Public lecture on brain science
Mongolian Neuroscience Society
House of Parliament
Ulanbaatar, Mongolia
24 September 2018

Space and time in the brain

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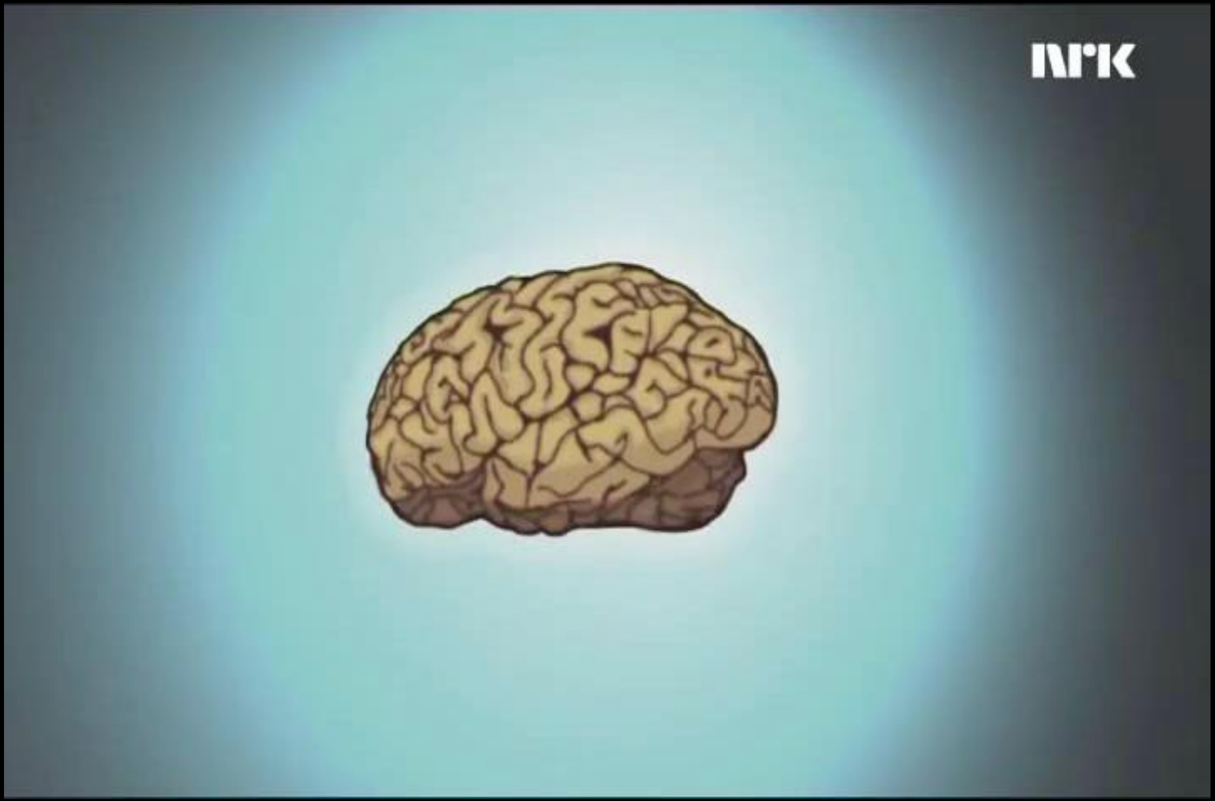
20th-21st century:
Breaking the psychology-physiology barrier

