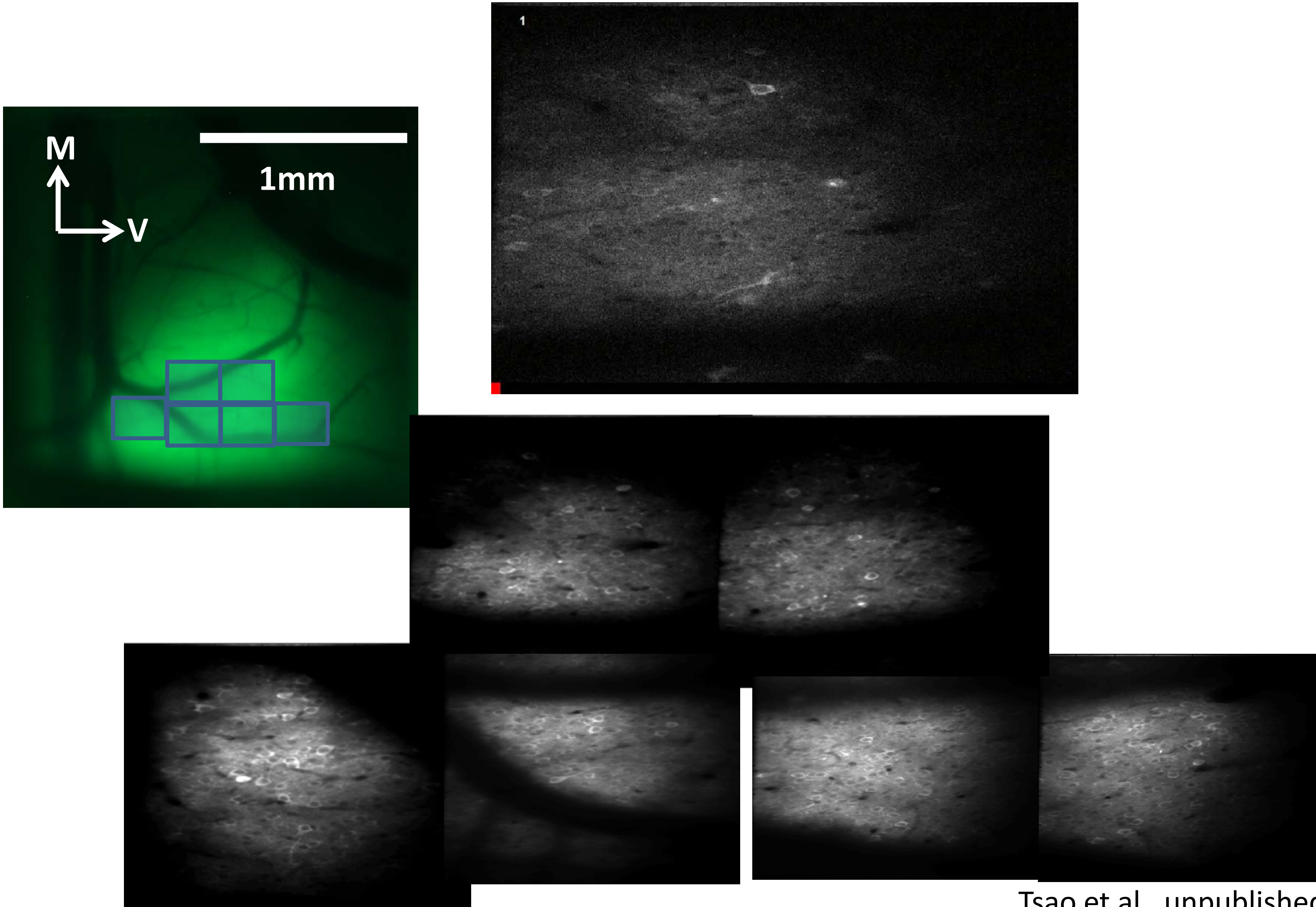
Imaging grid cells of GCaMP6-injected mice in a linear virtual environment





