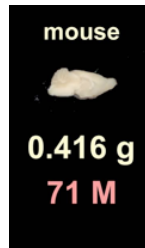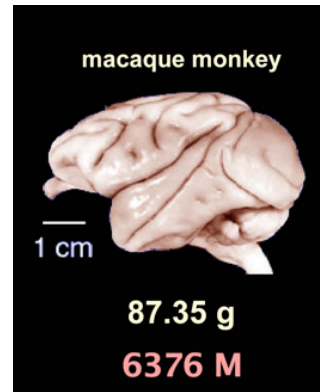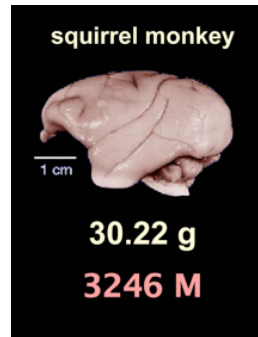# Grid Cells
and Neural Maps of Space

Edvard I. Moser
Kavli Institute for Systems Neuroscience,
Centre for Neural Computation,
NTNU, Trondheim

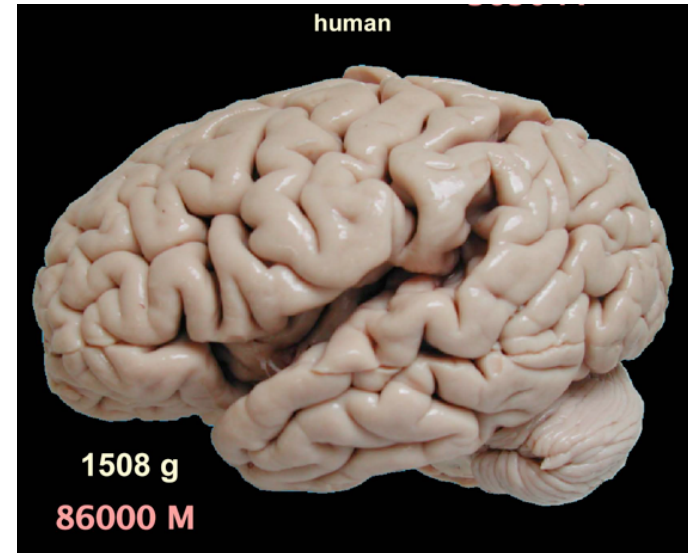# Understanding cortex –
# the origin of the expanded intellectual repertoire of primates

mouse
0.416 g
71 M

rat
1.802 g
200 M

20 M cortex

squirrel monkey
1 cm
30.22 g
3246 M

macaque monkey
1 cm
87.35 g
6376 M

Modified from Herculano-Houzel, Frontiers in Human Neuroscience, 2009

human
1508 g
86000 M

20000 M cortex

How does the cortex produce these proposed intellectual functions?

Significant progress in deciphering cortical computation has been made at the 'low end' of the cortex, near the sensory receptors (Hubel and Wiesel, …)
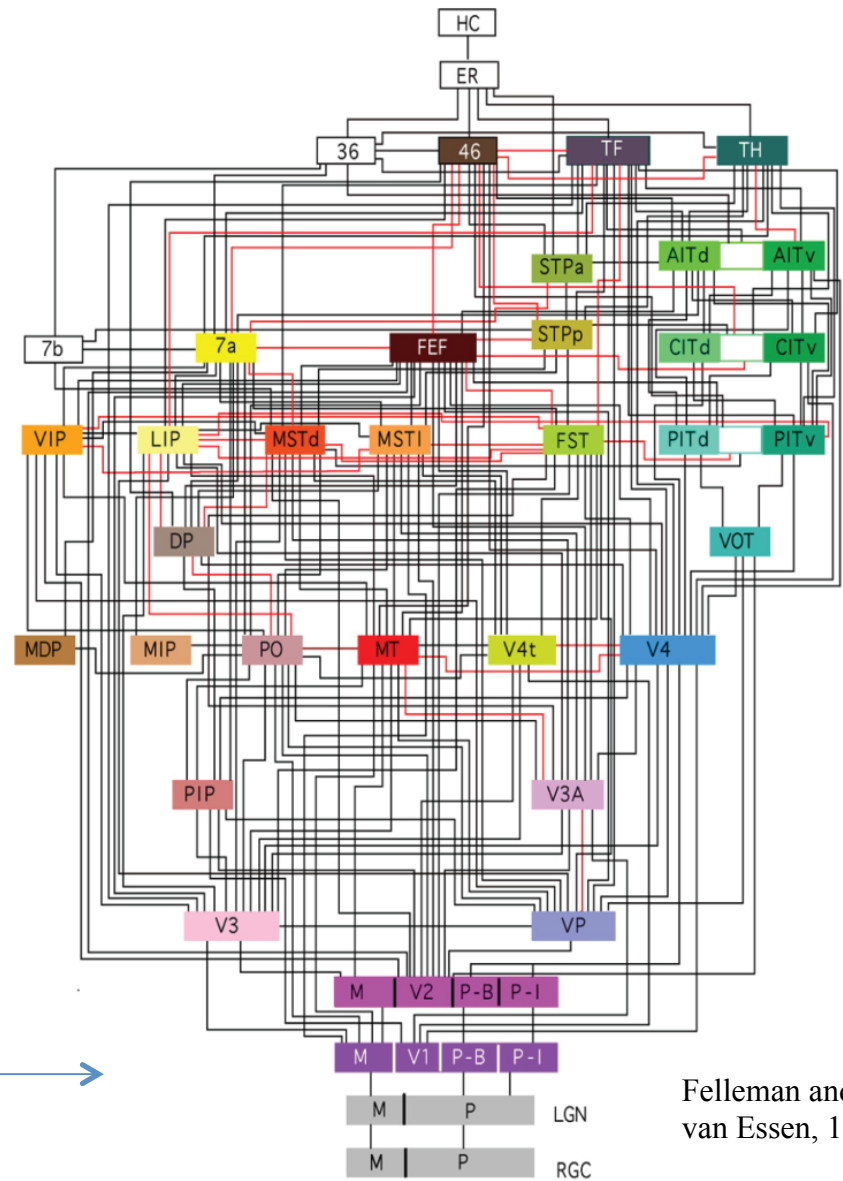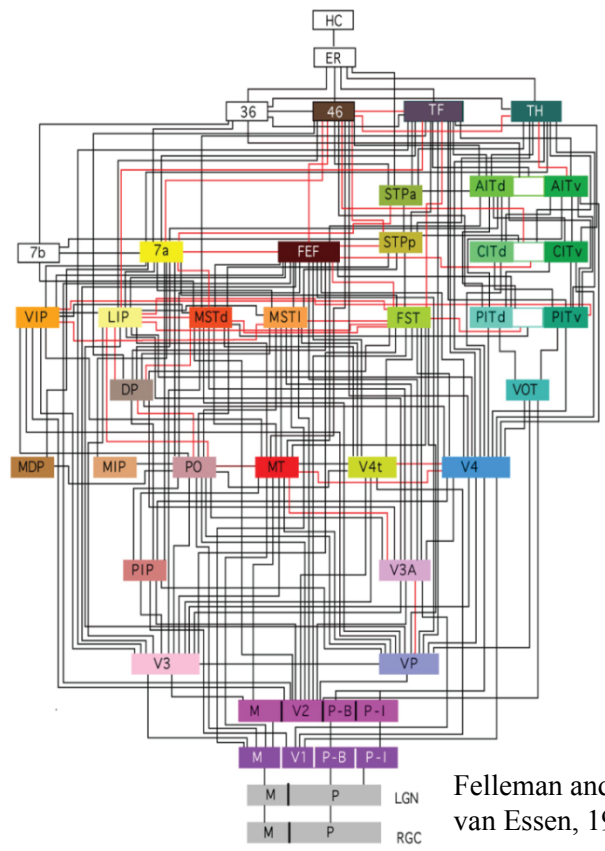

Felleman and van Essen, 1991

But it is particularly the high end of the cortical hierarchy – the association cortices – that has expanded in mammalian evolution
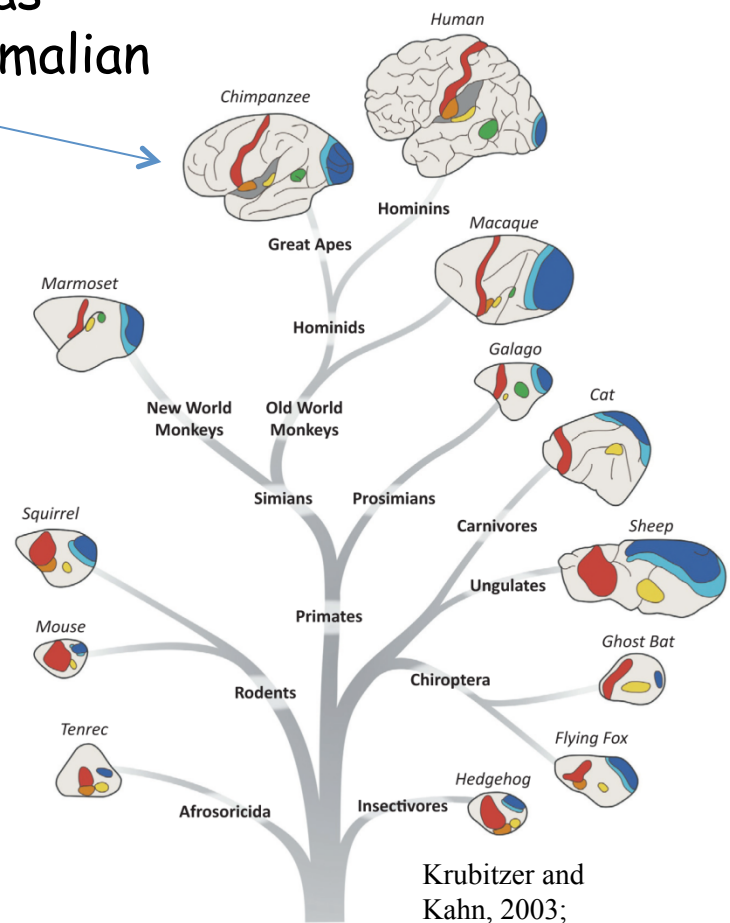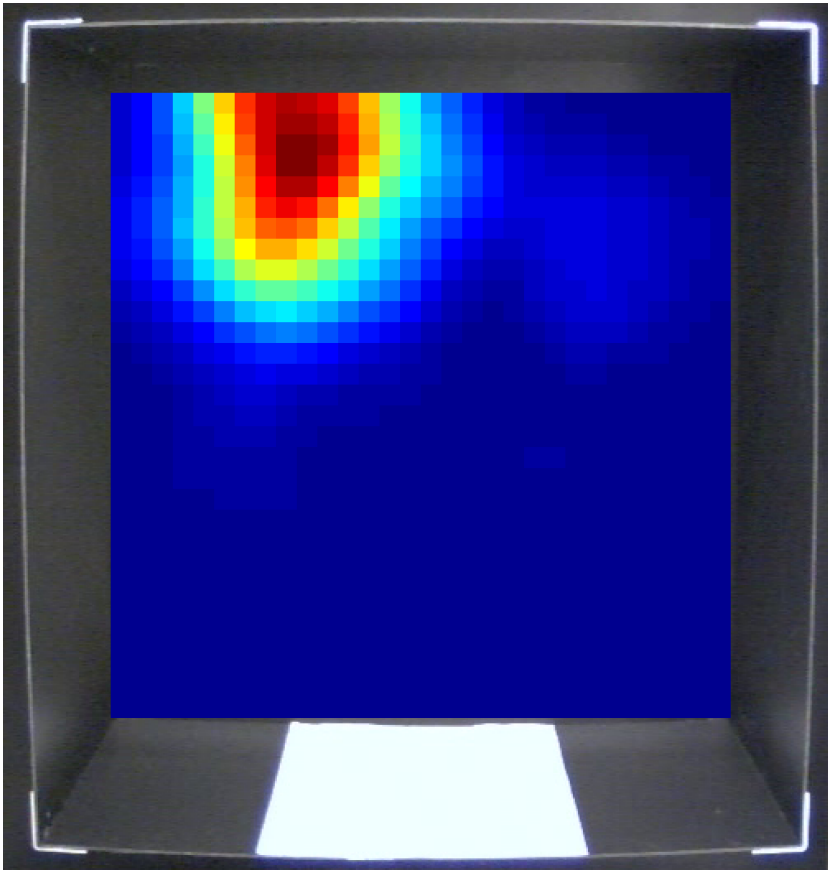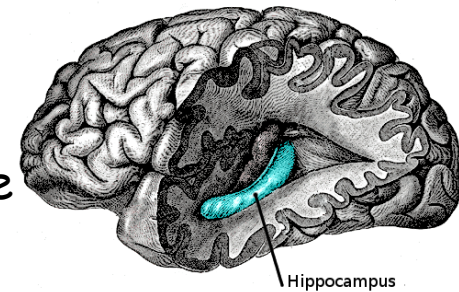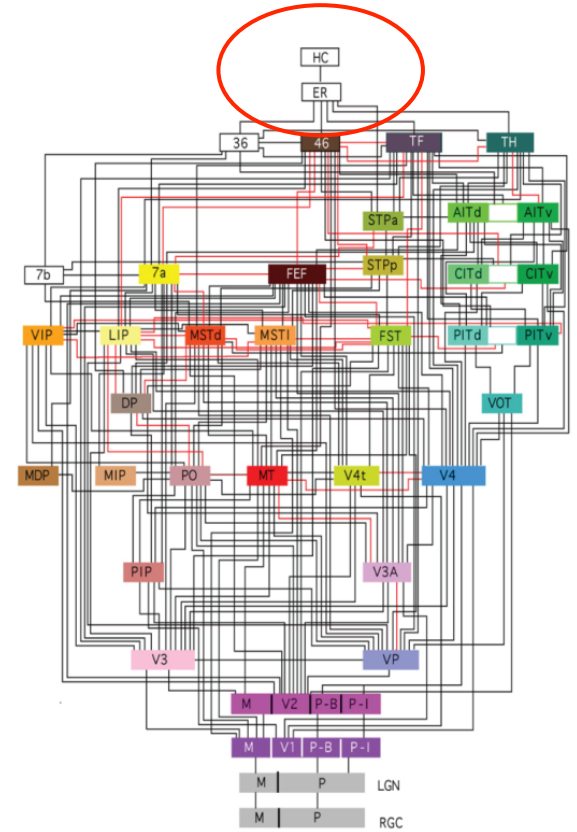

Krubitzer and Kahn, 2003; Buckner and Krienen, 2013

Felleman and van Essen, 1991

However, computation at the high end of the cortex still appears quite inaccessible….

... perhaps with an exception for some of the neural circuitry for space
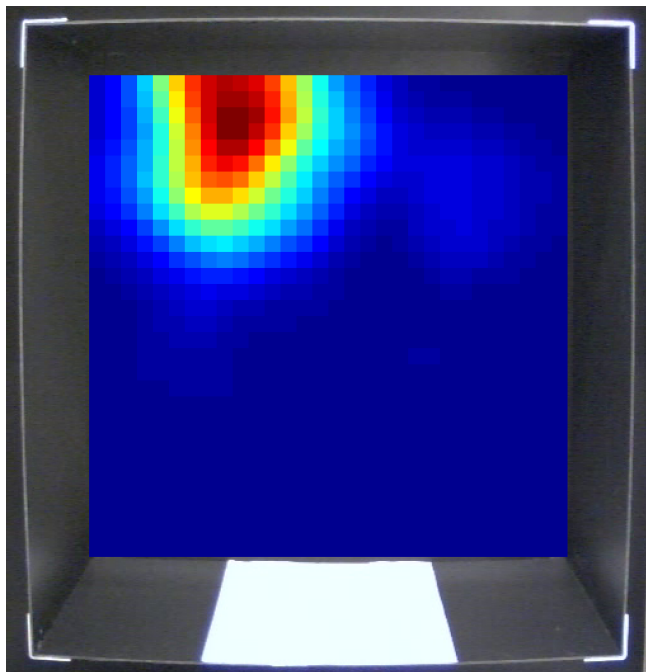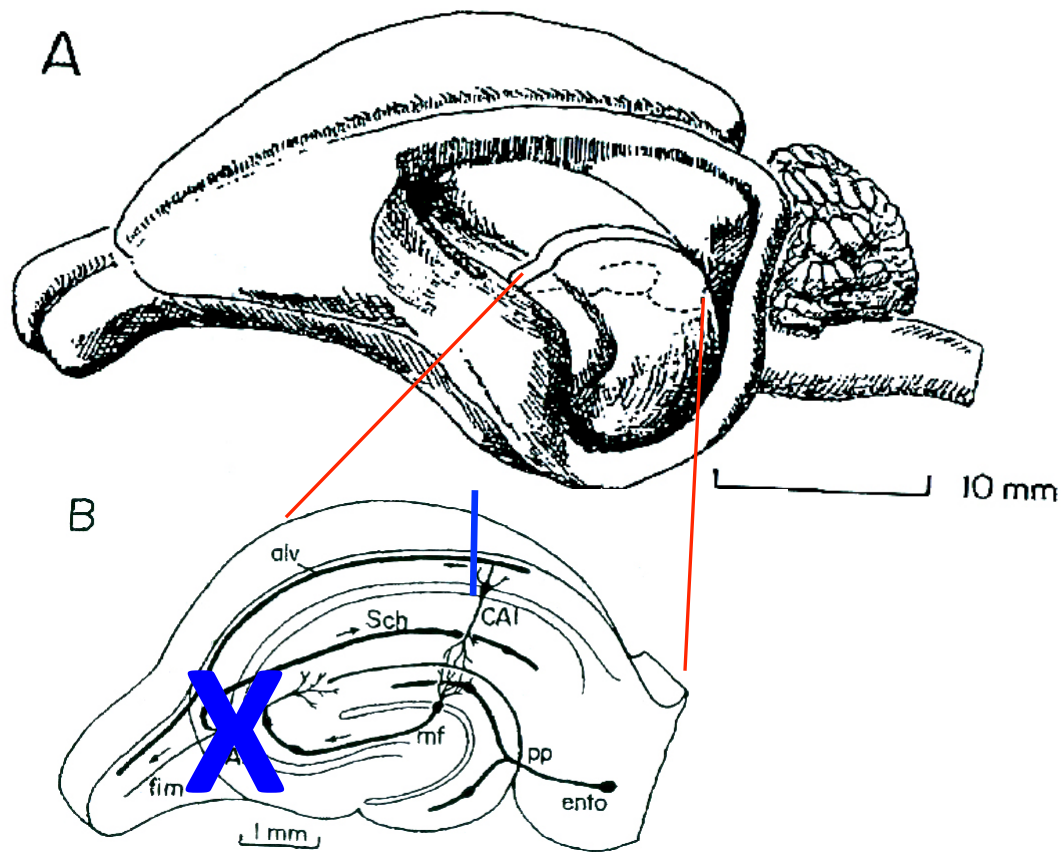

O´Keefe and Dostrovsky, 1971

The hippocampus contains place cells. The firing rates of these cells are clearly related to a property of the outside world – the animal´s location.