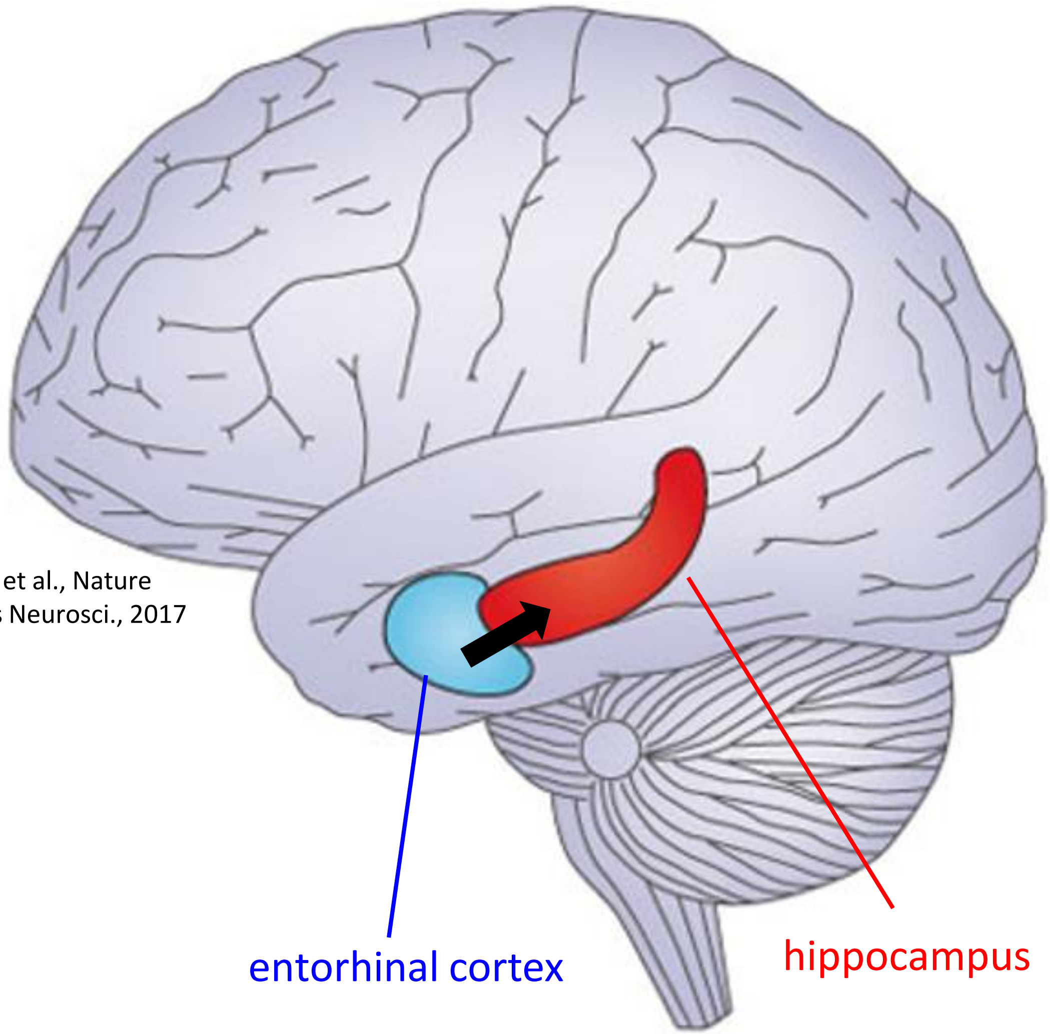


The human brain consists of 80-100 billion neurons,
each receiving connections from about 10 000 other cells.

First steps towards understanding the neural basis of subjective experience and behavior: The neural mechanisms of space

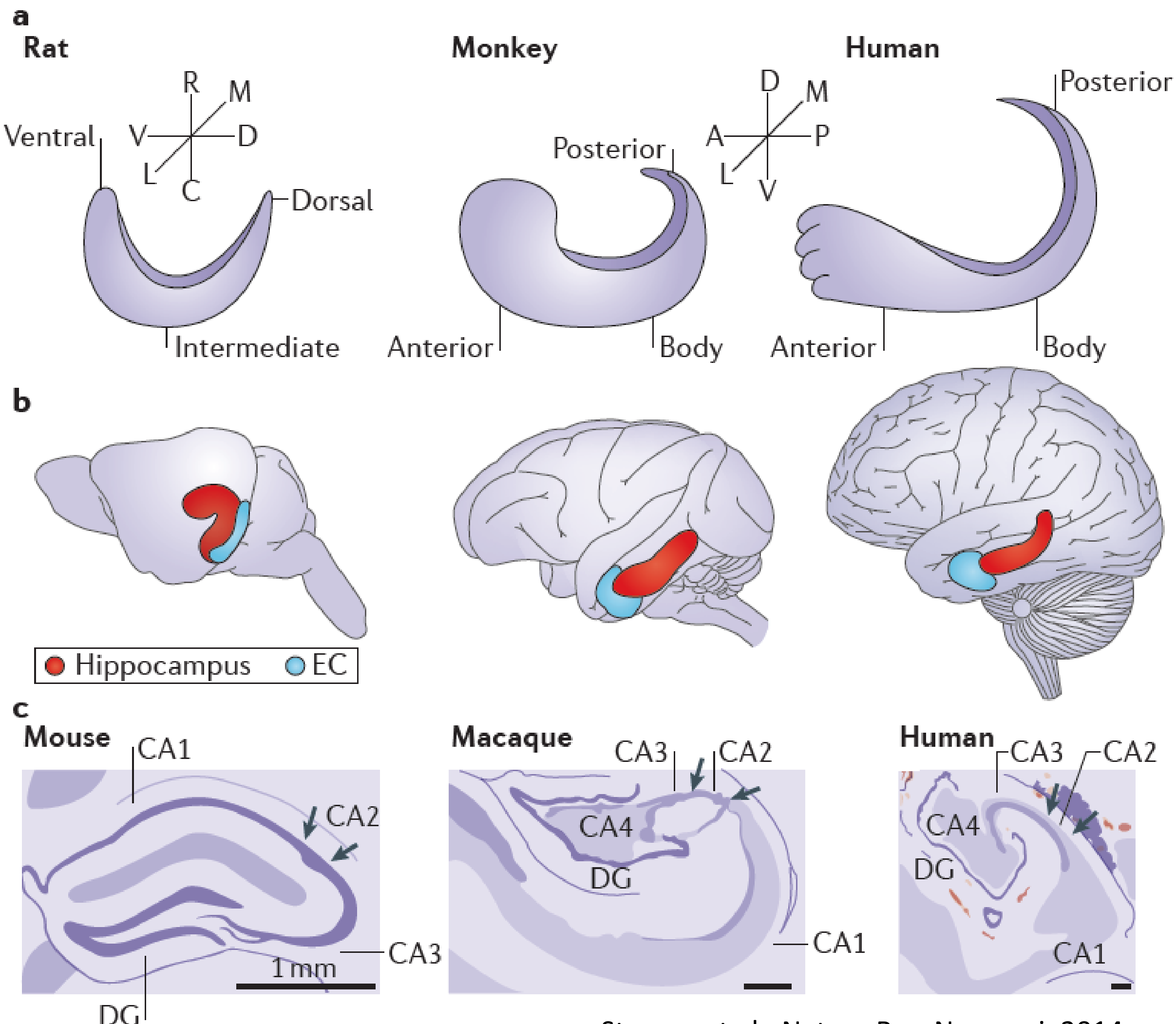
The brain's positioning system includes the hippocampus and the entorhinal cortex