Tsao et al., unpublished

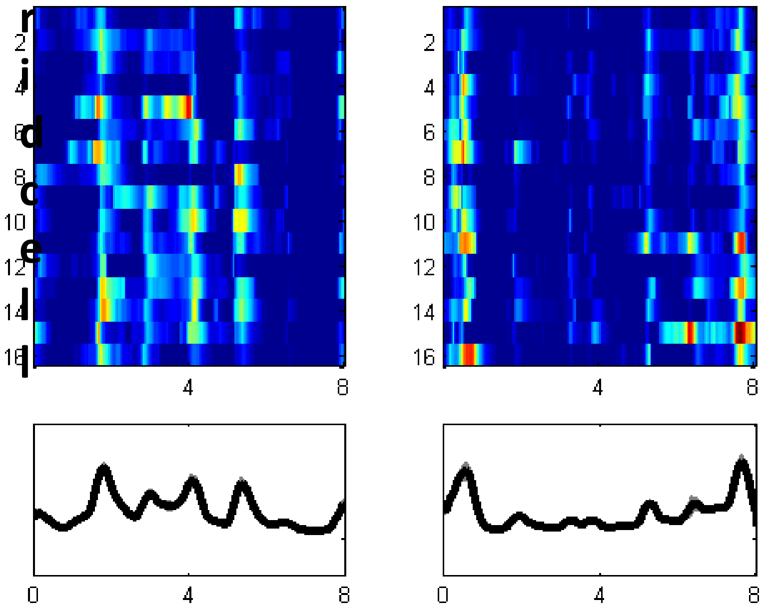
Hundreds of entorhinal cells can be imaged at cell or sub-cell spatial resolution in GcAMP6-expressing cells during virtual navigation

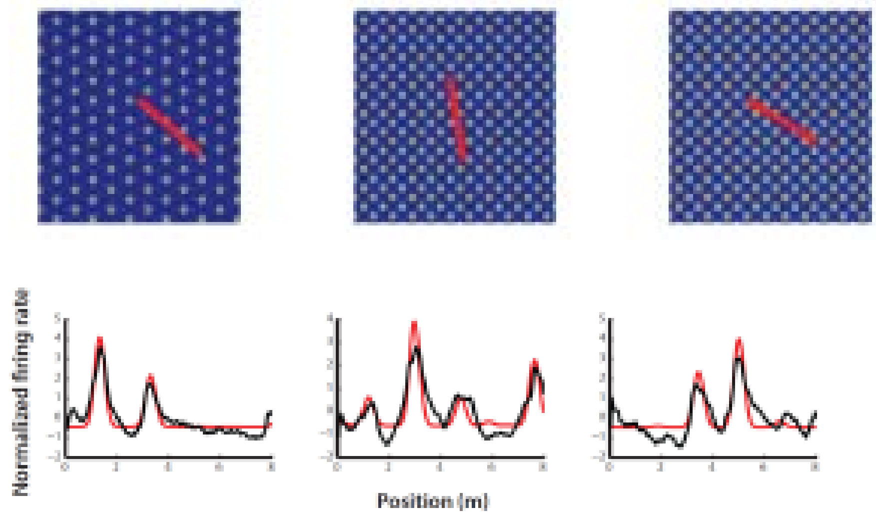


Tsao et al., unpublished

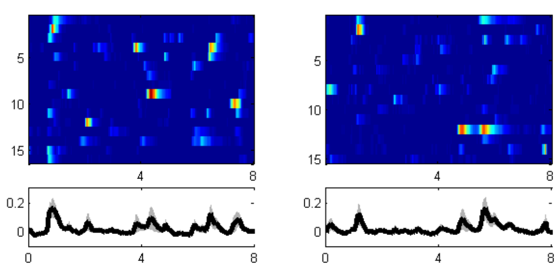
Grid cells can be identified as cells with periodic firing fields