# But where and how is the place signal generated?

O´Keefe and Dostrovsky, 1971

We recorded in CA1 after blocking the intrinsic 'trisynaptic' circuit (X) of the hippocampus to determine <u>if the origin of the place signal is intra-hippocampal</u> (Brun et al., 2002)

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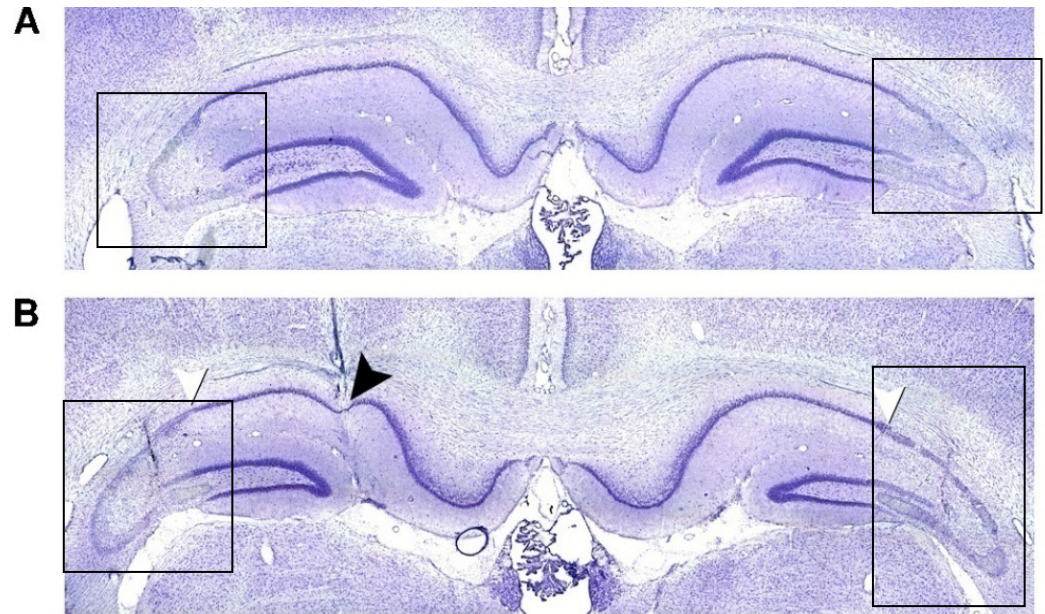

Brun et al. (2002). *Science* 296:2243-2246
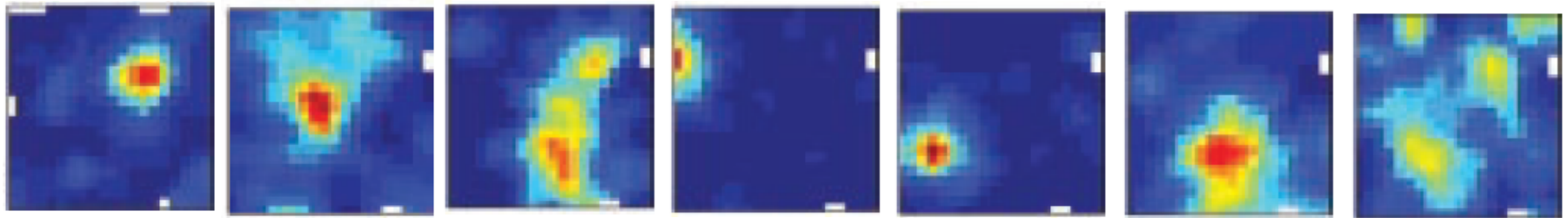
Best candidate: the entorhinal cortex
Particularly the medial part, which is strongly connected to visual regions

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

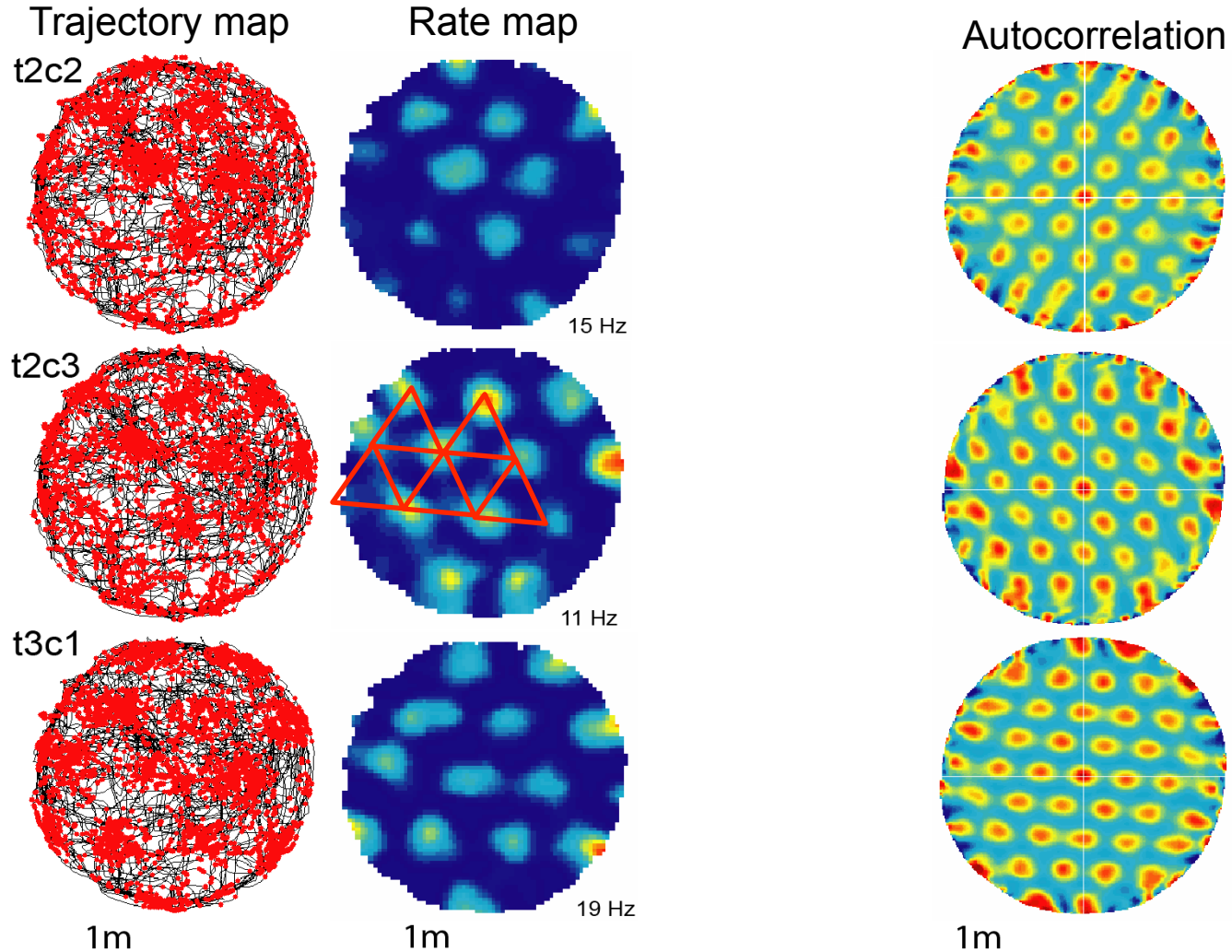Entorhinal cortex of a rat brain (seen from behind):

dorsal

intermediate

vental

S1
1
2
S1
3
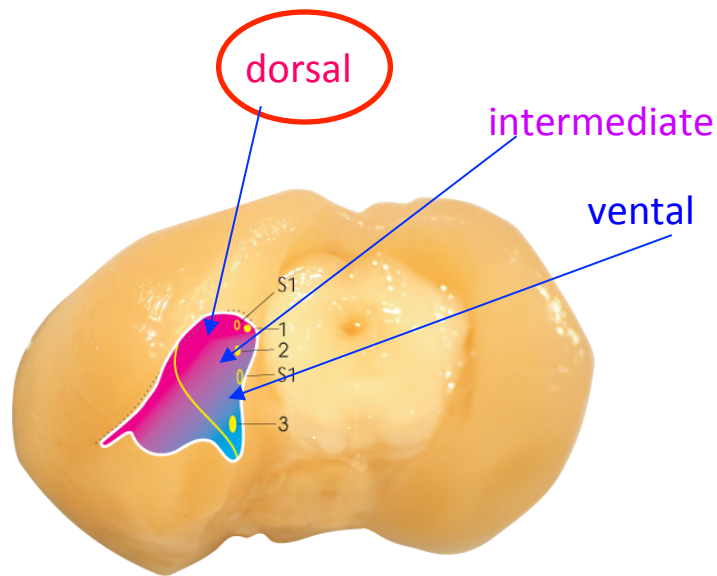
Fyhn et al. (2004). *Science* 305:1258-1264
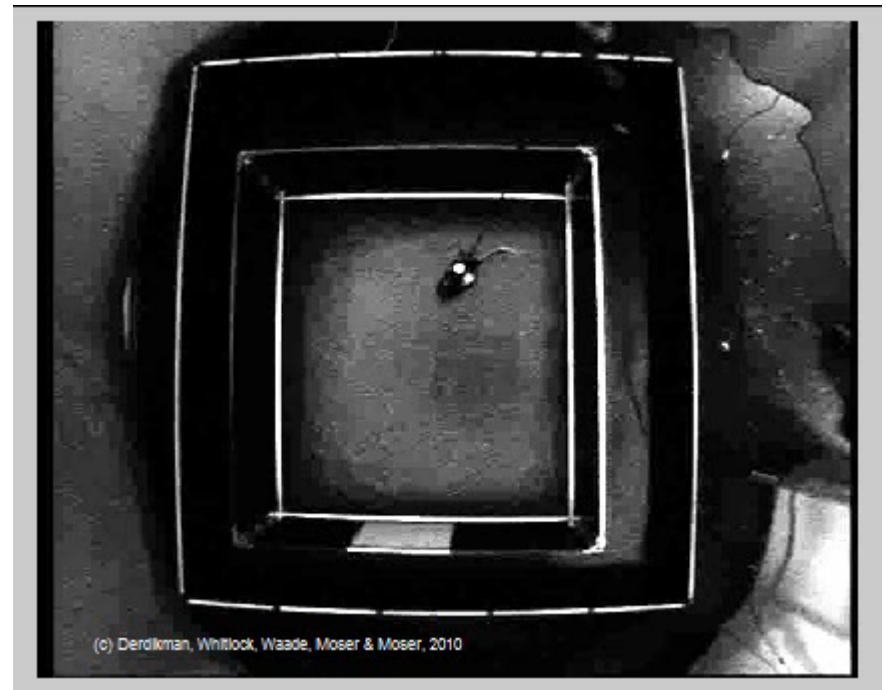

(c) Derdikman, Whitlock, Waade, Moser & Moser, 2010

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

# Recording in <u>larger</u> environments revealed firing fields with a <u>periodic hexagonal (triangular) structure</u>

Trajectory map   Rate map   Autocorrelation

t2c2

15 Hz

t2c3

11 Hz

t3c1

19 Hz

1m   1m   1m

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

The cells formed a grid that covered the entire available space – we called them grid cells
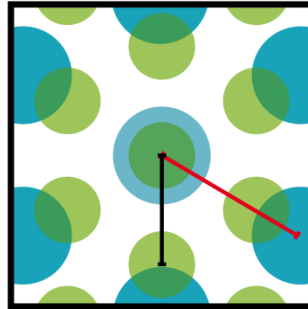

220 cm wide box
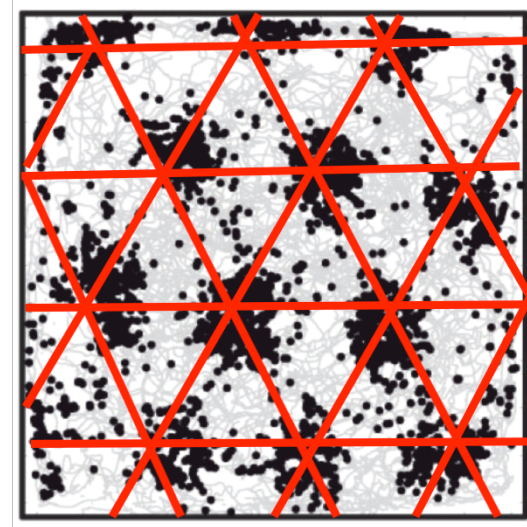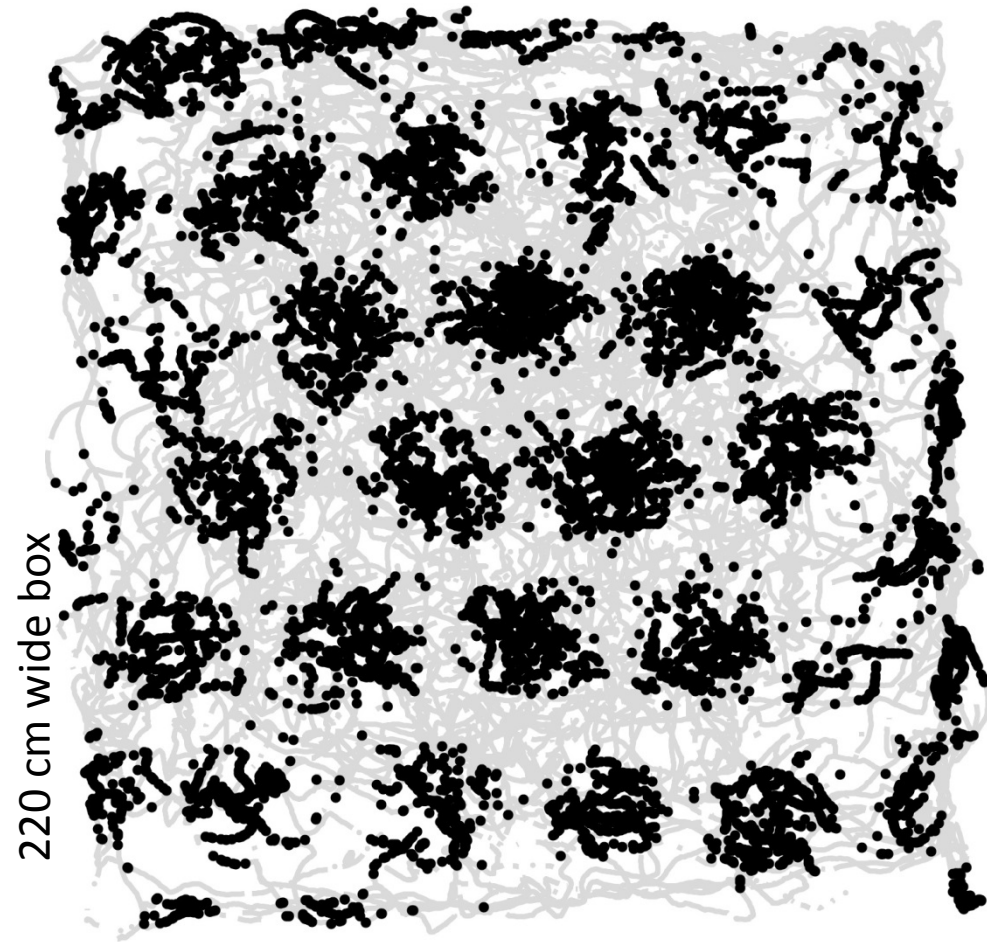
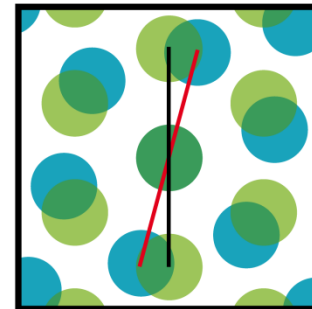# Grid cells have at least three dimensions of variation

1. Phase
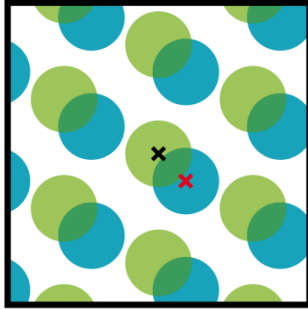
2. Scale

3. Orientation

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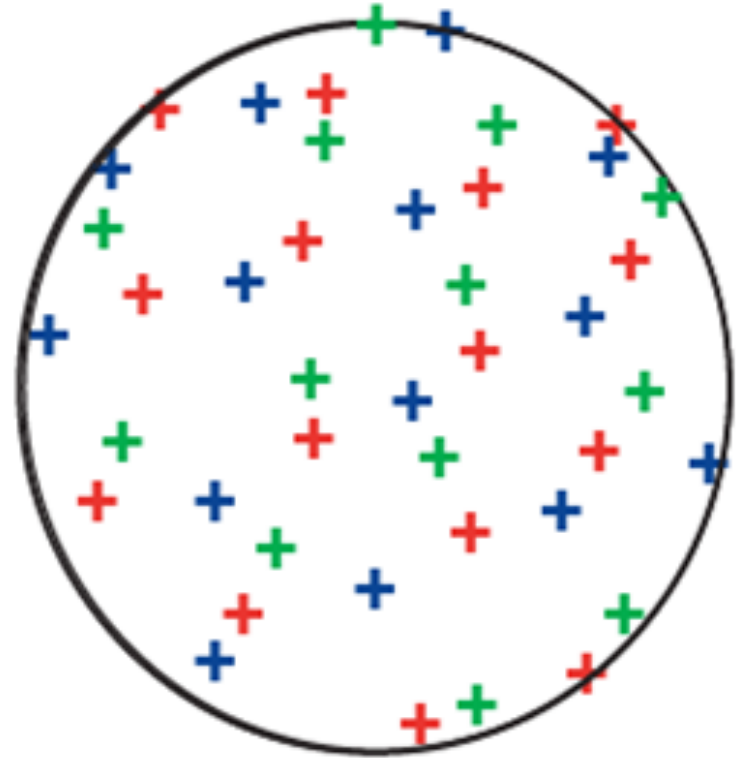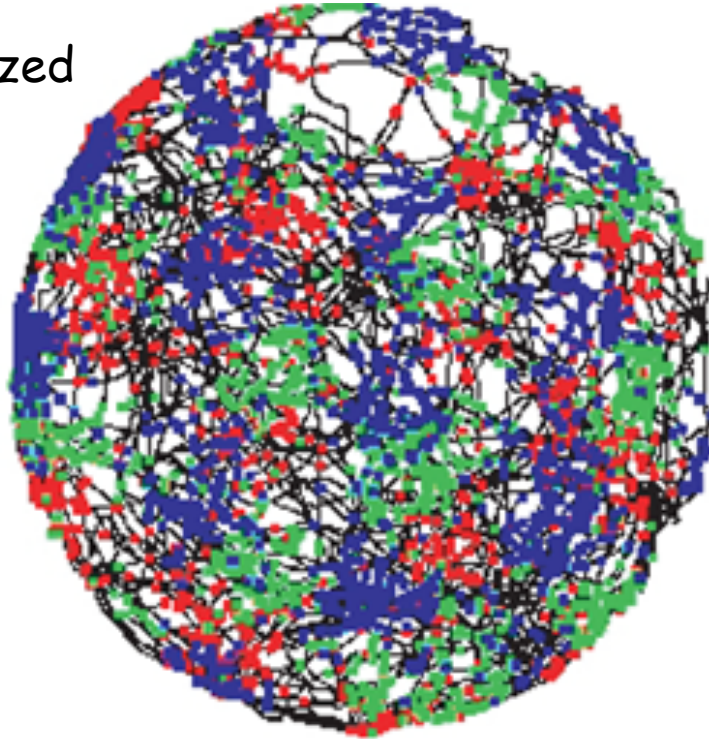How are these variations organized in anatomical space?