Strange et al., Nature Reviews Neurosci., 2017



But the human brain is complex and hard to study

Because of our common ancestry, the architecture of the brain – including the hippocampus - is very similar…



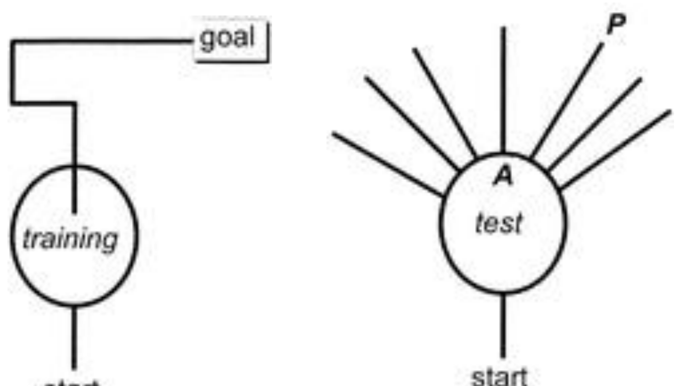
Strange et al., Nature Rev. Neurosci. 2014

… so the rat (or mouse) brain can teach us a lot!

History of the positioning system: Based on work in **rats**, Edward C. Tolman suggested in the 1930s-50s, that knowledge is based on an internal **map** of the environment (cognitive maps)

E.C. Tolman (1886-1959)

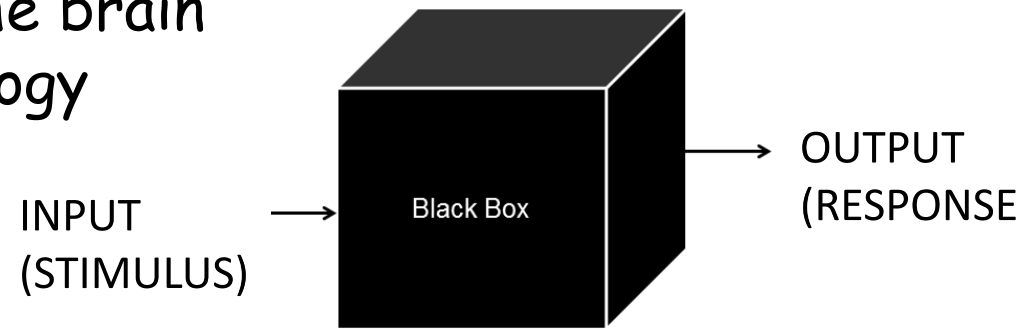
Tolman's shortcut-experiment:



The ability to take shortcuts and detours suggests that information is not stored as pure stimulus-response sequences but rather in some sort of map-like representation.

But where could such maps be?