Grid cell





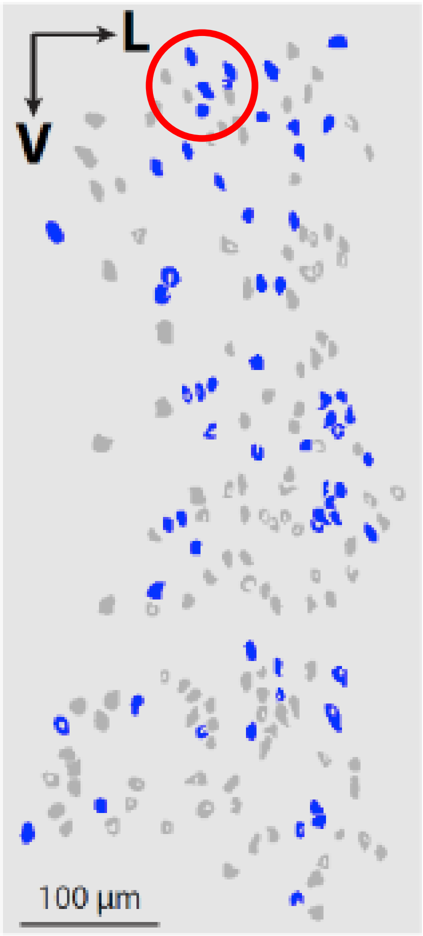
Non-gridcell



Tsao et al., unpublished

Grid cells are distributed but form functionally homogeneous clusters

Grid cells cluster more
than expected by chance:



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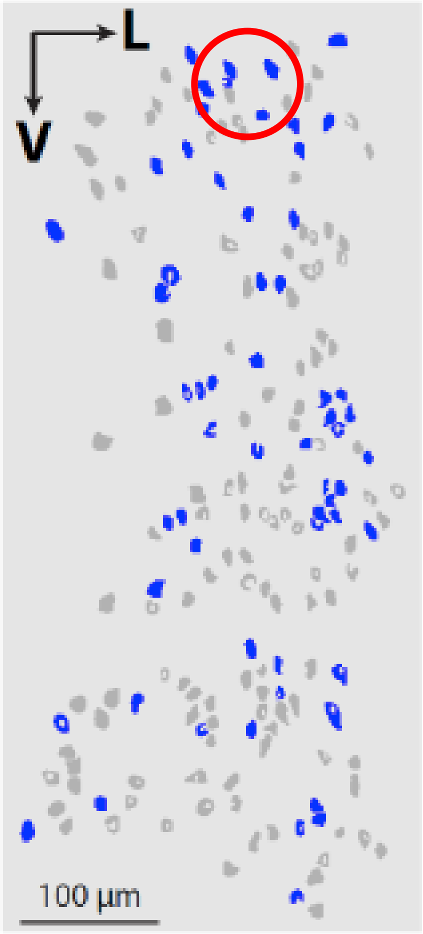

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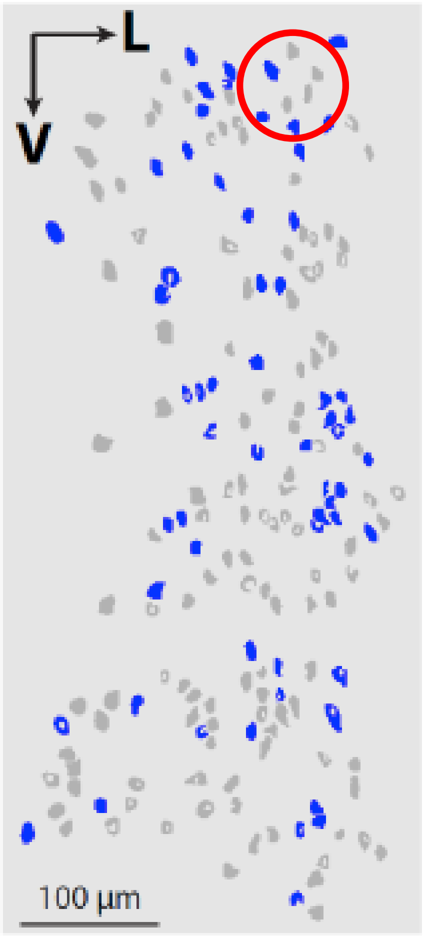