The phase (x, y-locations) of the grid seems to be represented non-topographically
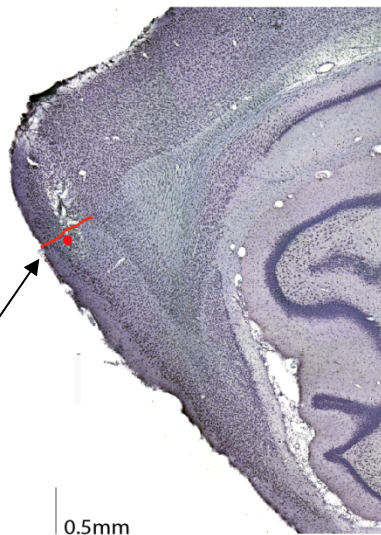
3 co-localized cells:

Cell 1
Cell 2
Cell 3
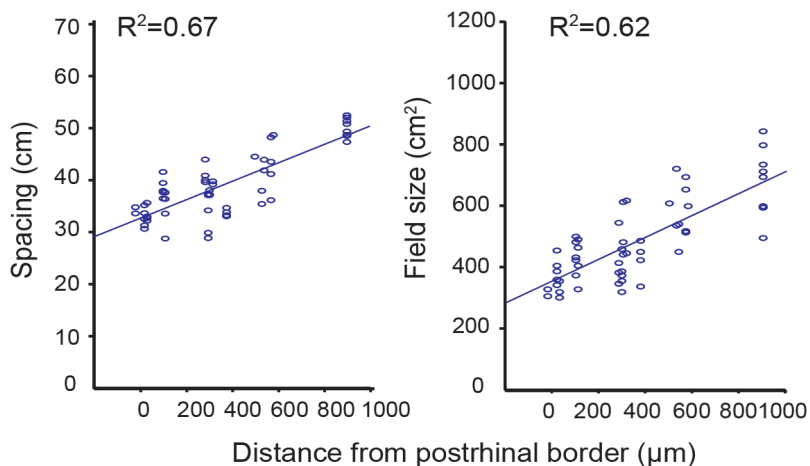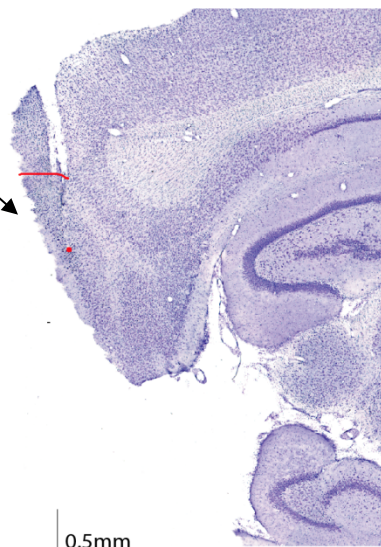

Hafting et al. (2005). *Nature* 436:801-806

... similar to the salt-and-pepper organization of many other cortical representations (orientation selectivity in rodents, odours, place cells)
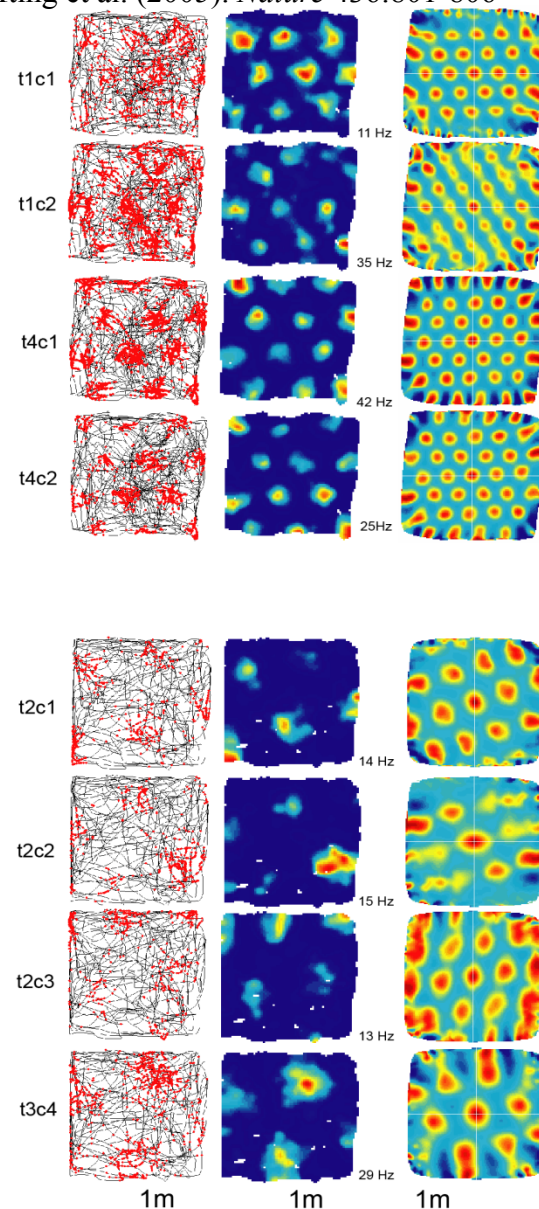
In contrast, the scale of the grid increases topographically along the dorso-ventral axis.

**Grid size increases from dorsal to ventral MEC**

0.5mm

0.5mm

R²=0.67

R²=0.62

Spacing (cm)

Field size (cm²)

Distance from postrhinal border (µm)

11 Hz
35 Hz
42 Hz
25Hz

14 Hz
15 Hz
13 Hz
29 Hz

1m   1m   1m

t1c1
t1c2
t4c1
t4c2

t2c1
t2c2
t2c3
t3c4

Grid cells with similar properties and a similar organization have since been reported in <u>bats, monkeys and humans</u>, suggesting they originated early in mammalian evolution
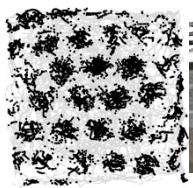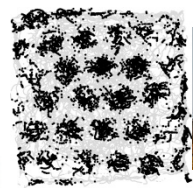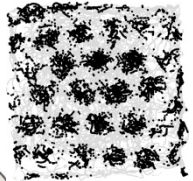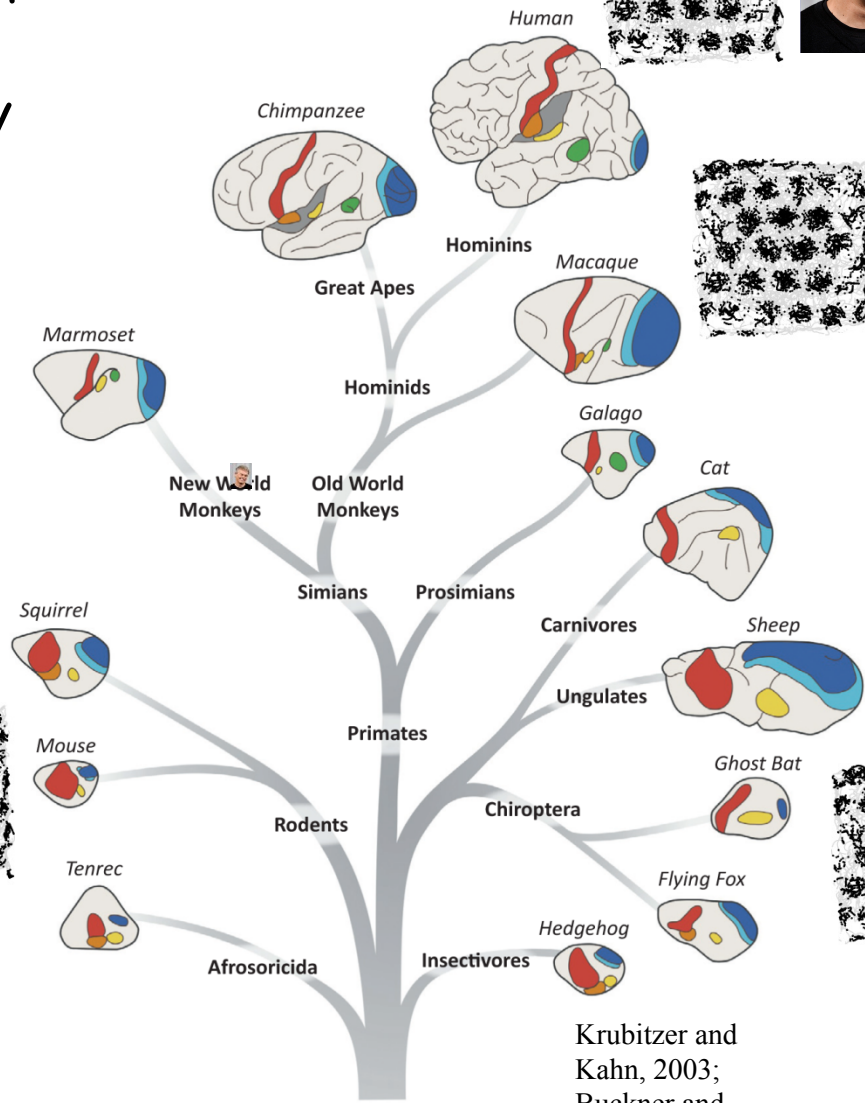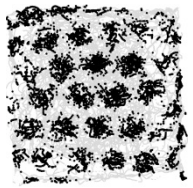
Krubitzer and Kahn, 2003; Buckner and Krienen, 2013

Mechanisms of the grid pattern

The facts that grid cells are found at the peak of the cortical hierarchy, far away from sensory inputs, and the absence of anything gridlike in any of the sensory inputs, point to an intrinsic mechanism for the grid pattern.
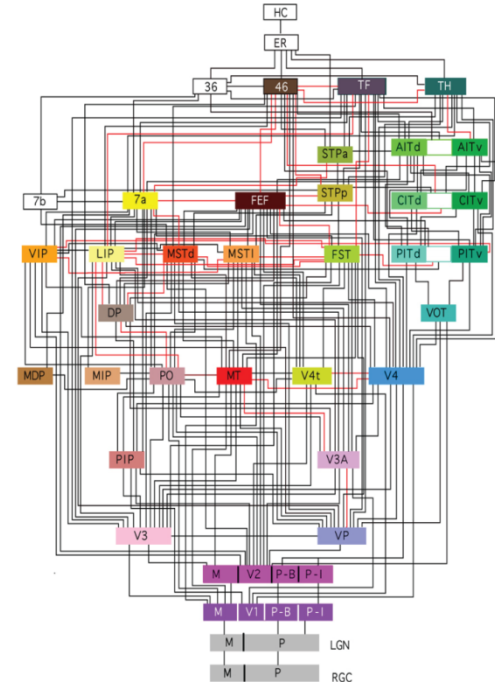
The common orientation of local grid cells and the coherent responses of local grid cell ensembles (Fyhn et al 2007; Yoon et al 2013) implies the involvement of network mechanisms.
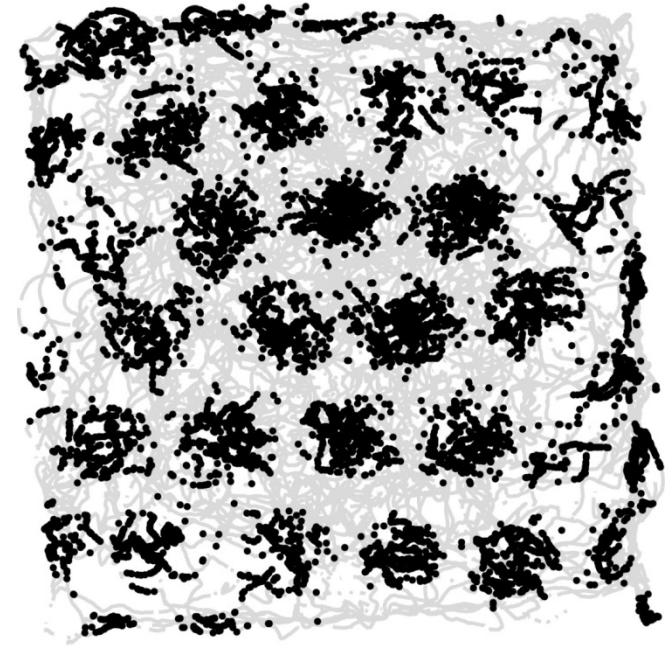
NETWORK MODELS FOR LOCALIZED FIRING HAVE TWO COMPONENTS

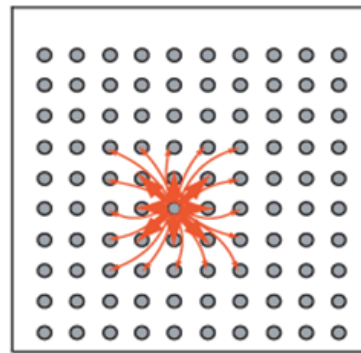1. Localized activity is generated spontaneously in continuous attractor networks with extensive recurrent connections (Tsodyks & Sejnowski, Sompolinsky, K Zhang, Samsonovitch and McNaughton, …).

Place cells arranged according to firing position (x,y). Cells with similar fields mutually excite each other.

Mexican hat
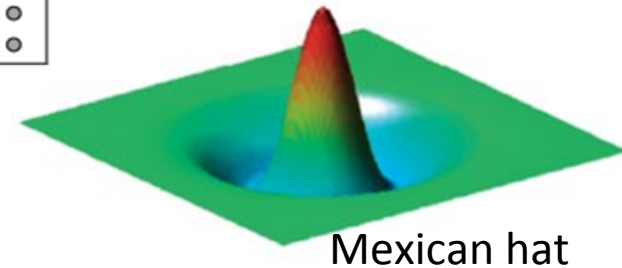
2. Activity is translated across the neural sheet <u>in proportion to</u> the speed and direction of the animal's movement, based on speed and direction inputs.

moving eastward

no motion

McNaughton et alr, Nature Rev Neurosci, 7:663-678.
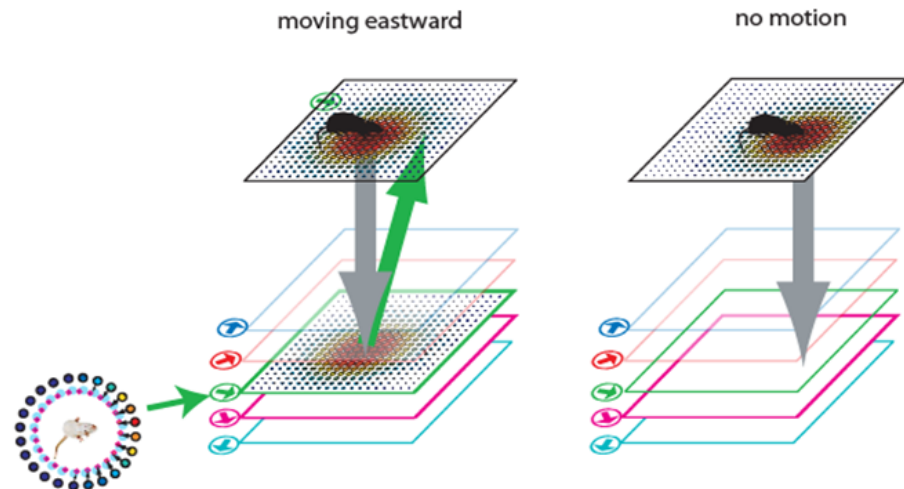
Origin of hexagonal structure

Activity blobs may emerge many places in the network.
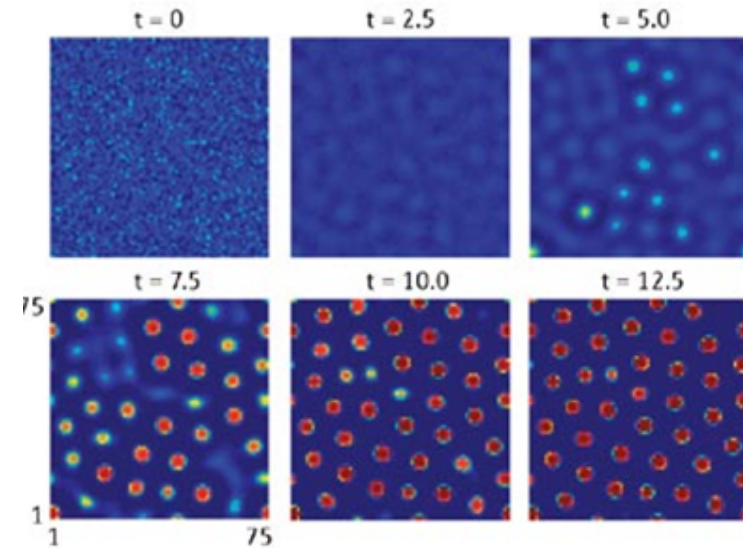Competition between blobs (with inhibitory surrounds) may yield a hexagonal pattern, in which distances are maximized.
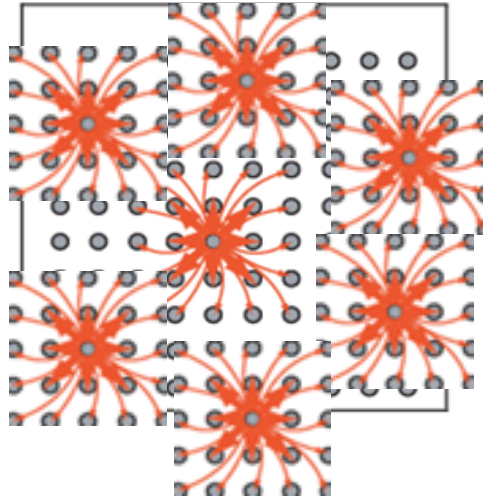
Fuhs and Touretzky, 2006

Again, when the activity bumps are translated across this network in accordance with the animal's movement, it will yield grid fields in individual cells