Obviously in the brain but the behaviourists in the 1930s-50s (including Tolman) treated the brain as a ´**black box**', and psychology avoided the brain…



Internal behavior of the code is unknown

But during the 1950s the climate changed, with renewed courage and optimism…:

… and microelectrodes for single-cell recording were developed: By 1955, David Hubel had developed the tungsten electrode

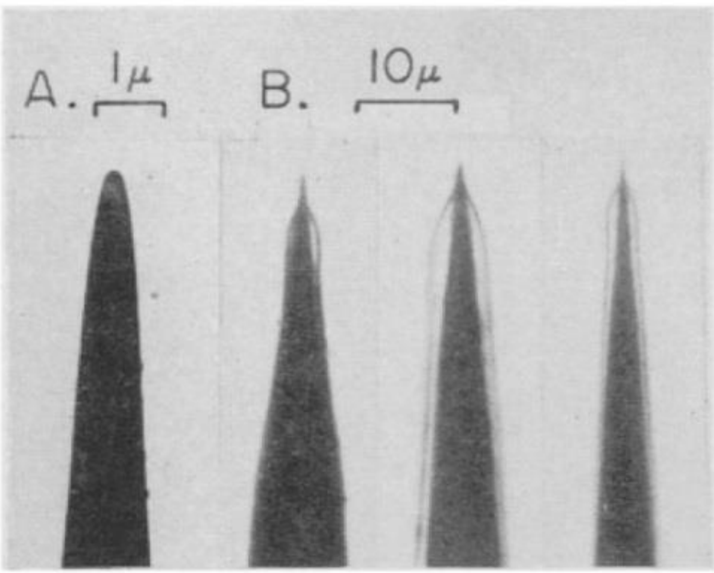


Fig. 1. (*A*) Electromicrograph of an uncoated, sharpened tungsten wire; (*B*) optical photomicrographs of coated electrodes immersed in water to show the coating.

0.06	94
0.2	96

on sarcoma-180 *in vivo* might be attributable to a metabolite of the analog formed by the liver or other normal tissues. An attractive possibility for consideration, as a metabolite of 6-azauracil, was its riboside (6-azauridine), since this derivative is formed by certain microorganisms and inhibits the growth of
6-azauracil-r
when *Strep*
in the prese
6-azauridine
biosynthetic
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hibitor, a th
cell protein,
served 24 h
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the chemic
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ing the grow
sults obtained with the biosynthetic material are shown in Table 1.

The activity of 6-azauridine was an-

…y uridine: as is shown in …e molar ratio of metabolite …t necessary to abolish almost the action of 6-azauridine (at …ed, 0.2 μmole/ml) was 1/10. … tenfold higher concentration under these conditions, no toxic effects on the cells was …eoxyuridine was also active … the inhibitory activity of …; however, quantitative data its activity and its possible the cells have not yet been …rther work will be concerned …tion of related analogs and …sides, the effects of other pos…ng agents and their compara…, and the effects of the agents …l lines in tissue culture (*11*).

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ARNOLD D. WELCH
…t of Pharmacology,
…rsity School of Medicine,
…, Connecticut

References and Notes

…andschumacher and A. D. Welch, …search 16, 965 (1956); F. Šorm and J. Škoda, *Collection Czechoslov. Chem. Commun.* 21, 487 (1956).
2. H. T. Hakala, L. W. Law, A. D. Welch. *Proc. Am. Assoc. Cancer Research* 2, 113 (1956).
3. H. Eagle, personal communication.
4. ——, *Science* 122, 501 (1955).
5. R. E. Handschumacher, *Biochim. et Biophys. Acta,* in press.
6. ——, in preparation.
7. The small amounts of 6-azauridine were generously supplied by R. E. Handschumacher of our laboratories.
8. The sarcoma 180 cells used in the tissue-culture studies were derived from a strain isolated and generously supplied by George Foley, Children's Cancer Research Foundation, Boston, Mass.
9. W. R. Earle and F. Highhouse, *J. Natl. Can-* … *Exp.*

…to break, such as in chronic unrestrained preparations, with muscle, and in the human being during neurosurgical pro-

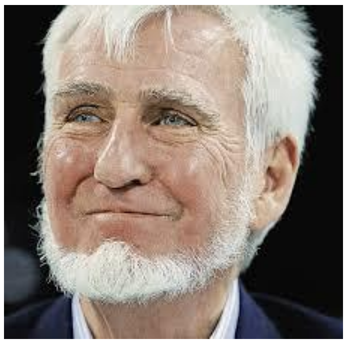
cedures. Early experience made it clear that, while tip diameters of the order of 20 μ may at times be adequate for resolution of unitary spikes recorded extracellularly, tips 5 μ or less are much more satisfactory, and that intracellular recording usually demands tips of less than 1 μ in diameter. Since steel wire becomes too fragile near the tip when thus sharpened and also requires too thick a shaft, tungsten was selected as by far the stiffest, easily available metal.