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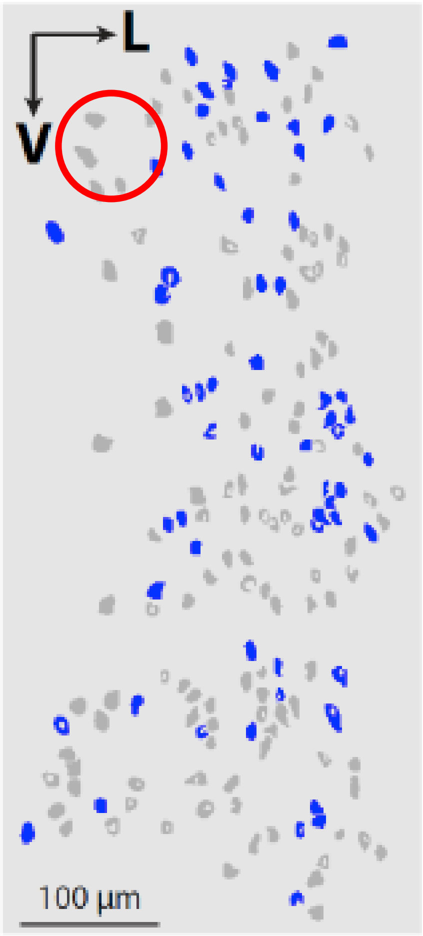

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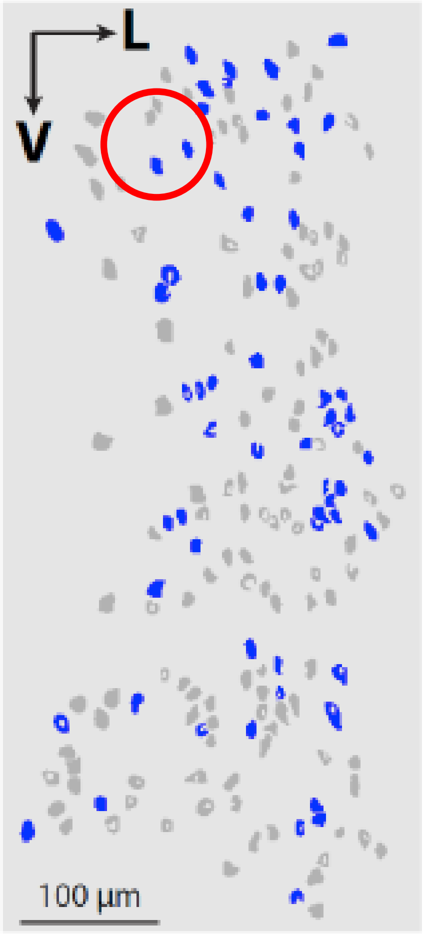