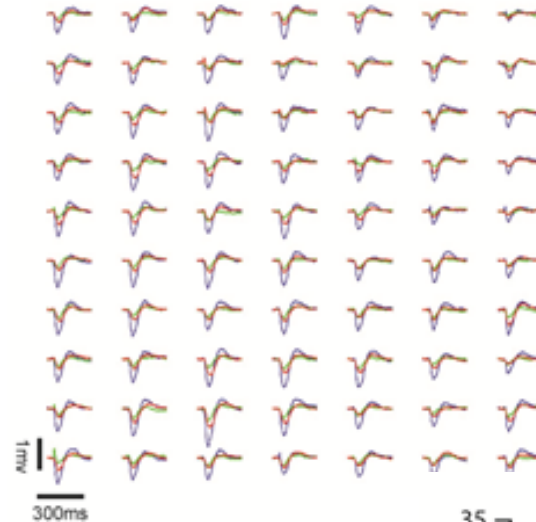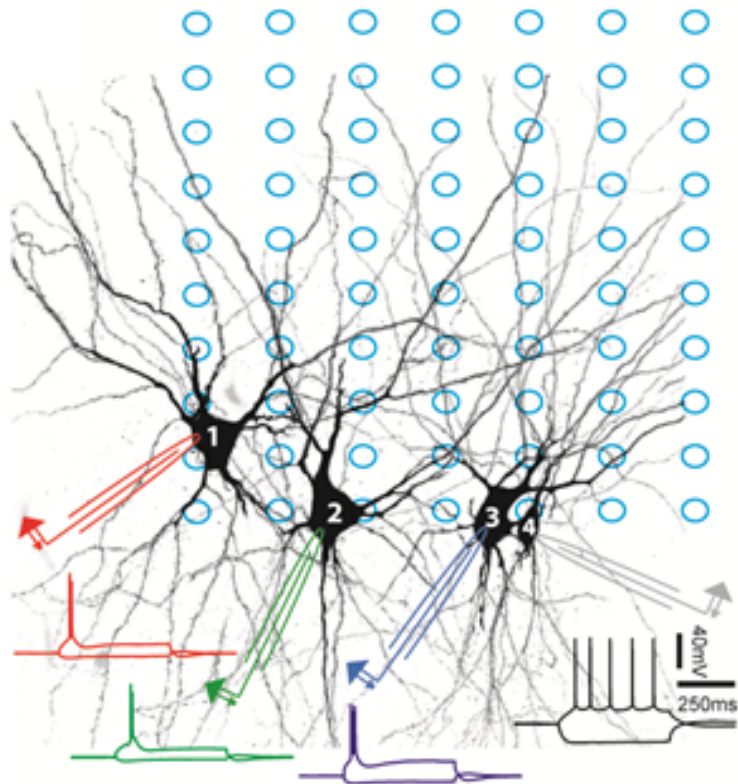However, the excitatory connections of the Mexican hat are almost completely absent between stellate cells in entorhinal cortex, where the number of grid cells is largest.
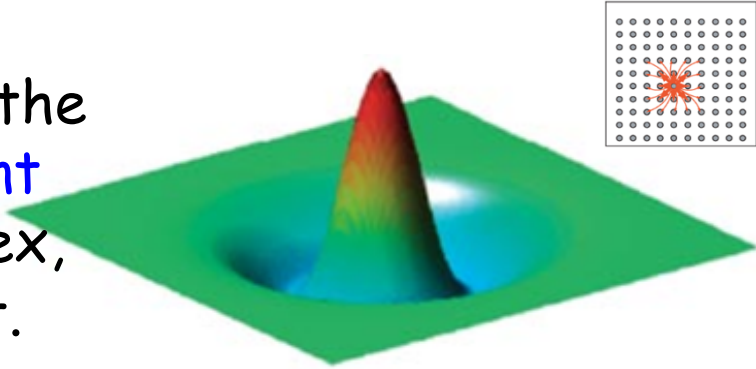
All connectivity is inhibitory (via inhibitory interneurons).

Couey, Witoelar, Zhang, Zheng, Ye, Dunn, Czajkowski, Moser, Moser, Roudi and Witter, Nature Neurosci 16, 318-324
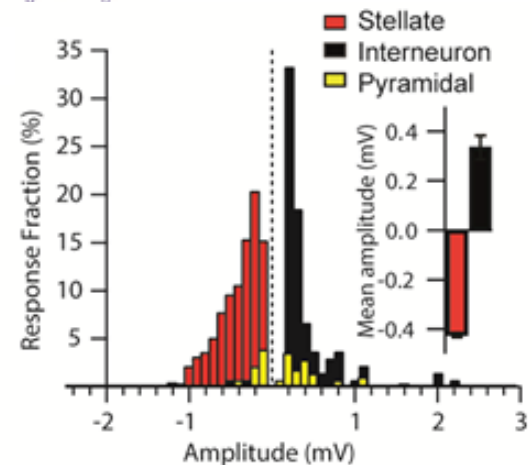
Quadruple patch recordings from more than 600 stellate-cell pairs confirm this conclusion:

Excitatory connections are almost completely absent between stellate cells. Connections are all inhibitory.

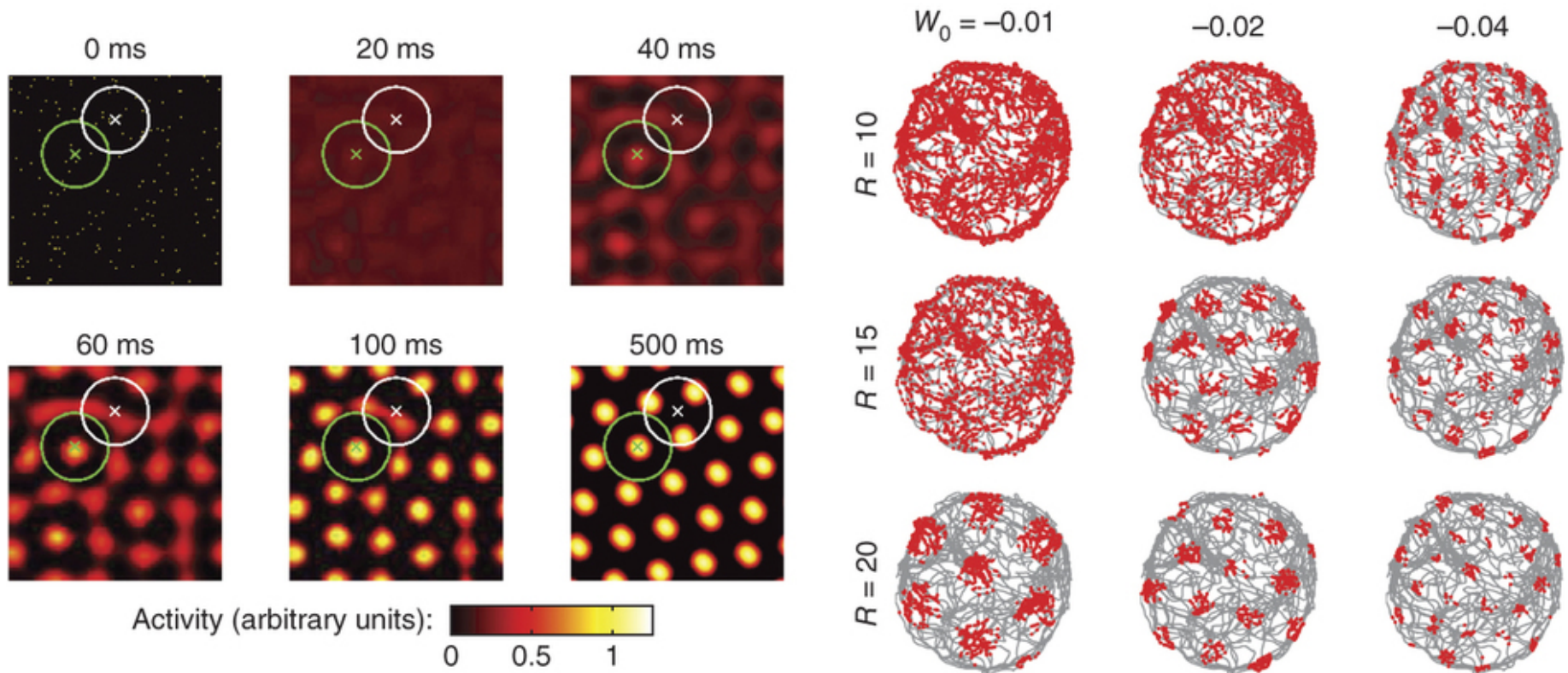Couey, Witoelar, Zhang, Zheng, Ye, Dunn, Czajkowski, Moser, Moser, Roudi and Witter, Nature Neurosci 16, 318-324
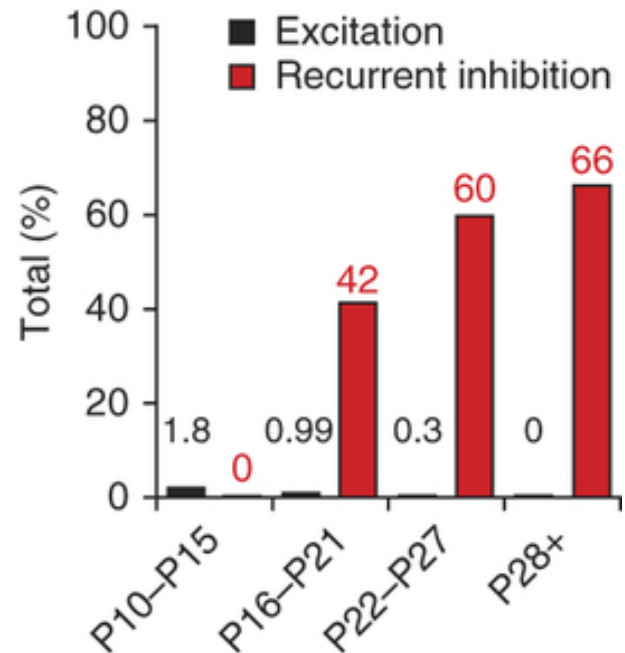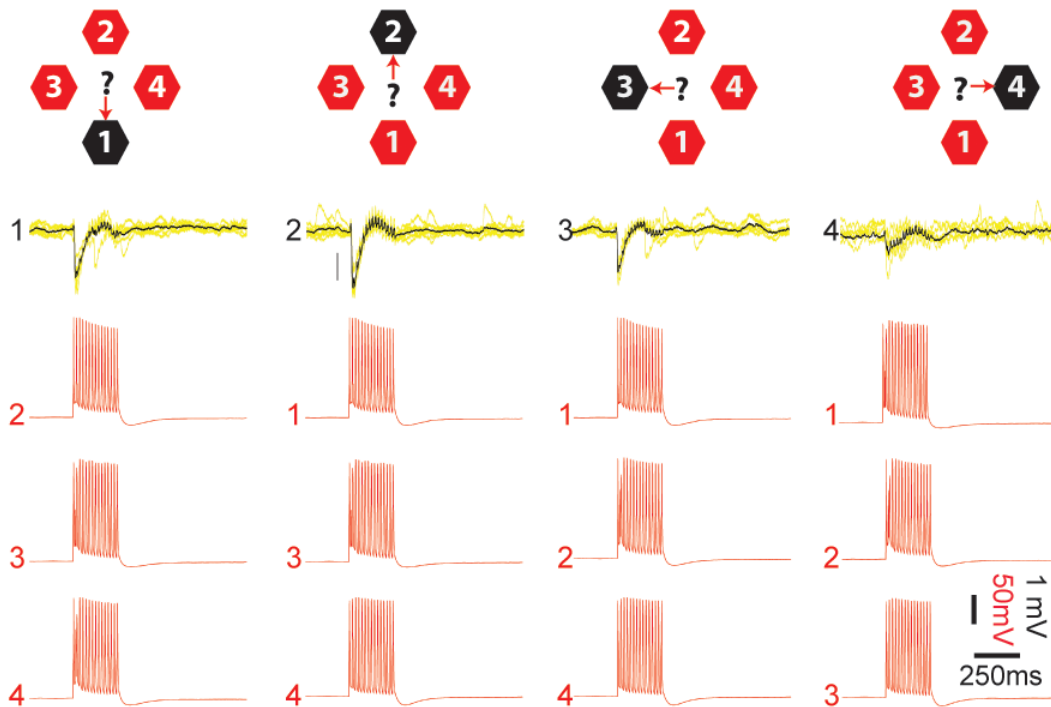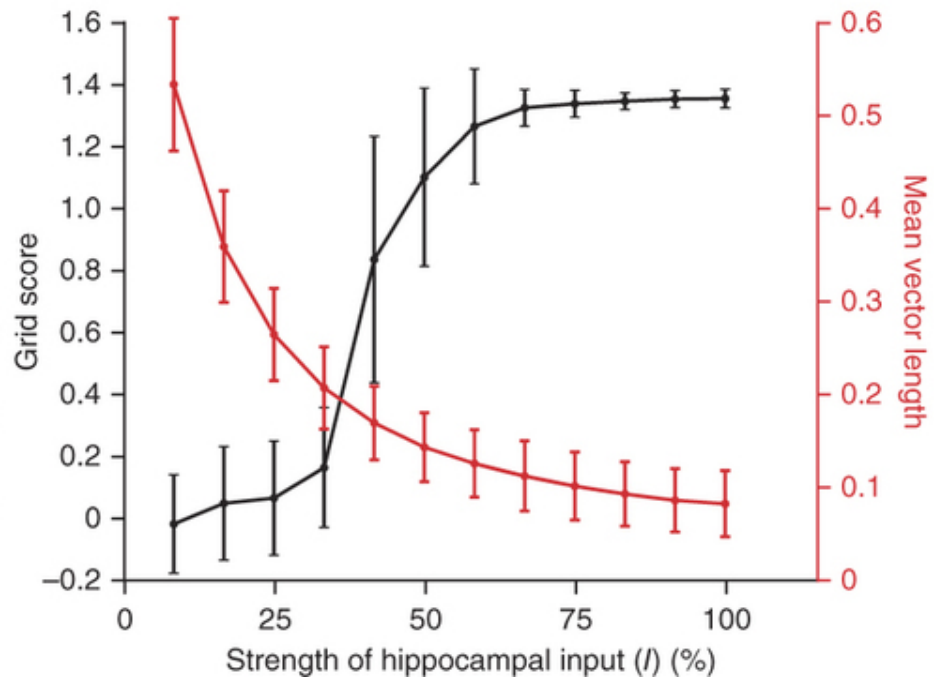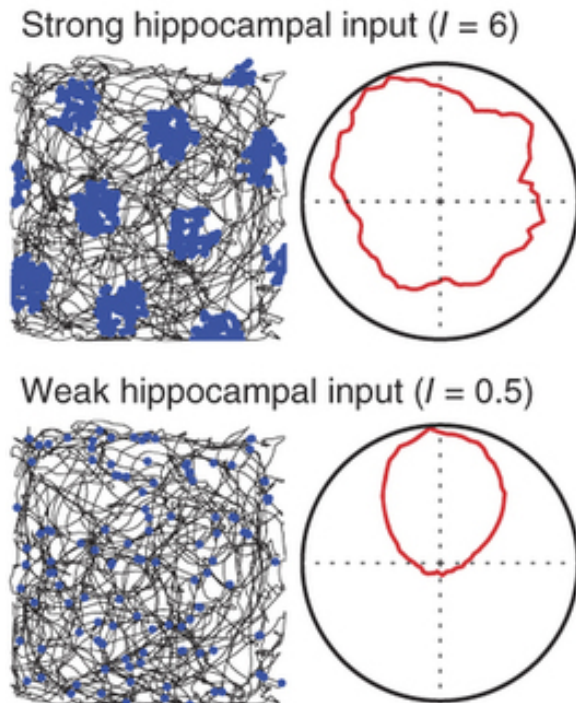
Competitive inhibitory interactions, with a constant magnitude and a fixed radius, are sufficient for neural network activity to self-organize into a stable hexagonal grid pattern (closest packing)….

Activity (arbitrary units): 0 0.5 1

Couey, Witoelar, Zhang, Zheng, Ye, Dunn, Czajkowski, Moser, Moser, Roudi and Witter, Nature Neurosci 16, 318-324
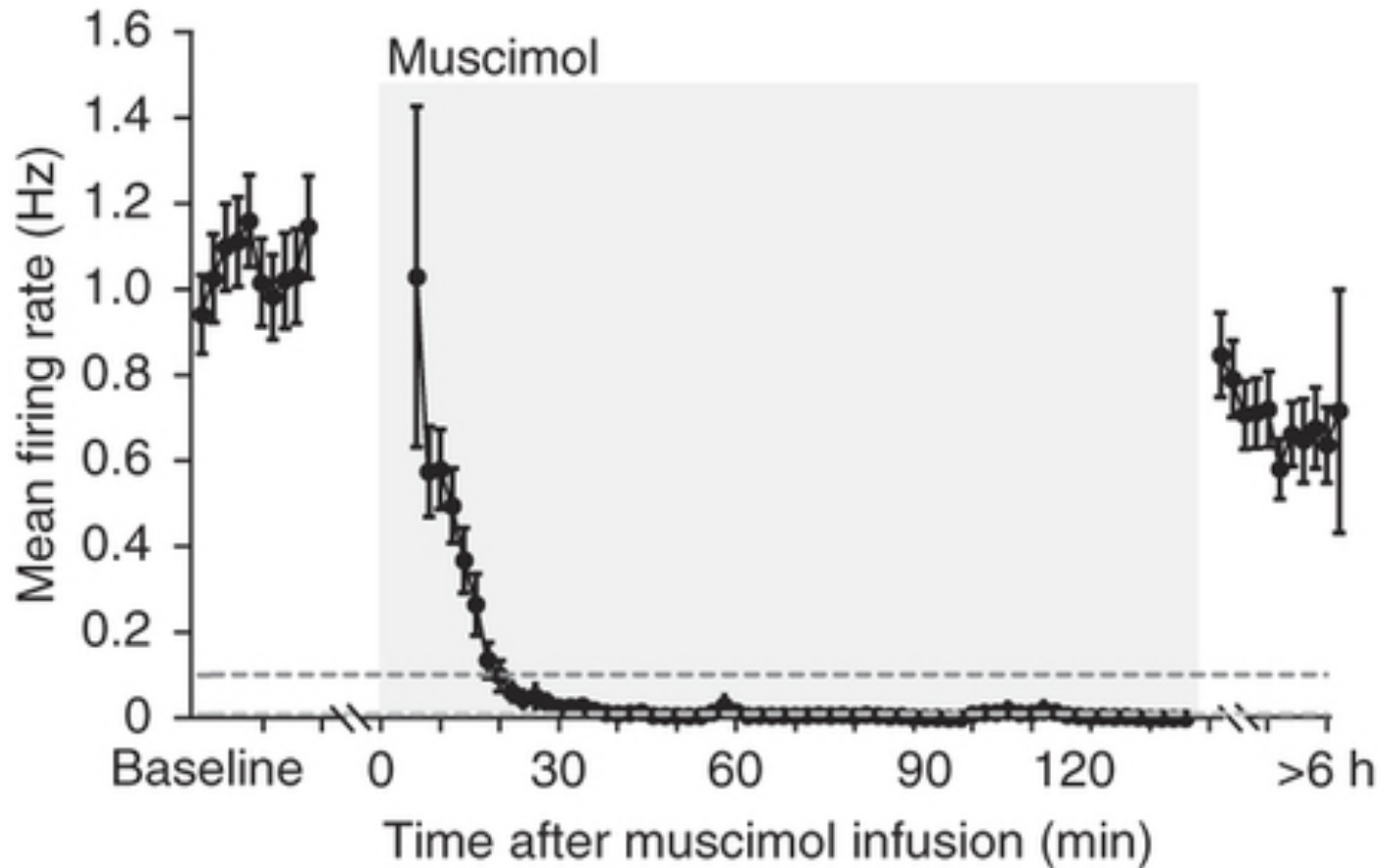
See also Burak and Fiete 2009

... on one condition:
that the network gets tonic external excitation to enable firing despite the intrinsic inhibition.