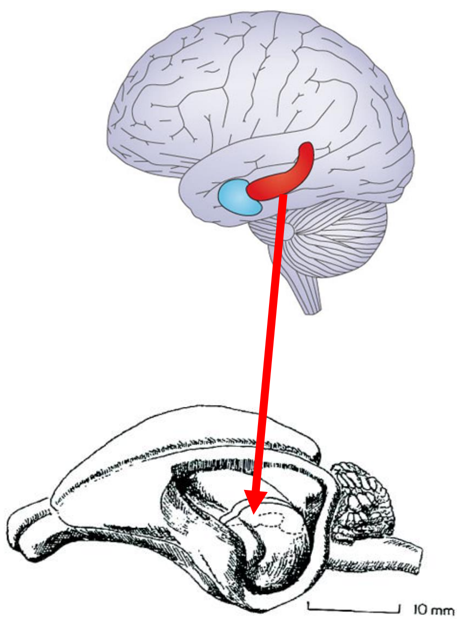
The electrode consists of an electrolytically sharpened tungsten wire insulated to the tip with a suitable lacquer. A wire 125 μ (5 mils) in diameter and about 1 inch long is bent slightly near one end which is then mounted in a 27-gage hypodermic needle. Because crimping of these needles results in perfectly satisfactory electric contact, no attempt has been made to solder the tungsten. Electropolishing is then carried out by a method analogous to that described by Grundfest *et al.* (*1*) for steel: the terminal few millimeters are immersed in a saturated aqueous potassium nitrite (KNO_2) solution, and an alternating current is passed between the wire and a nearby carbon rod, using 2 to 6 v, which may be conveniently obtained from a 6.3-v filament transformer fed by a Variac (*2*). The optimum voltage is not critical, but currents that are too low or too high tend to cause pitting.

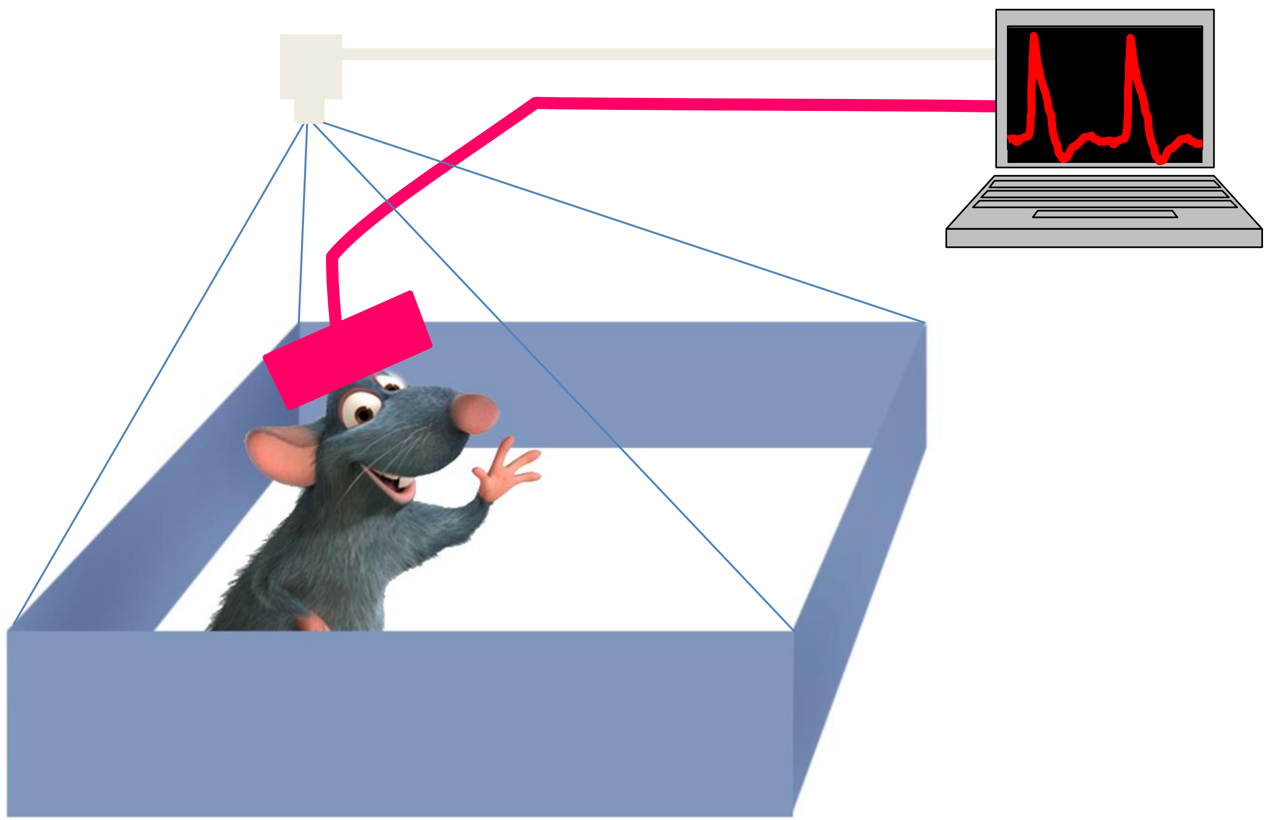
brimful of freshly stirred lacquer, and then slowly raised. When the tip