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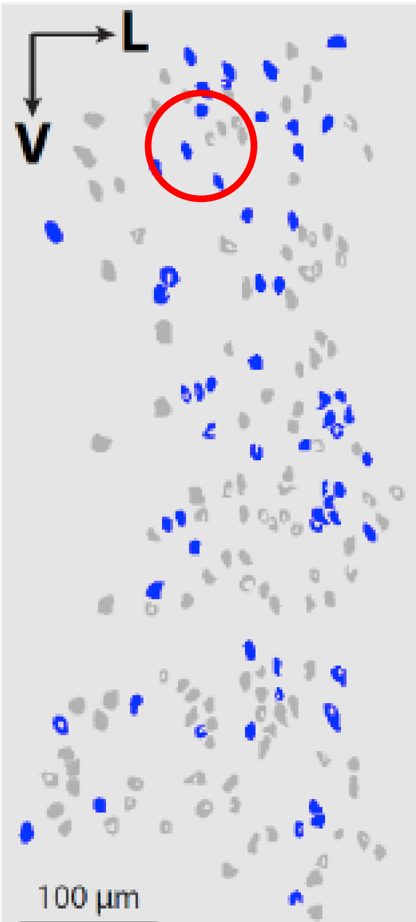
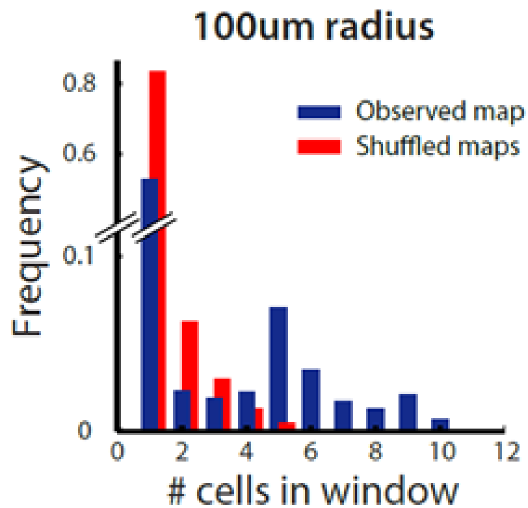
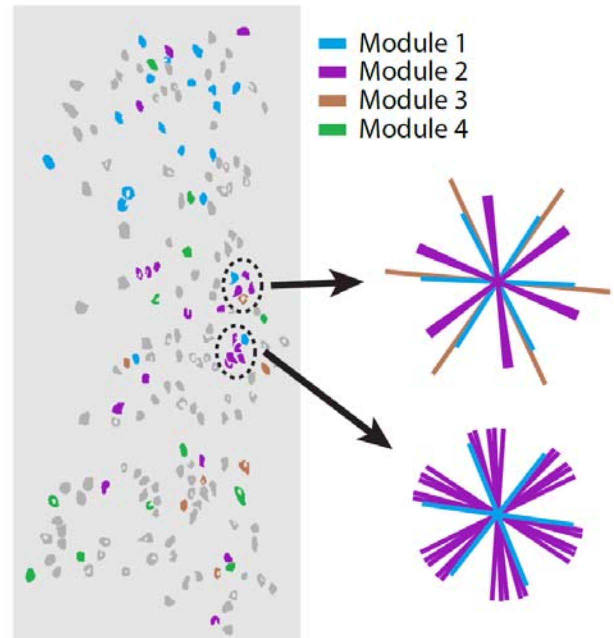
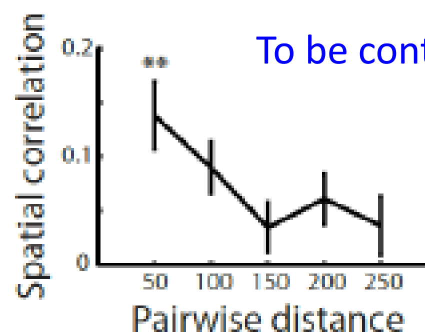




Grid clusters belong preferentially to the same grid module:



Adjacent grid cells have grid phases that are more similar than than expected by chance:



To be continued…

Tsao et al., unpublished

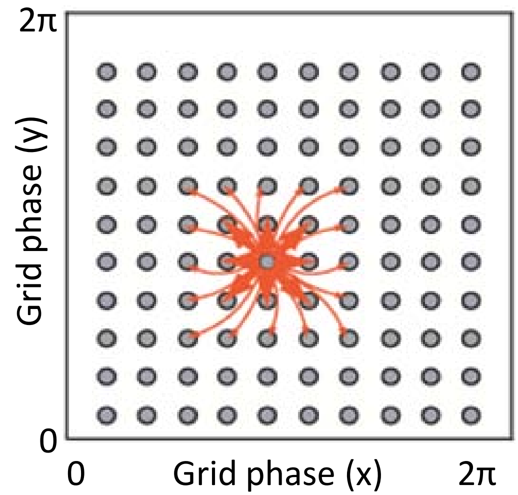
3. Mechanism of hexagonal symmetry: How is the grid pattern generated?

Most (all) network models for grid cells involve continuous attractors...