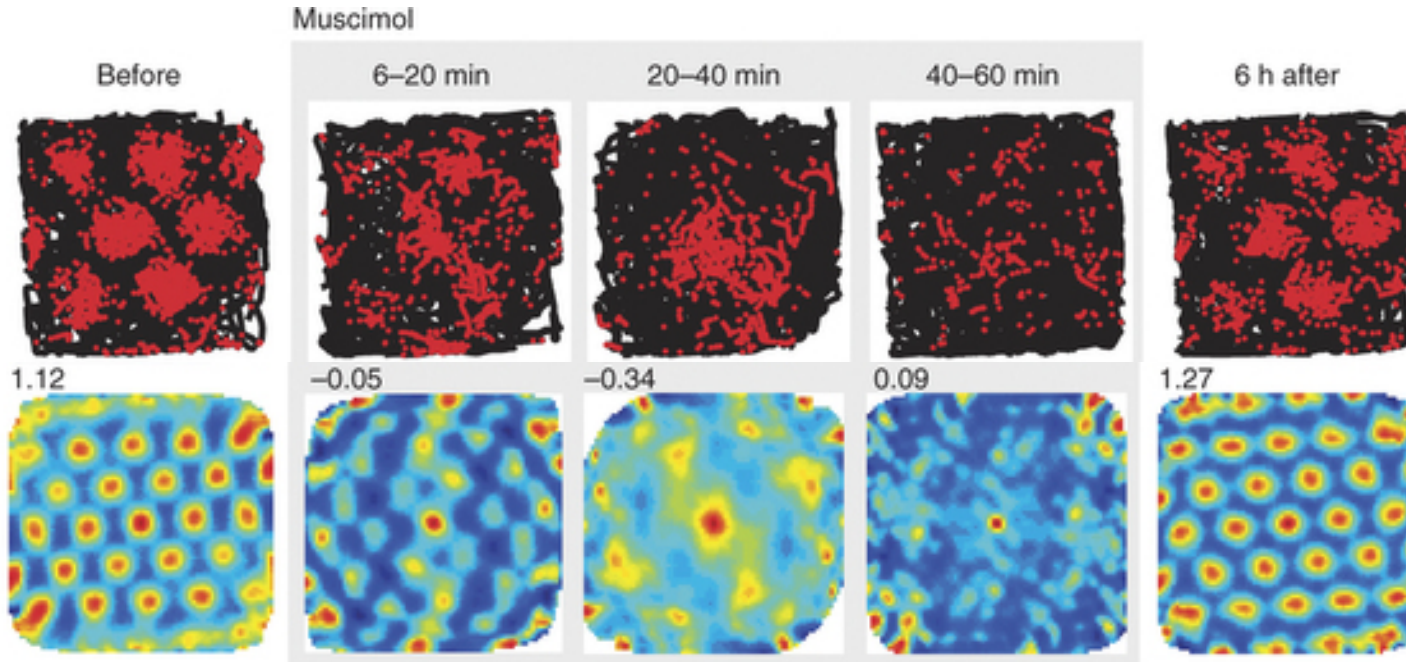Removing external excitation in the model abolished the grid pattern and made cells responsive to directional input

Bonnevie, Dunn, Fyhn, Hafting, Derdikman, Kubie, Roudi, Moser and Moser, Nature Neurosci 16, 309-317

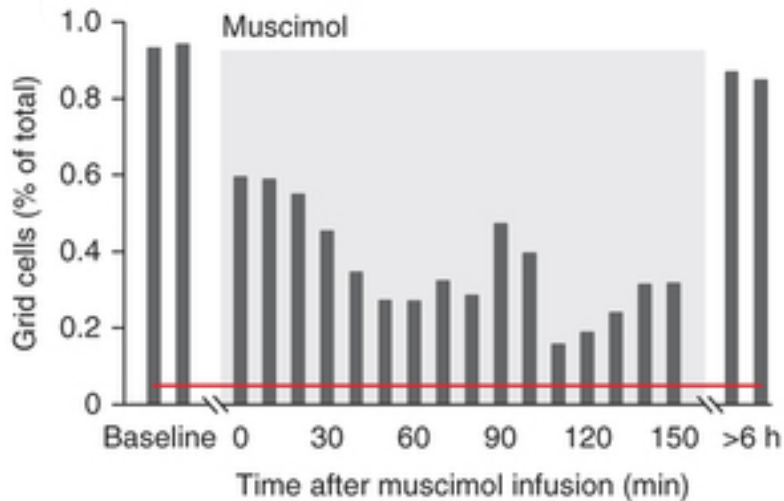We tested this experimentally by silencing the hippocampus, one of the major excitatory inputs to the grid network.

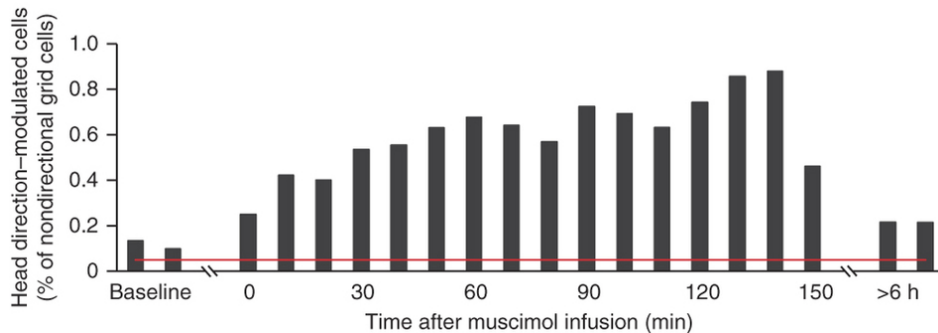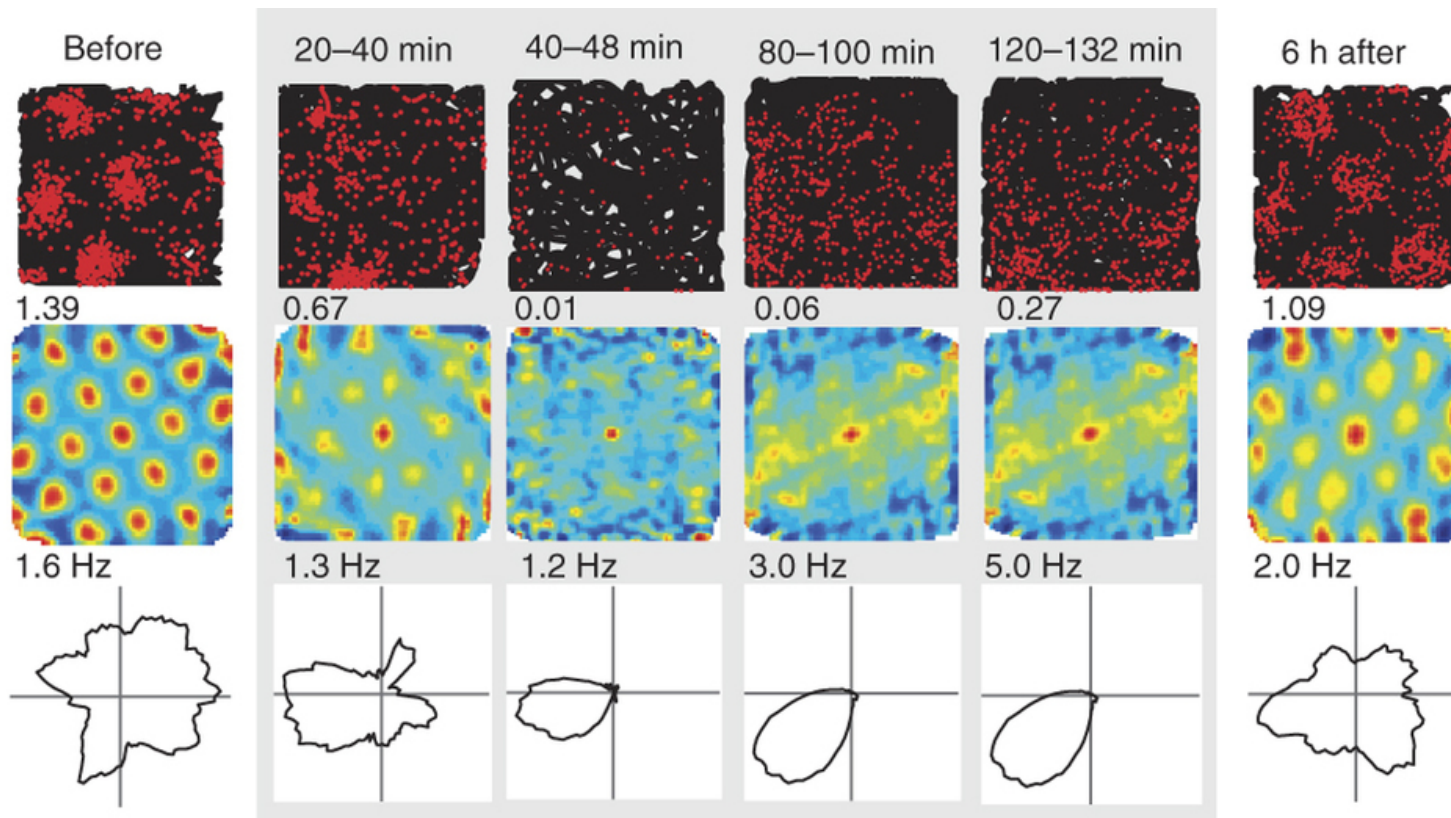Bonnevie, Dunn, Fyhn, Hafting, Derdikman, Kubie, Roudi, Moser and Moser, Nature Neurosci 16, 309-317

Hippocampal inactivation disrupted the grid pattern...

Bonnevie, Dunn, Fyhn, Hafting, Derdikman, Kubie, Roudi, Moser and Moser, Nature Neurosci 16, 309-317
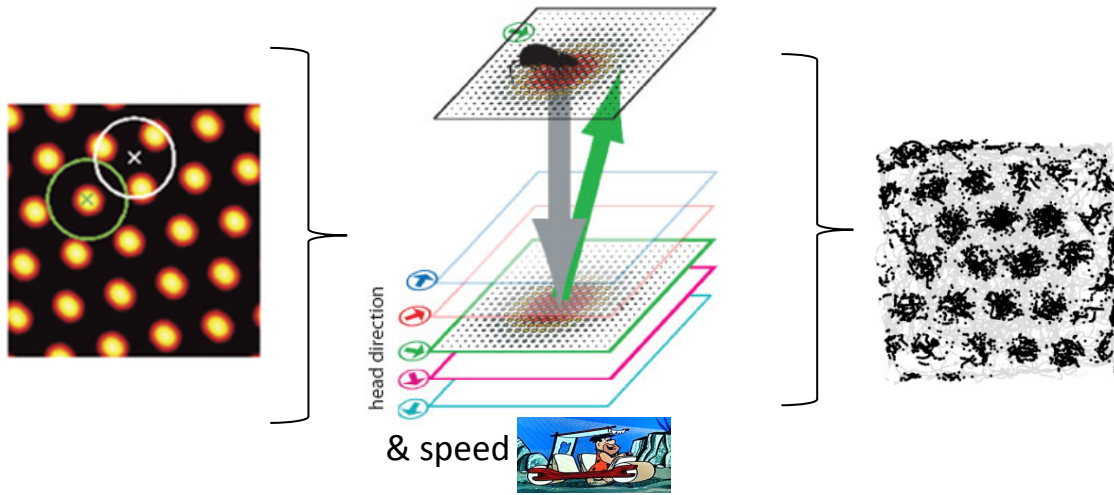
...at the same time as the former grid cells became direction-tuned

...consistent with a continuous attractor mechanism where the Mexican hat connectivity is replaced only with an inhibitory surround

Are grid cells formed by a continuous attractor mechanism then?

No, still a working hypothesis.

A network mechanism is possible but the detailed implementation is not known.

Challenges:

(1) Preferential connectivity between grid cells with similar phase has not been demonstrated. But such specificity exists in other systems.

(2) Continuous attractor do not currently handle noise in the connectivity – such noise might trap the attractor bump..

(3) Attractors do not exclude alternative mechanisms (Kropff and Treves), especially at early developmental stages before recurrent inhibitory connections are present

One or several grid maps?

A prediction of the attractor-network models:

The correspondence between velocity of movement in the environment and displacement in the neural sheet can only be maintained if the grid network has a common grid scale and grid orientation
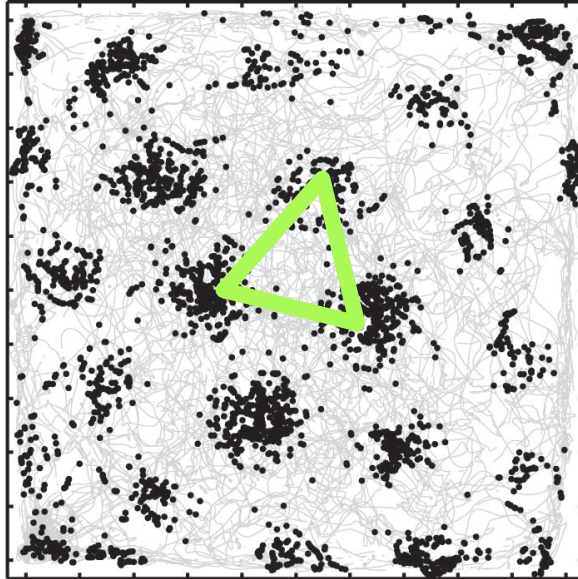

McNaughton, Battaglia, Jensen, Moser and Moser, *Nature Reviews Neuroscience*, 2006
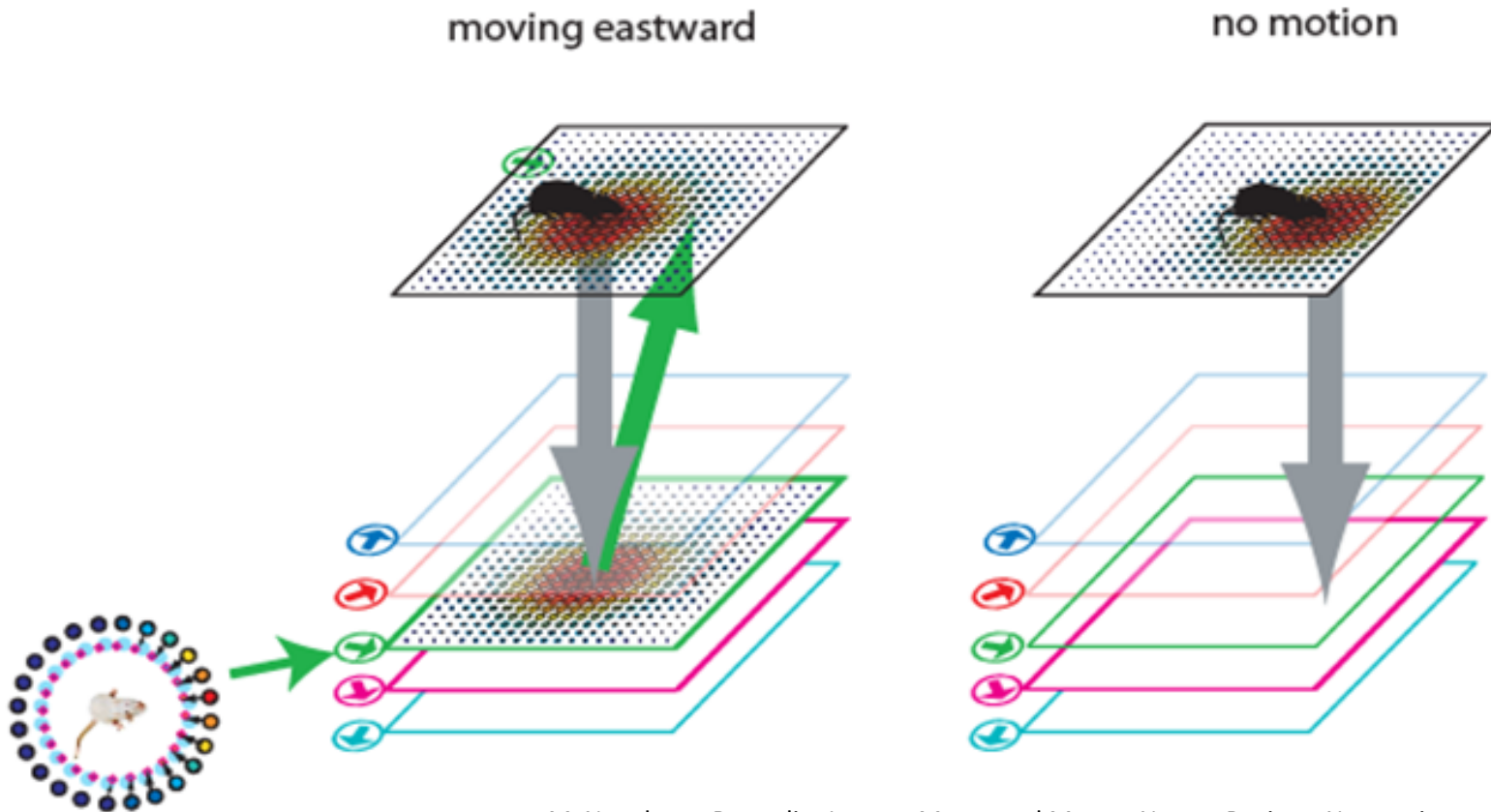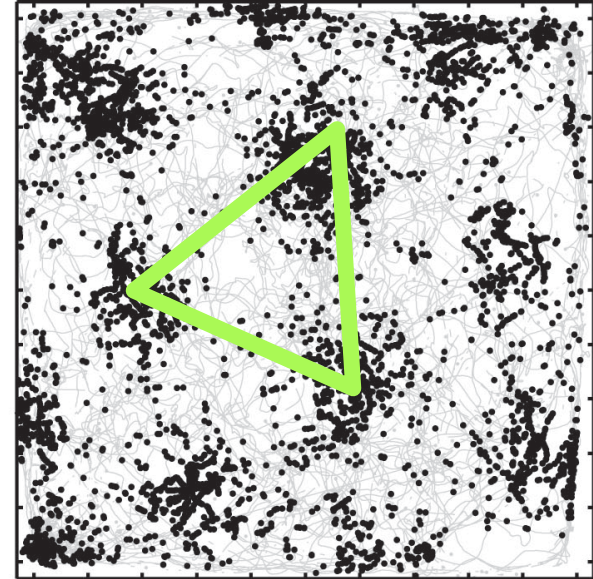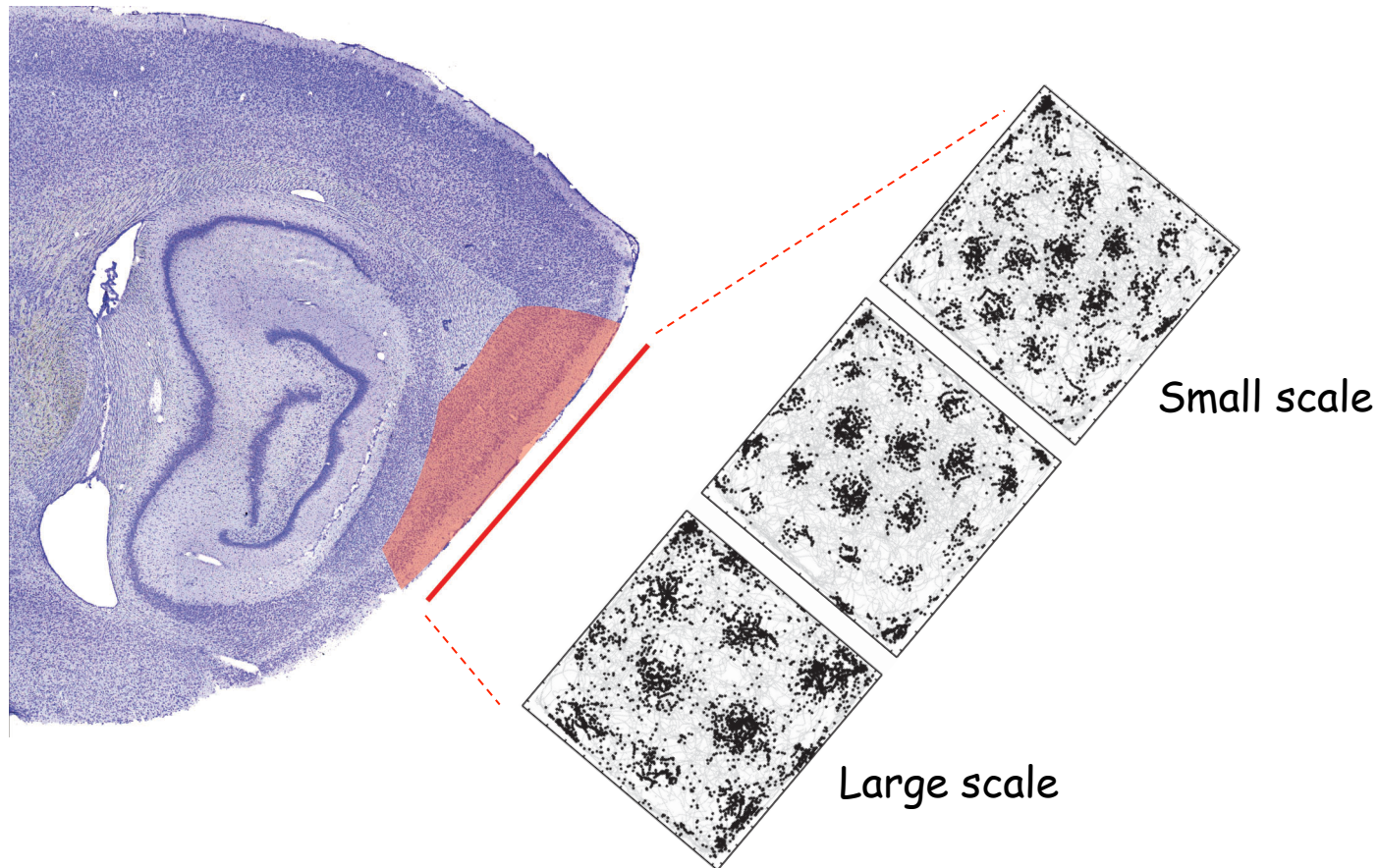
But grid cells have multiple scales