… and conceptual frameworks were introduced (Hebb, Konorski)

And around 1970, John O'Keefe used microelectrodes to record electrical activity from single neurons in the hippocampus of freely moving rats…

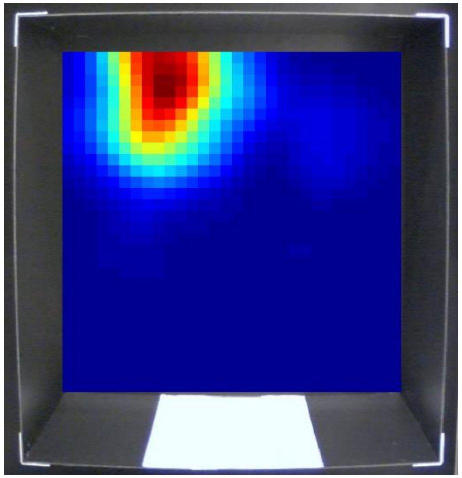




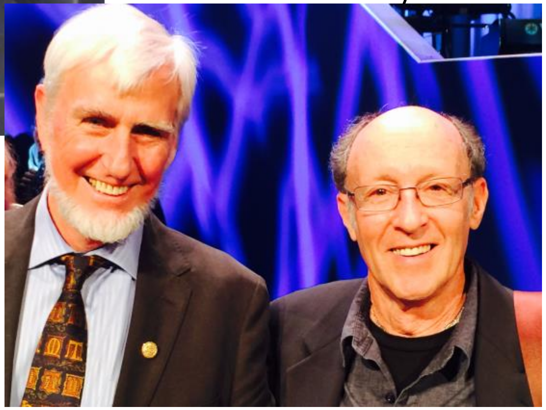


… and found place cells (O'Keefe and Dostrovsky, 1971)

The firing of these cells is strongly related to a property of the outside world – the animal´s location.



John O'Keefe and Lynn Nadel



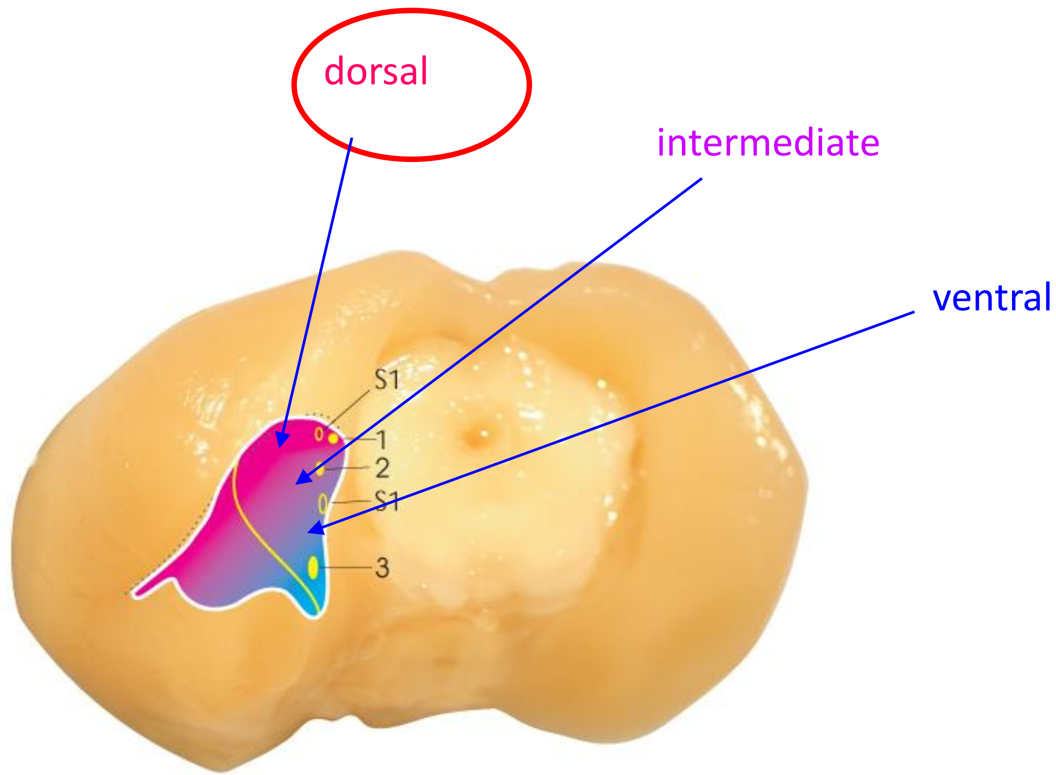
The Hippocampus as a Cognitive (Tolmanian) Map