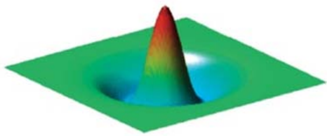
...where

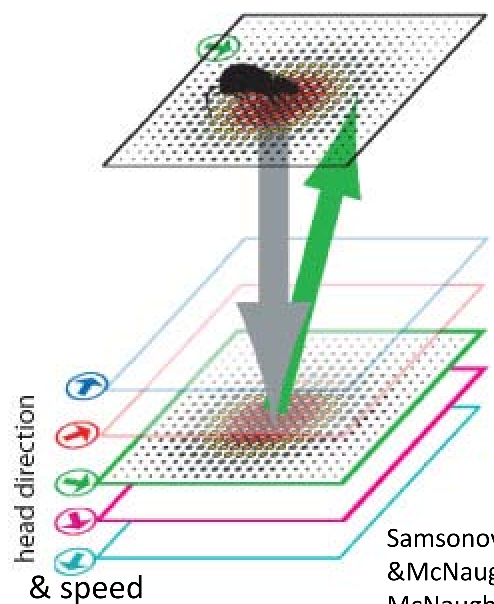
- localized firing may be generated by mutual excitation between cells with similar grid phase

- 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).





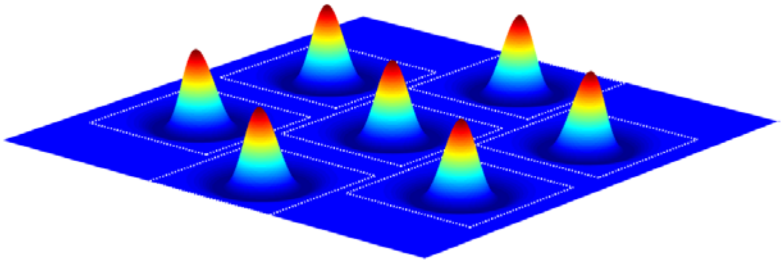
Samsonovitch &McNaughtn 1997; McNaughton et al. 2006

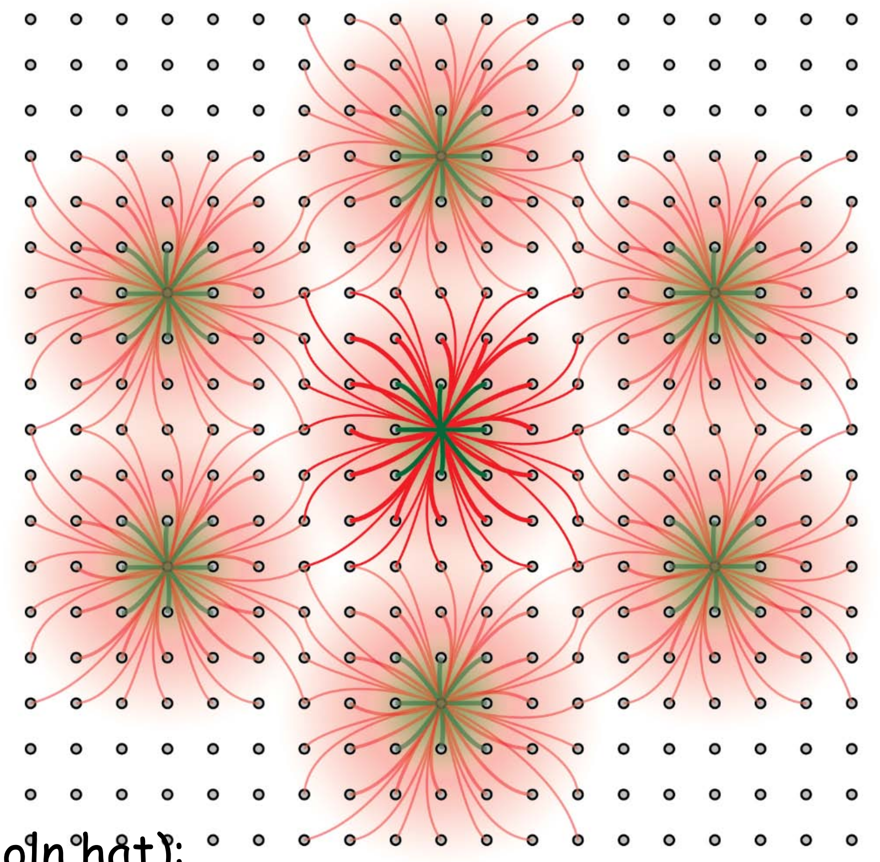
THIS EXPLAINS LOCALIZED FIRING BUT WHERE DOES THE HEXAGONAL PATTERN COME FROM?