Cell 1
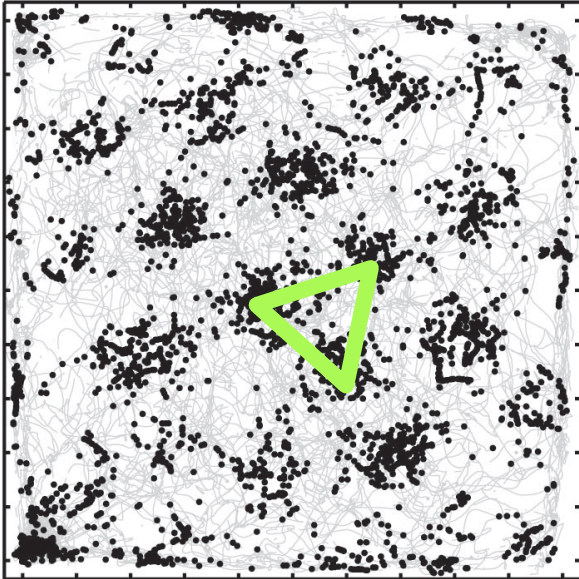
Cell 2

Cell 3

The scale of grid cells increases topographically along the dorso-ventral axis of the medial entorhinal cortex

Small scale

Large scale

Is the topographic mapping of scale continuous or modular? Only a modular organization, with constant spacing and orientation within each module, would be consistent with the attractor models.

Samples of grid cells have generally been too small to tell (5-10 cells/ rat), although early studies hinted at modularity (Barry et al 2007).

To determine if the grid scale is modular, we <u>increased the sample size</u> to <u>almost 200</u> grid cells per animal
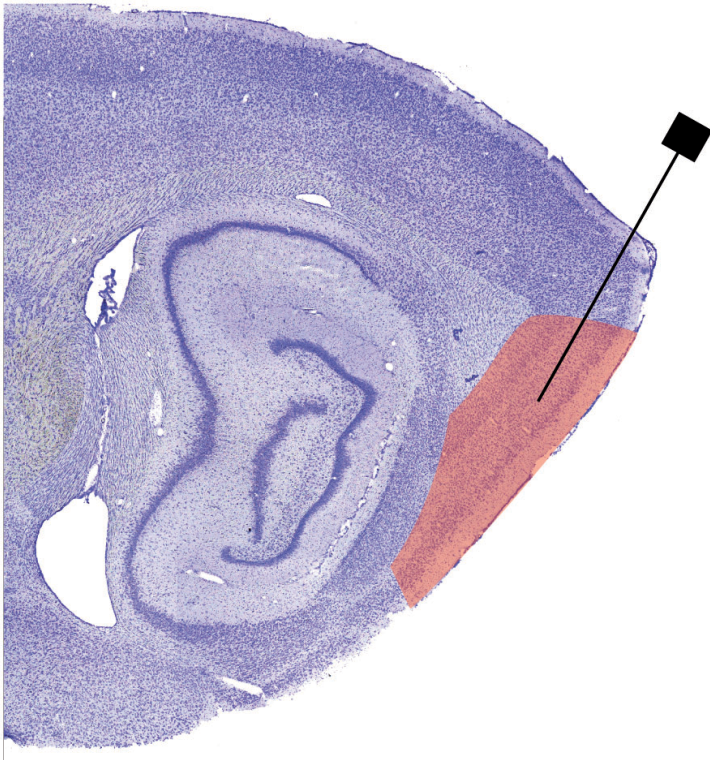

<u>Tangential approach:</u>
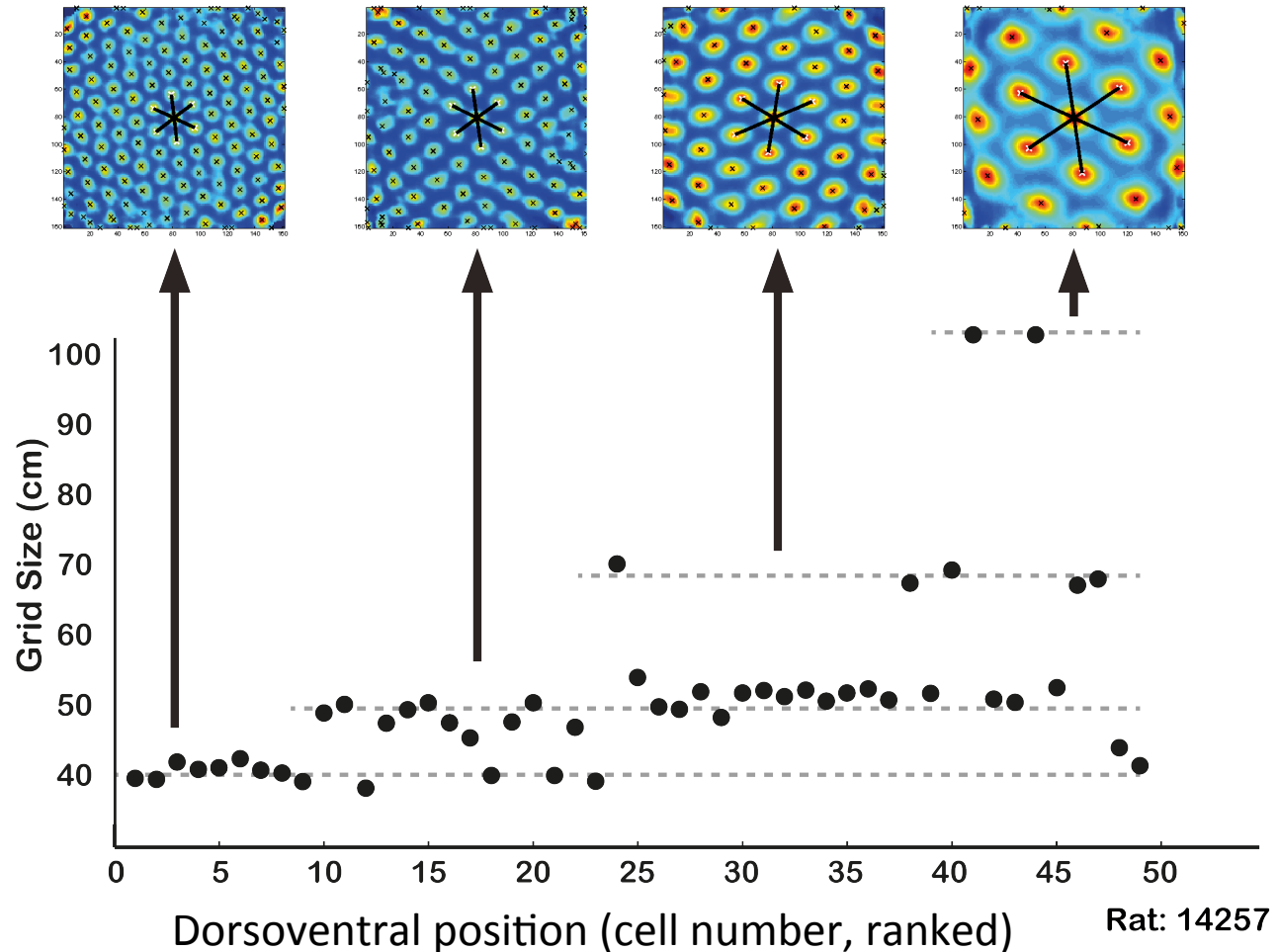Large numbers of grid
cells successively
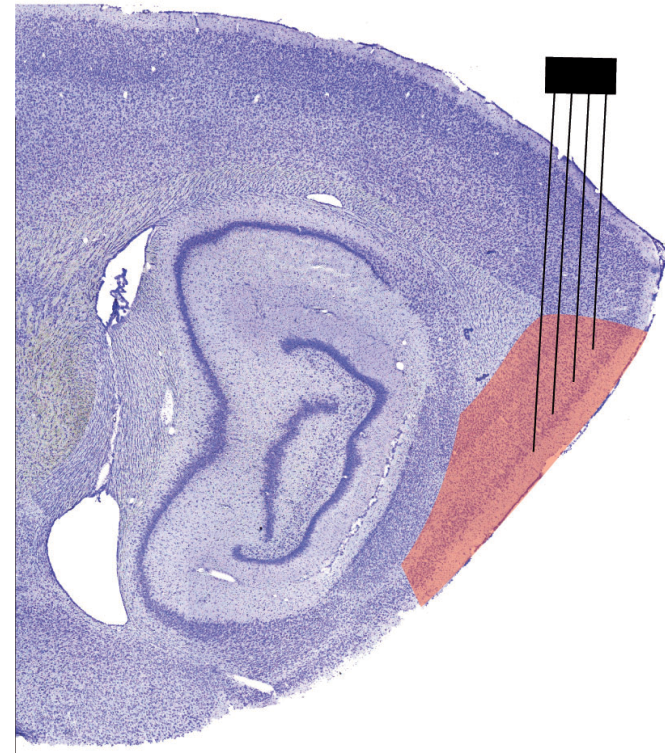
<u>Multisite approach:</u>
Large areas
at the same time

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

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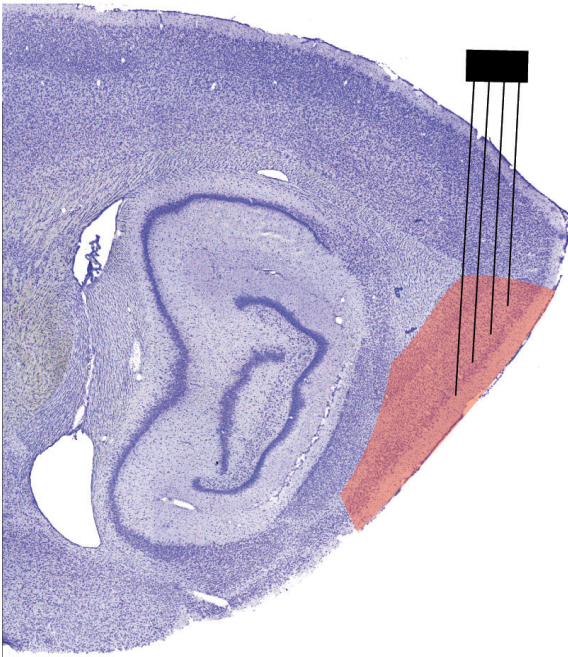The steps in grid spacing are discrete, suggesting that grid cells are organized in modules
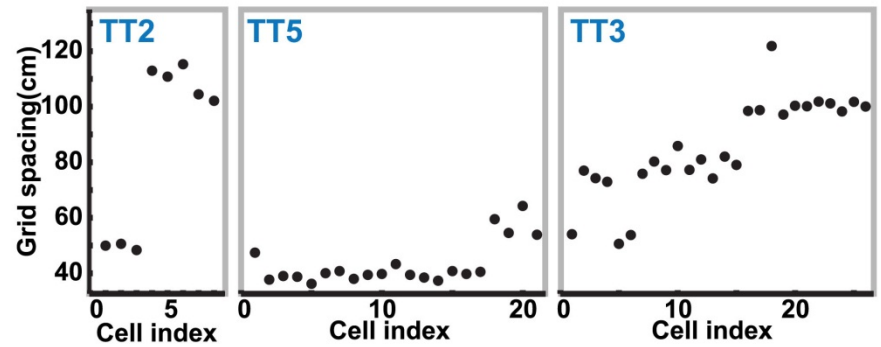

Dorsal → Ventral

Grid Size (cm)

Dorsoventral position (cell number, ranked)

Rat: 14257
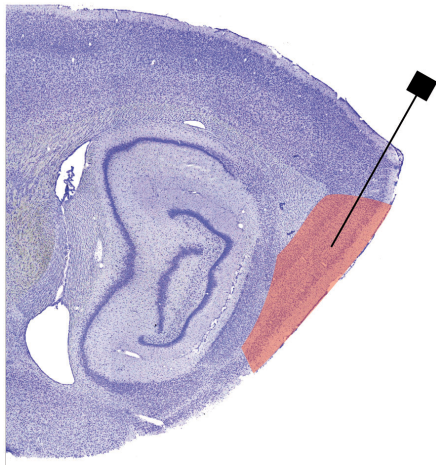
Modules were identified by a k-means clustering procedure

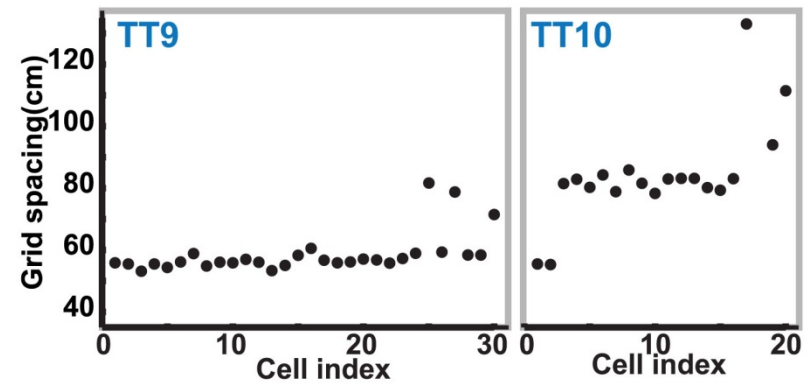Stensola, Stensola, Solstad, Frøland, Moser, Moser, *Nature*, 492, 72-78 (2012)

Multisite approach:
Same result – steps in grid spacing are discrete

Grid modules on individual tetrodes

Rat: 15708

Rat: 15314

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

How **independent** are the grid-space modules?
Do they differ on **other grid properties**?