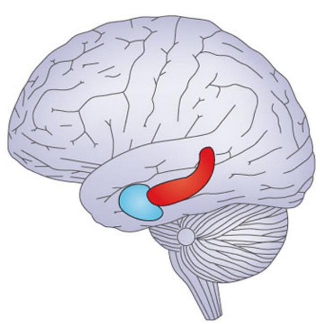
Where does the place-cell signal come from?

August 1996:
Trondheim, Norway

We recorded from dorsal medial entorhinal cortex (MEC), which provides the strongest input to the dorsal hippocampus where the place cells had been found

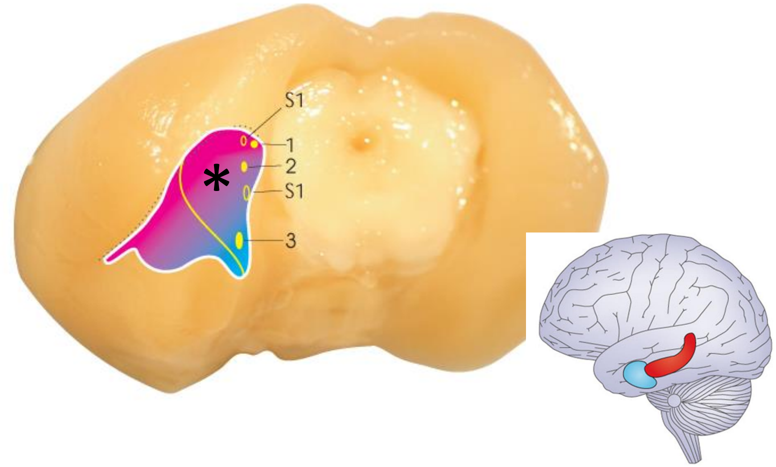
Entorhinal cortex of a rat brain (seen from behind):



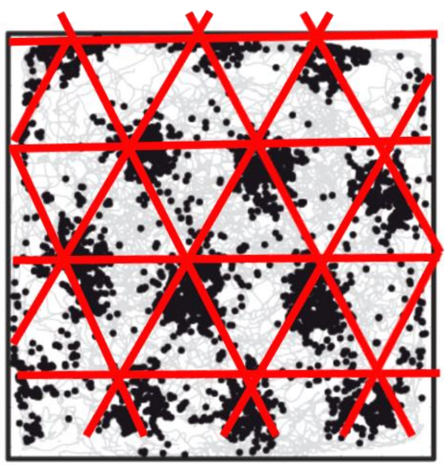


Fyhn et al. (2004). *Science* 305:1258-1264

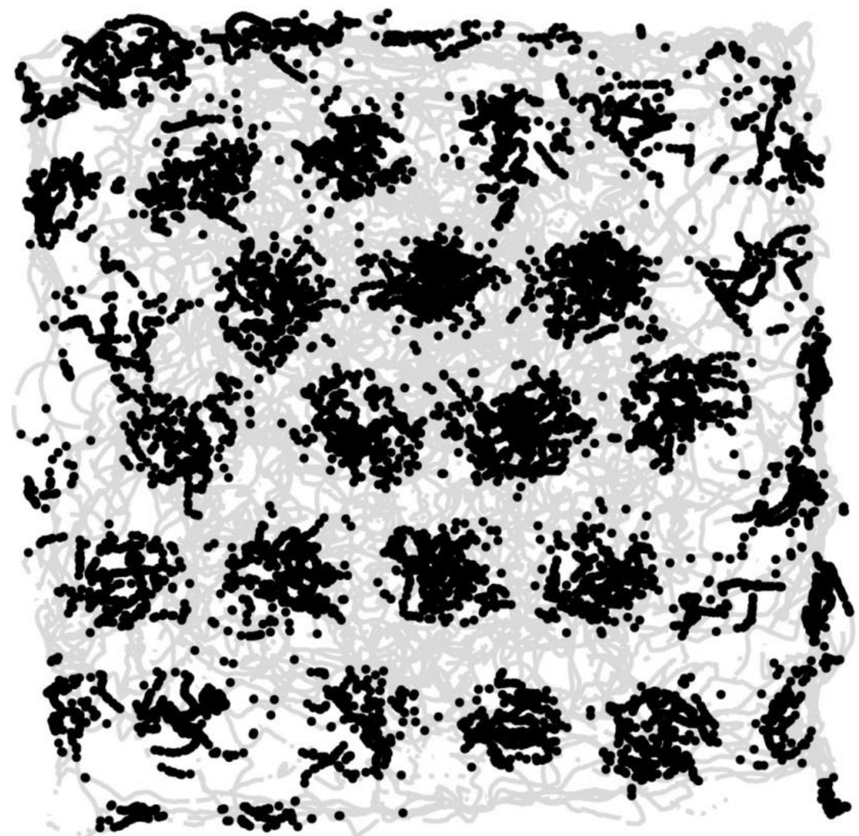
2005: We discovered grid cells in the medial entorhinal cortex (*) - cells that have spatial fields with a periodic hexagonal structure – the metric of the brain's map of space