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.

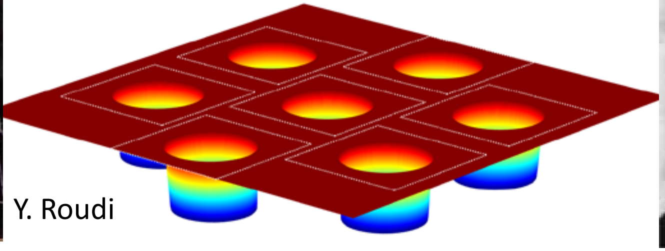




(Tor Stensola)

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

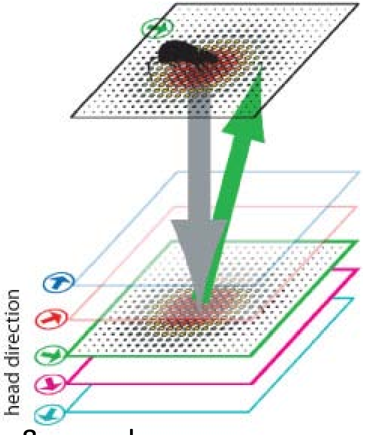
Y. Roudi



Self-organization of grid network in a continuous attractor model

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

Y. Roudi



& 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.

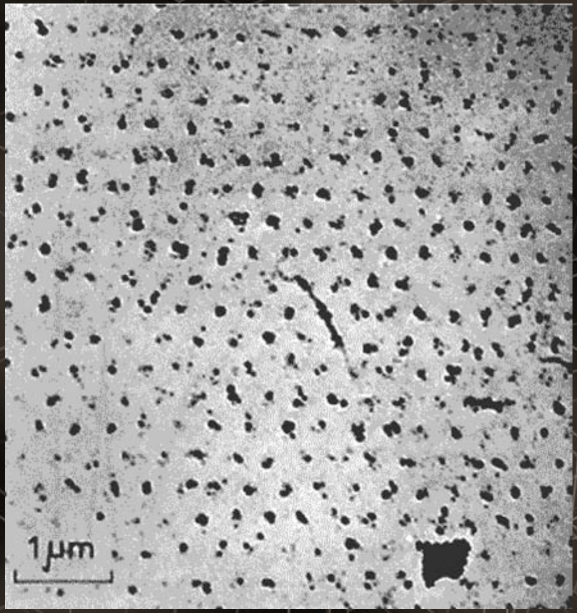
> HALF A CENTURY HAS PASSED AND TOLMAN´S MAP *HAS* BEEN ´PHYSIOLOGIZED´

"Today, however, I believe that this (physiologizing) is where the great new break-throughs are coming.."

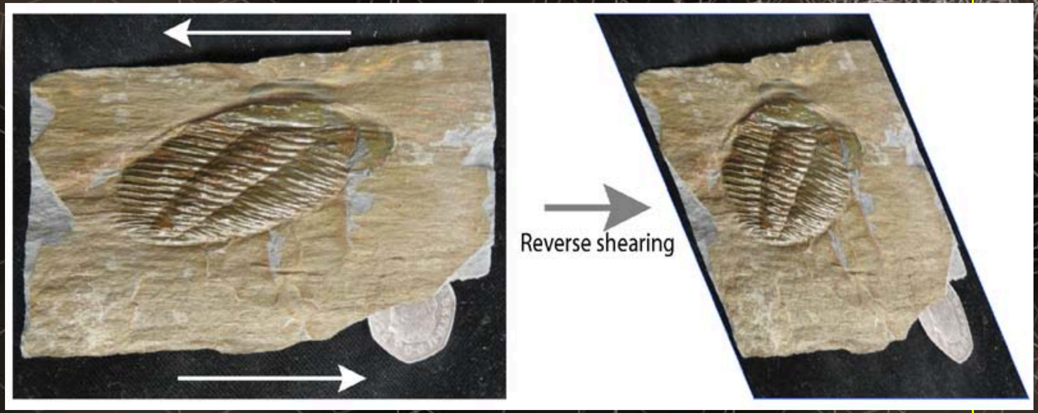
E.C. Tolman (1958)