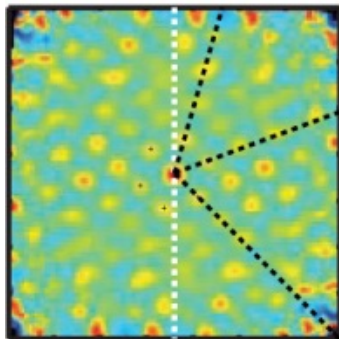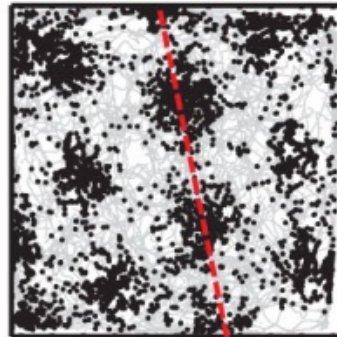Multisite recordings showed that individual animals have more than one **grid orientation...**

Stensola, Stensola, Solstad, Frøland, Moser, Moser, *Nature*, 492, 72-78 (2012)
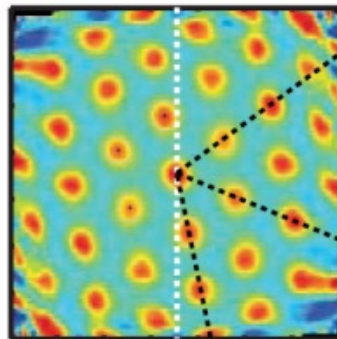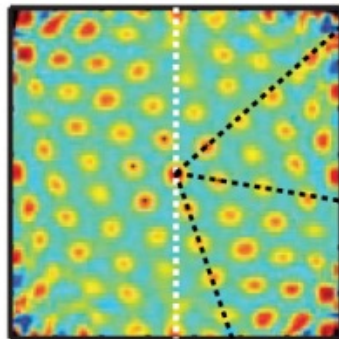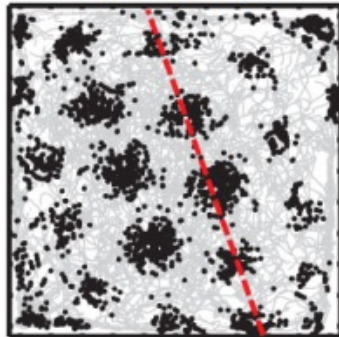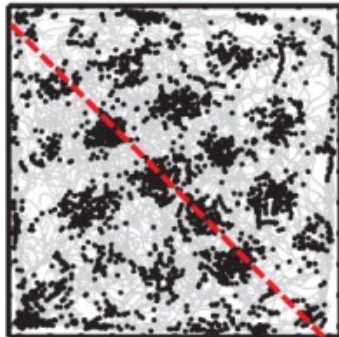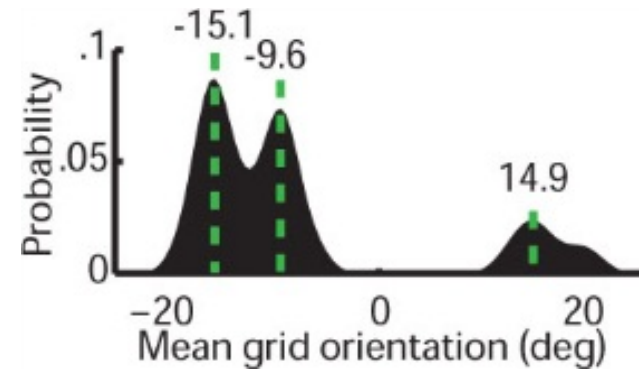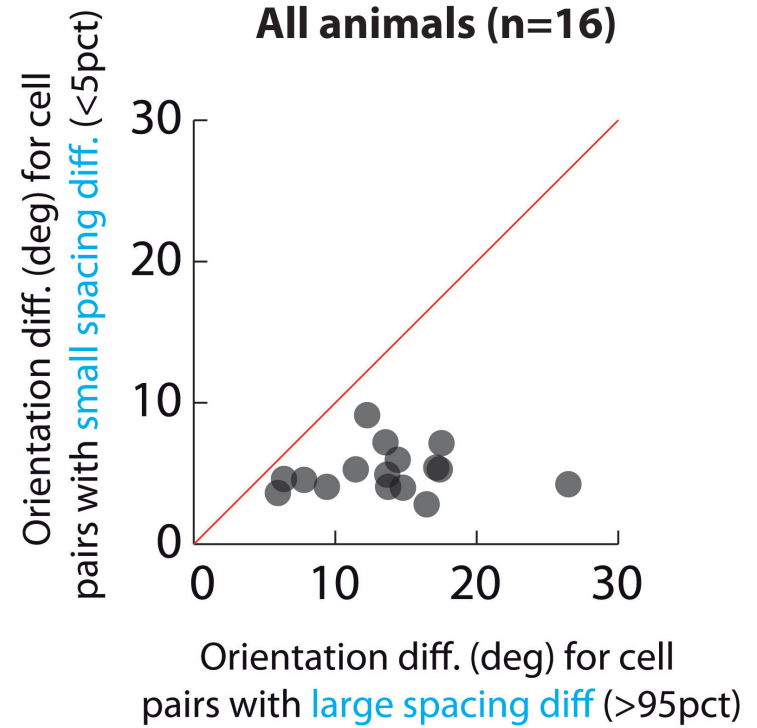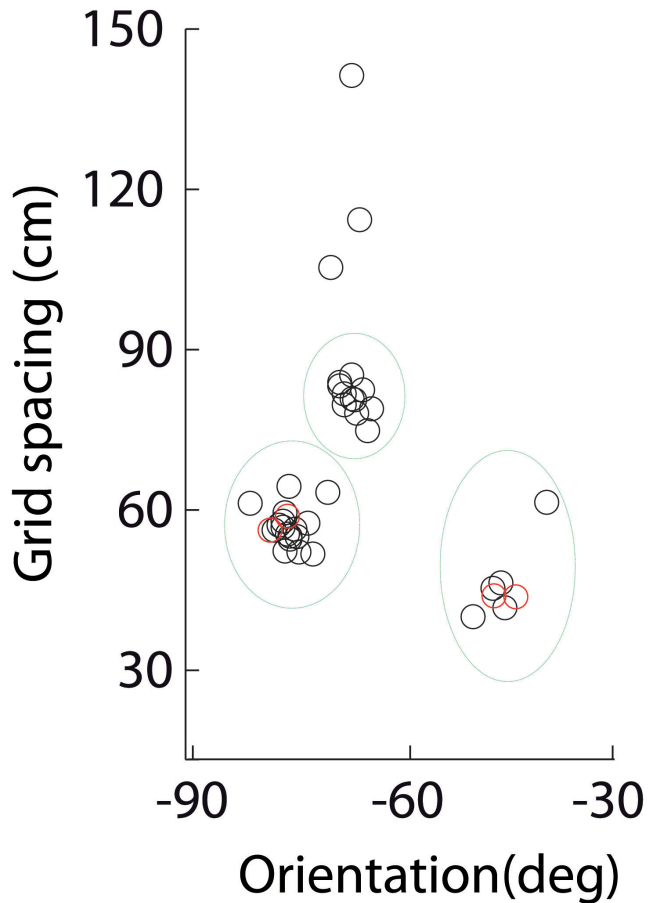
... and that grid-orientation is co-modular with grid scale
(i.e. scale modules and orientation modules have <u>shared boundaries</u>)

Example animal:
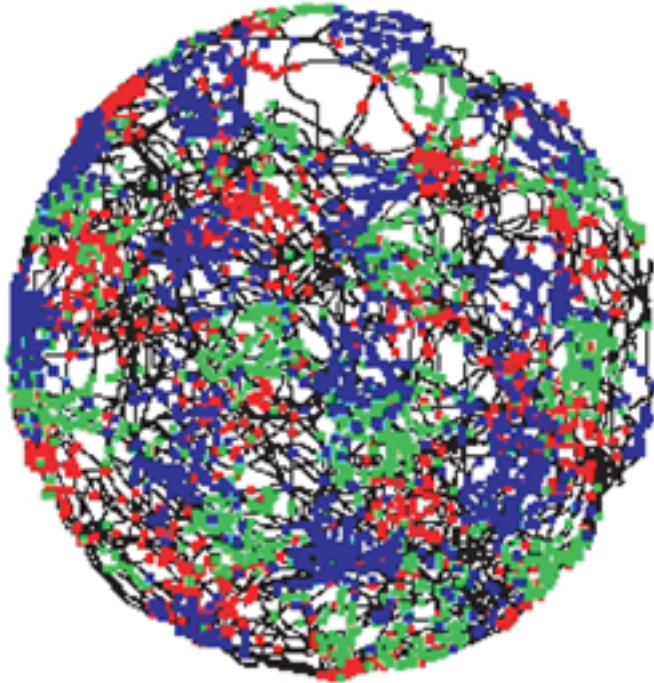

All animals (n=16)

Grid spacing was also co-modular with grid asymmetries (ellipticity) and theta modulation of the grid cells.

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

But within modules, the grid map is rigid and universal: Scale, orientation and phase relationships are preserved across environments…
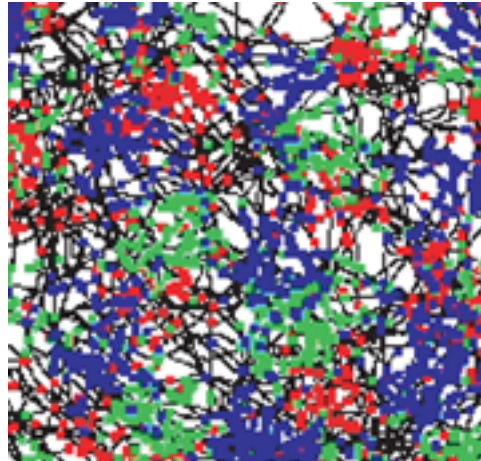
Room 1   Room 1   Room 2

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

… in sharp contrast to the place-cell map of the hippocampus, which shows a nearly-random selection of place field combinations

How many grid modules are there?
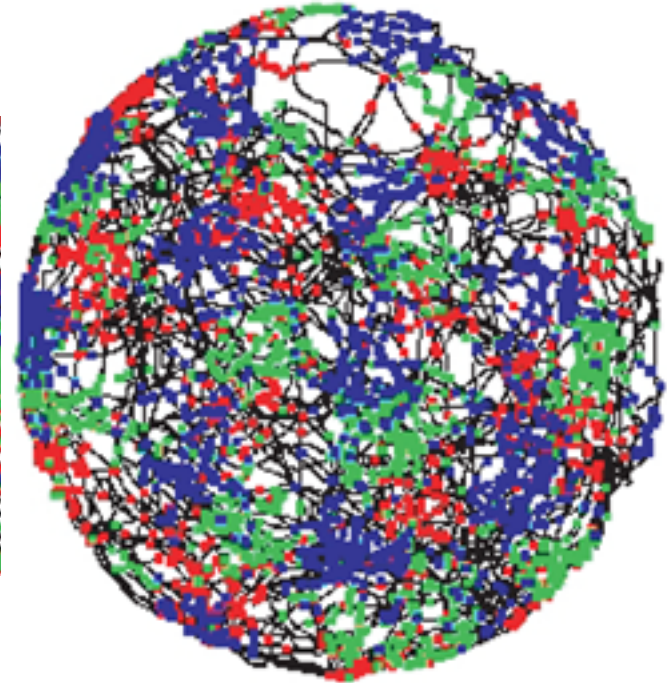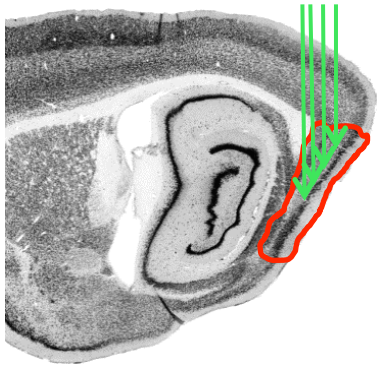
When grid cells were recorded across more than 50% of the medial entorhinal cortex, discrete modules appeared at all locations...

Grid modules on individual tetrodes

Rat: 15708

Rat: 15314

Medial MEC flat map, rat 14147:
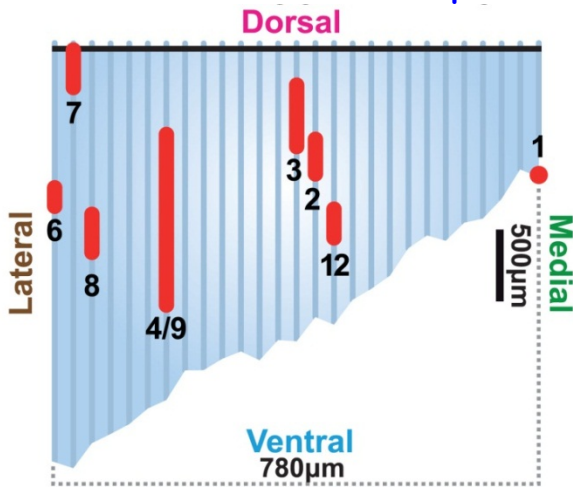
0.6mm in the ML axis;
0-75% of the DV axis

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

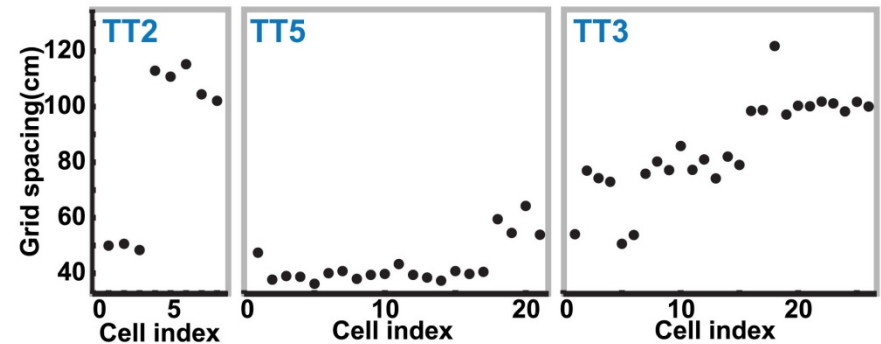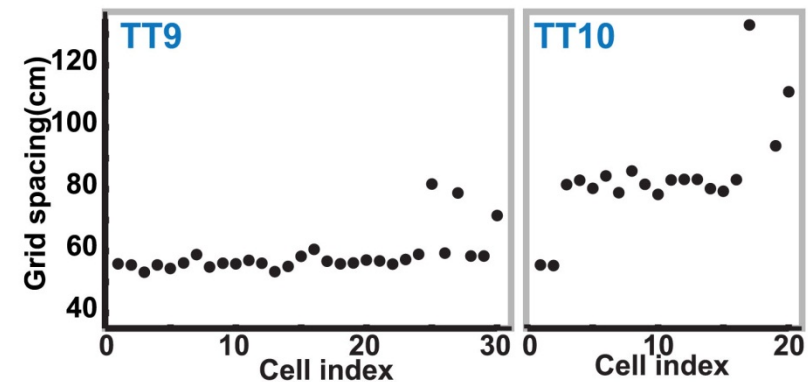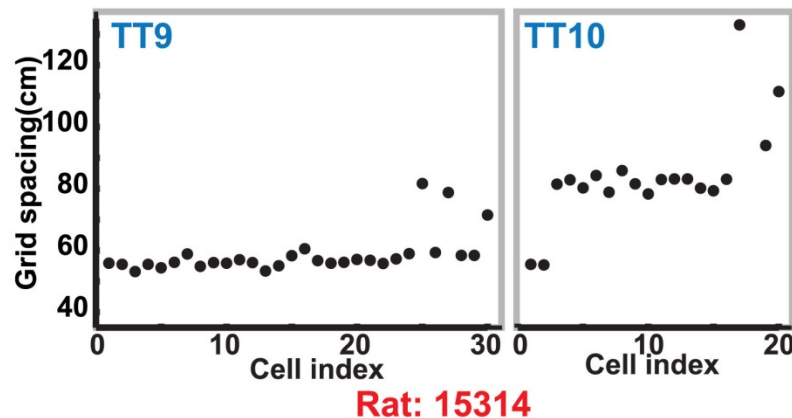# ... but the same ~4 clusters were expressed throughout the sampled area of the entorhinal cortex

Grid modules on individual tetrodes

Rat: 15708

Rat: 15314
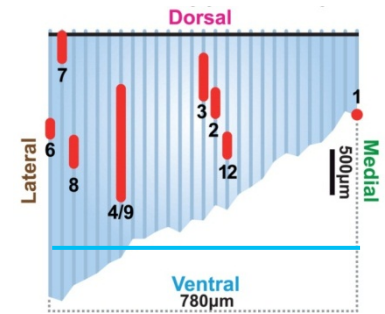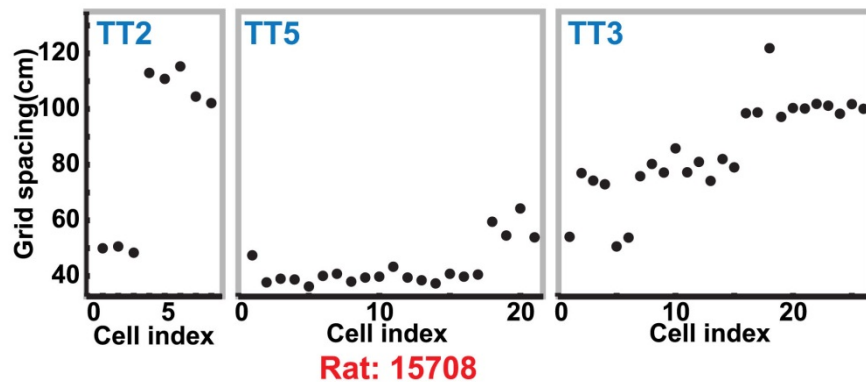
9 tetrodes, rat 14147, n=176 cells:
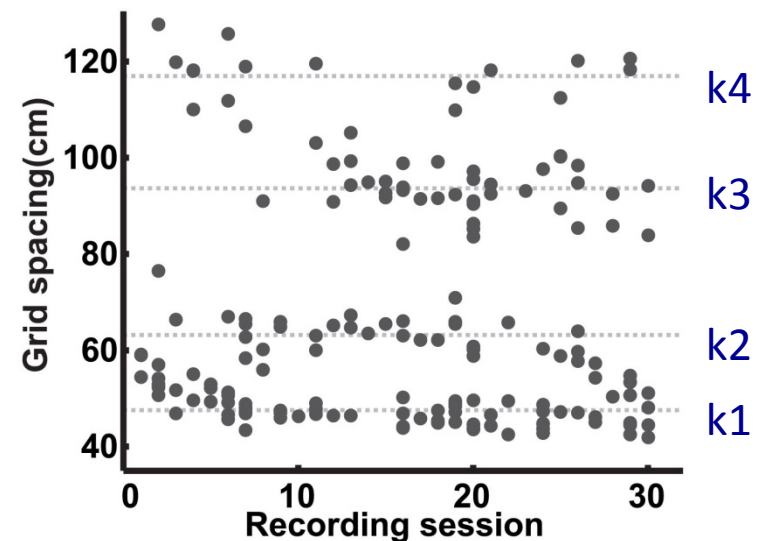
A total of 4+ modules was recorded over more than 50% of medial entorhinal space

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

How are these modules mapped onto the entorhinal surface?

1. Recordings along a horizontal (mediolateral) strip showed no modularity

Stensola, Stensola, Solstad, Frøland, Moser, Moser, *Nature*, 492, 72-78 (2012)
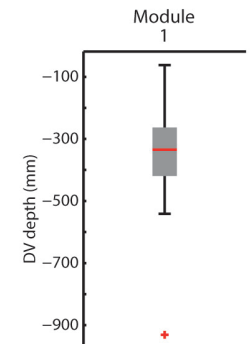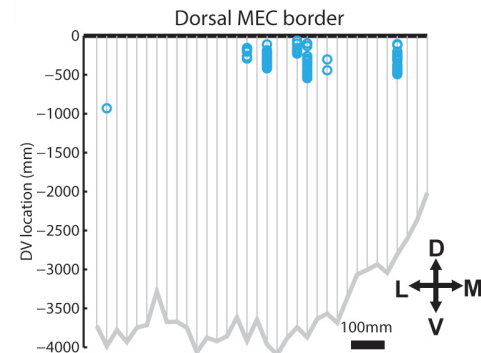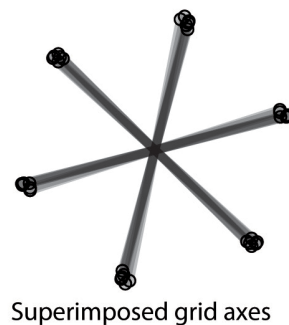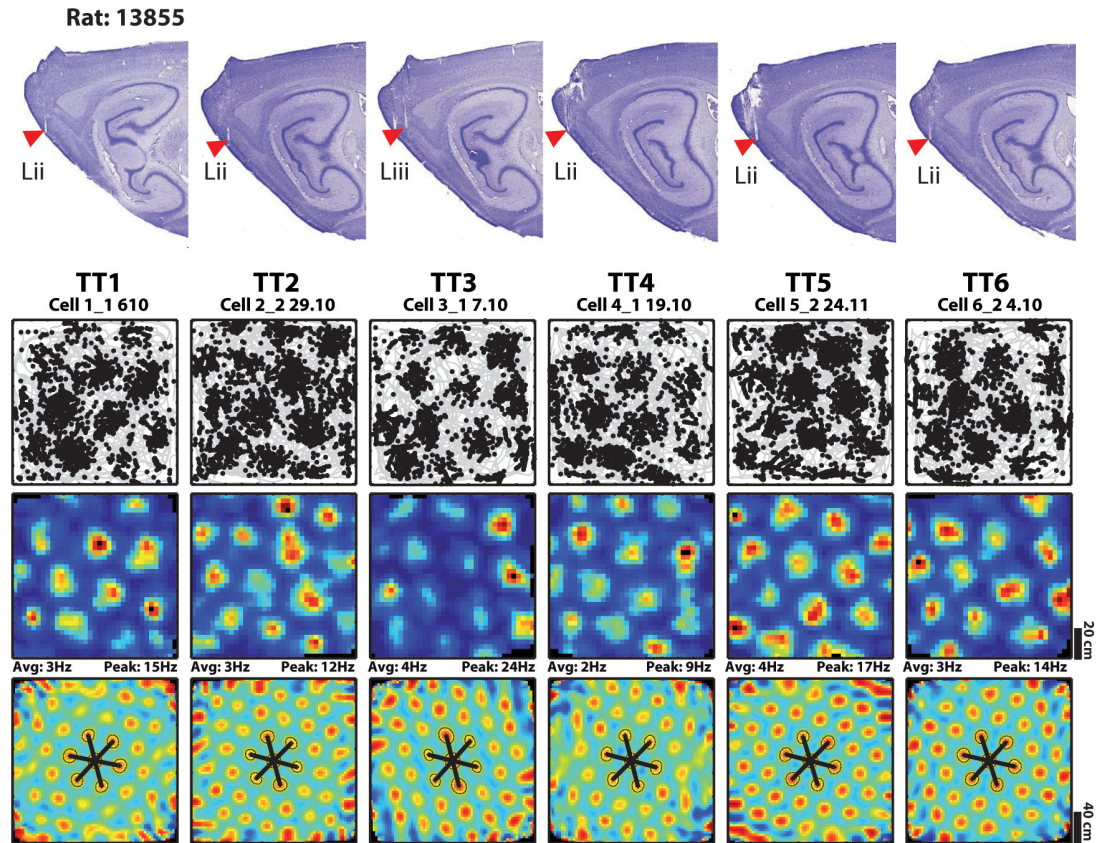
2. Recordings along <u>both axes</u> (dorsoventral and mediolateral) suggested that grid modules change <u>only along the dorsoventral</u> axis, i.e. are organized as <u>horizontal bands</u>

Stensola, Stensola, Solstad, Frøland, Moser, Moser, *Nature*, 492, 72-78 (2012)
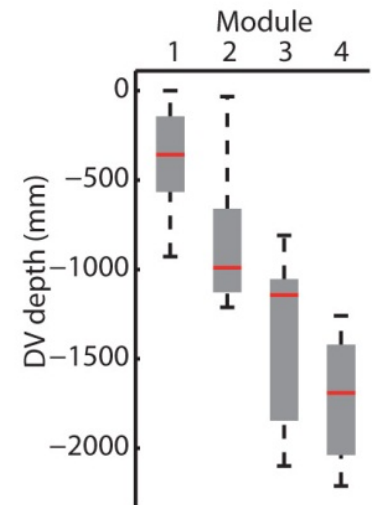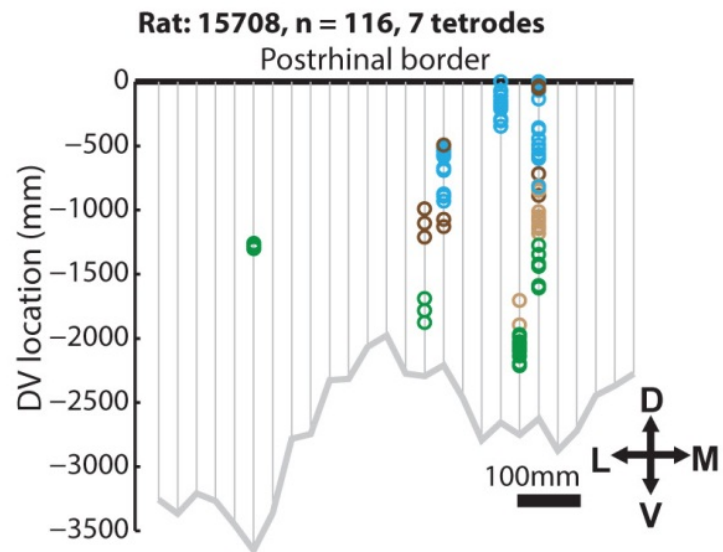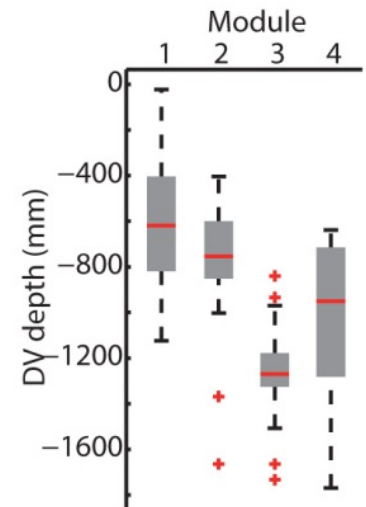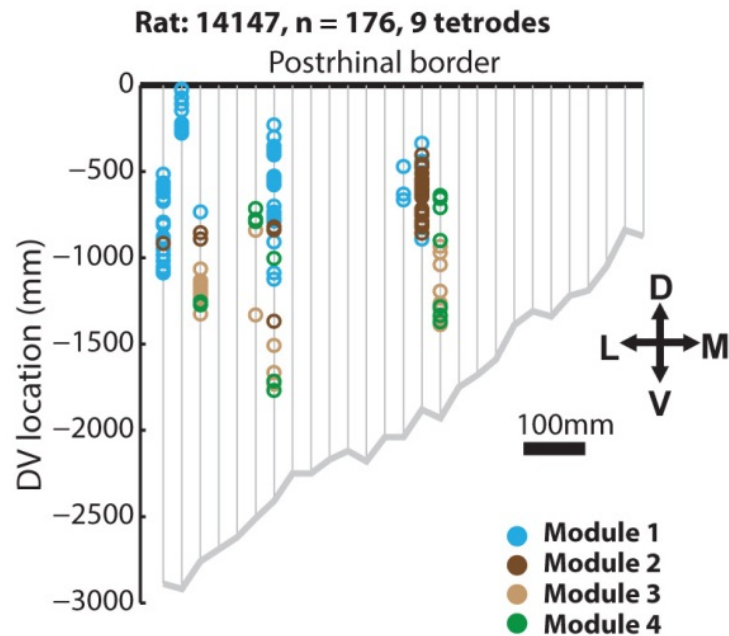
3. But the modules exhibit anatomical overlap

Rat: 14257
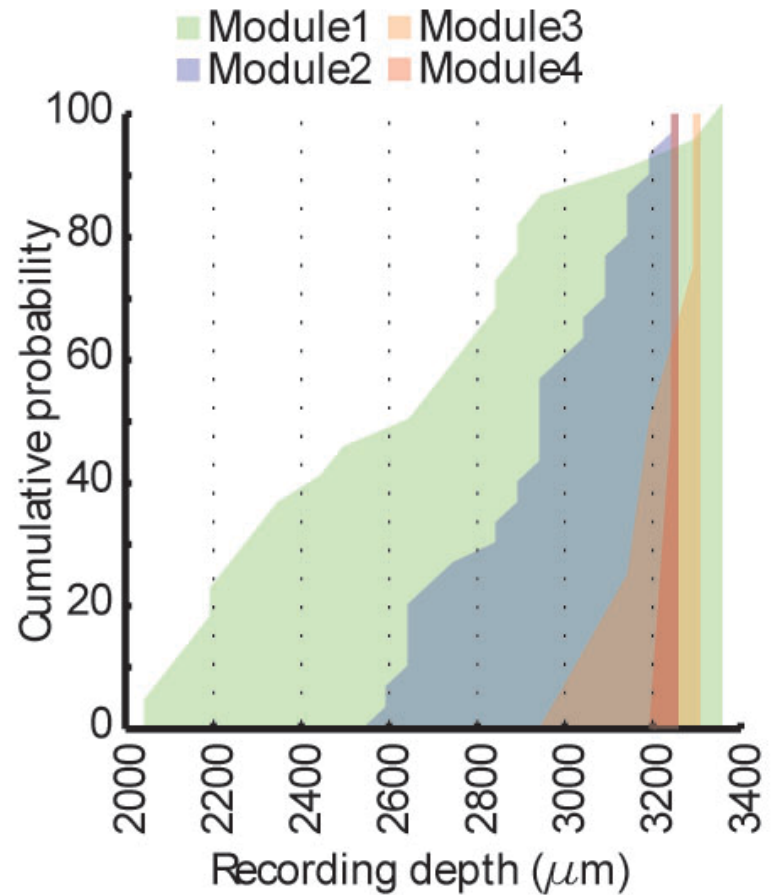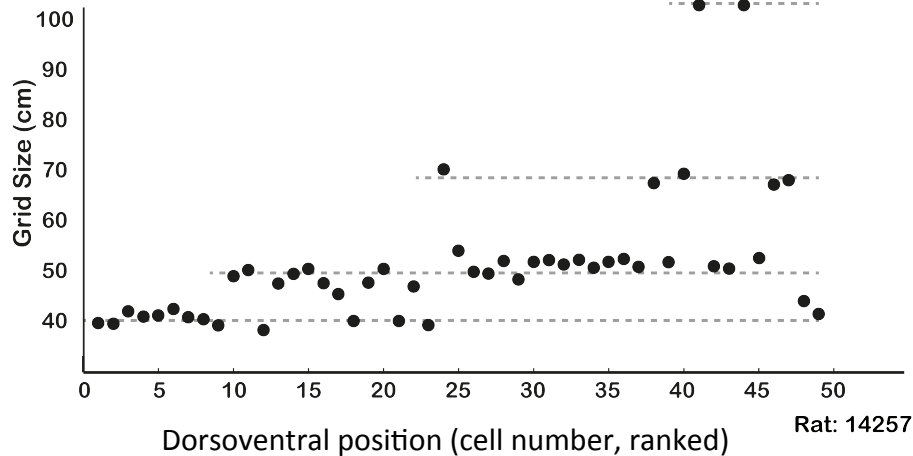
The number of modules increases from dorsal to ventral MEC

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

How rigid is the grid map?
Absolute scale values differ between animals

All animals had discrete modules but <u>the exact scale of the individual modules varied between animals,...</u>

...which explains why modules were not visible in group data.

Rat: 14147 n=176 14257 n=62 15708 n=116

Orientation of grid axis

Mean grid scale (cm)

All animals(n=16)

Module

Stensola, Stensola, Solstad, Frøland, Moser, Moser, *Nature*, 492, 72-78 (2012)
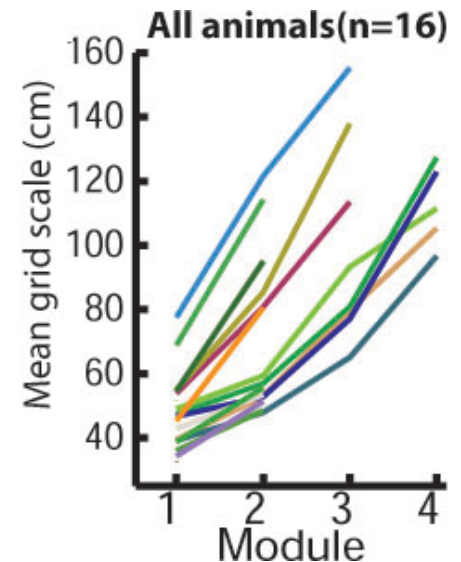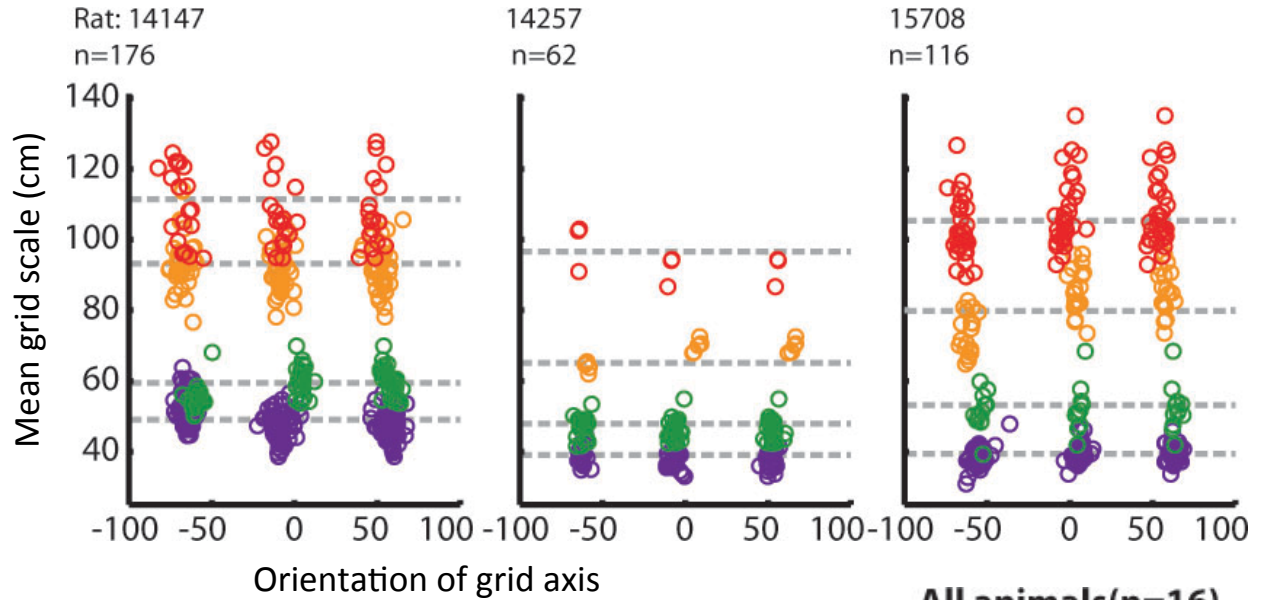
But the scale ratio across modules is constant!

Average ratio: 1.421

1.401   1.429   1.434

Scale ratio

M2/1   M3/2   M4/3

x1.42   x1.42   x1.42   x1.42

Module: **1**   **2**   **3**   **4**

Probability

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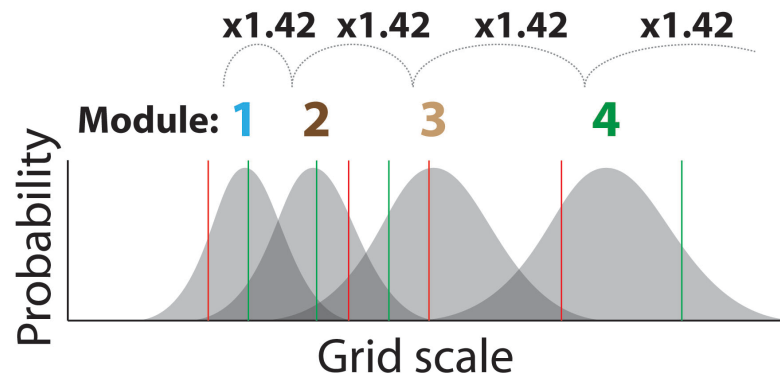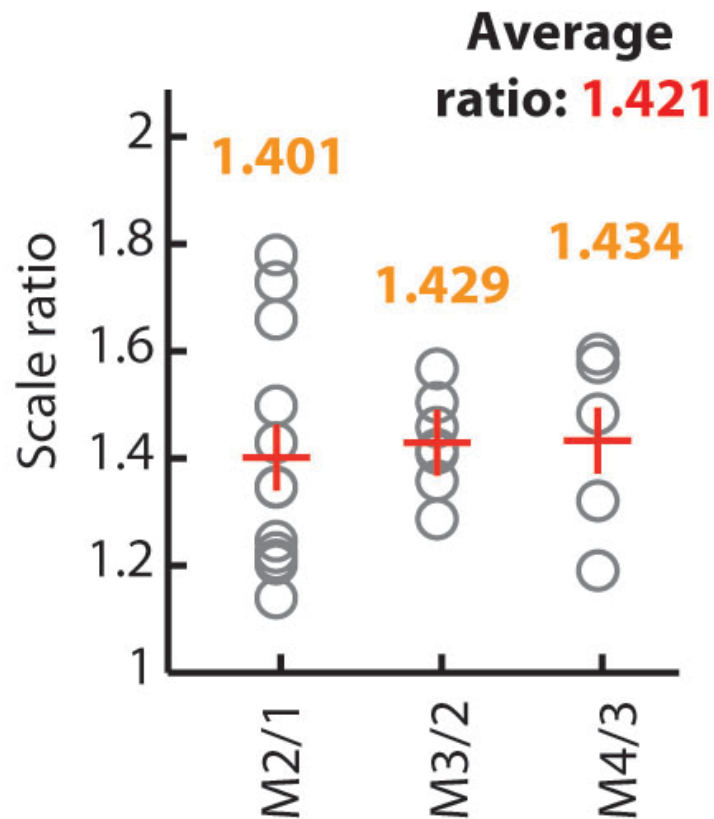
Stensola, Stensola, Solstad, Frøland, Moser, Moser, *Nature*, 492, 72-78 (2012)

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

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).

All work:
May-Britt Moser

Entorhinal maps:
Vegard Brun
Marianne Fyhn
Torkel Hafting
Sturla Molden
Francesca Sargolini
Trygve Solstad
Charlotte Boccara
Emilio Kropff
Alessandro Treves
Bruce McNaughton
Menno Witter

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Aree Witoelaar
Benjamin Dunn
Menno Witter
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Sheng-Jia Zhang
Jing Ye
Rafal Czajkowski
Tora Bonnevie

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The Kavli Foundation,
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European Commission's 7th
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ERC Advanced Investigator Grant
scheme,
Louis Jeantet Foundation

Speed cells:
Emilio Kropff
Eric Carmichael
Rita Baldi
Path integration:
Dori Derdikman

Grid orientation:
Tor Stensola
Hanne Stensola

Grid modules:
Tor Stensola
Hanne Stensola
Kristian Frøland
Trygve Solstad

Grid cells and grid coherence:
Marianne Fyhn
Torkel Hafting
Sturla Molden
Alessandro Treves

Inhibitory
connectivity:
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Menno Witter
SJ Zhang