SUMMARY

- Grid cells define **hexagonal arrays** that tessellate local space.
- Grid modules are **organized** in anatomical space.
- Grid cells cluster discontinuous **modules**.
- The intrinsic functional organization of a grid module is **preserved** across environments.
- Fine-scale grid-cell architecture can be investigated with **2-photon** calcium imaging.
- Grid cells may be generated by **attractor** networks.



Abrikosov, 1957



Courtesy Pete Lawrance

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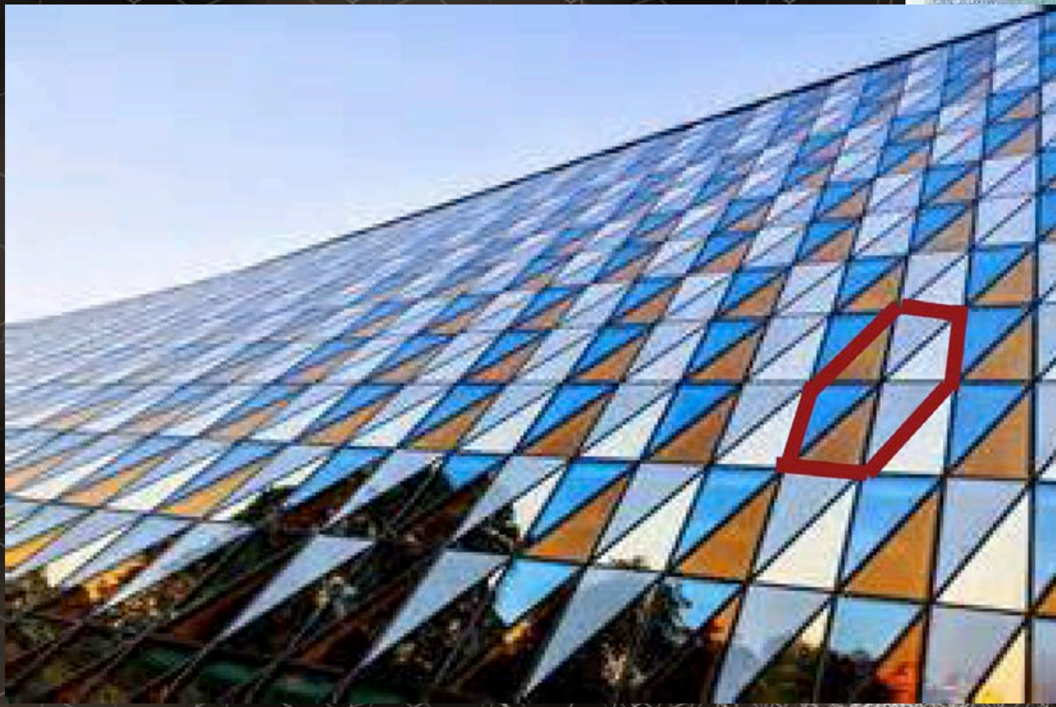
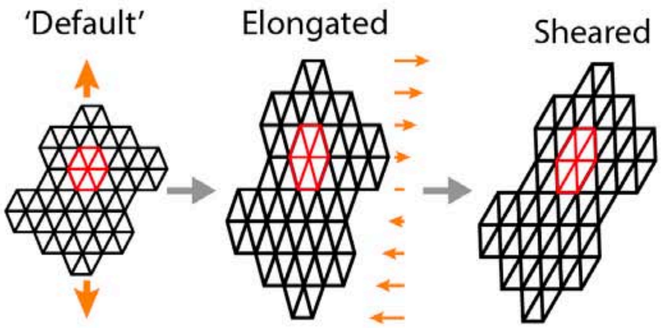



HUNDRA KRONOR
100


'Default'
Elongated
Sheared

A. Wagner