The fields form a grid that covers the entire space available to the animal.

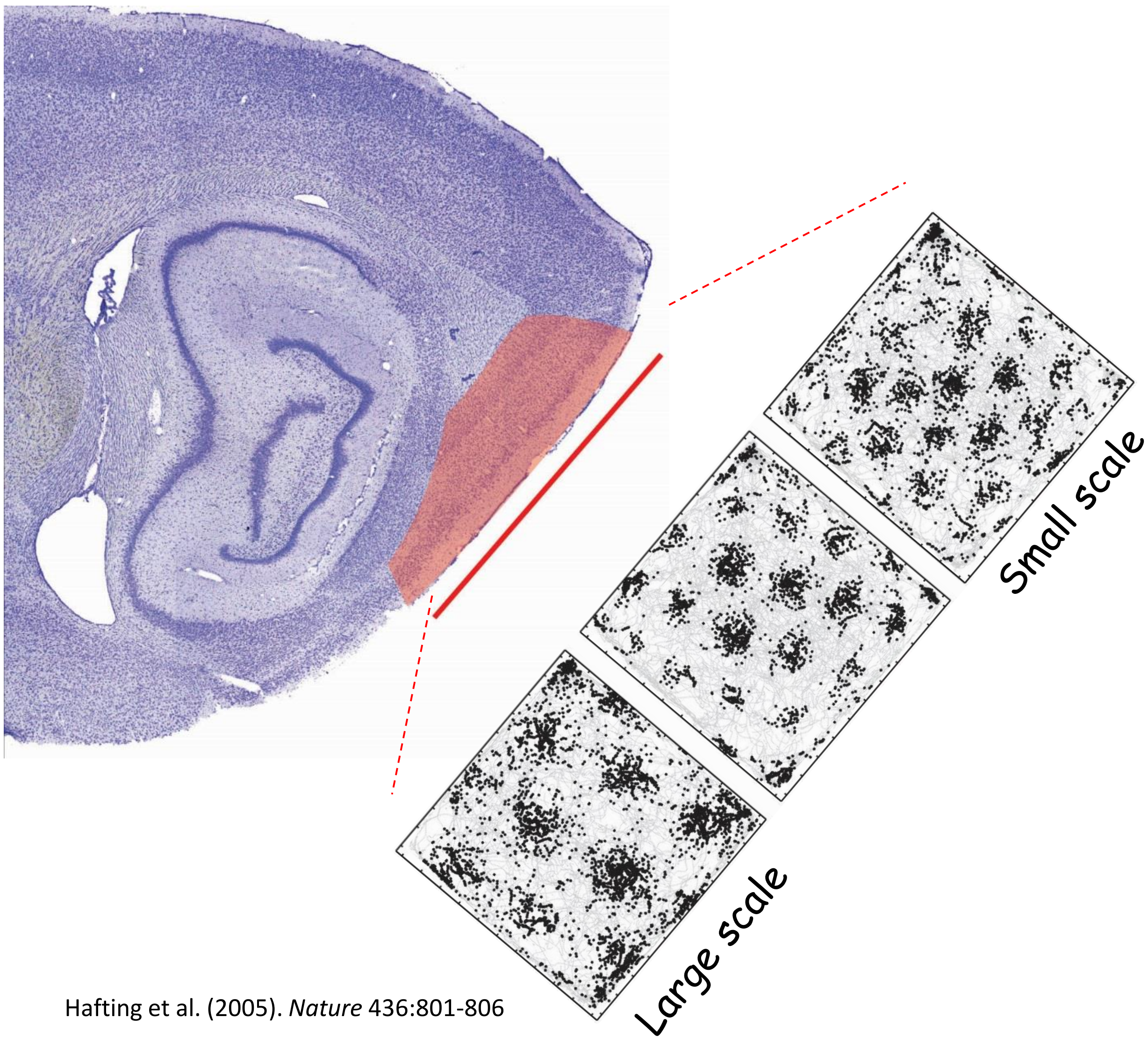


Hafting et al. (2005). *Nature* 436:801-806



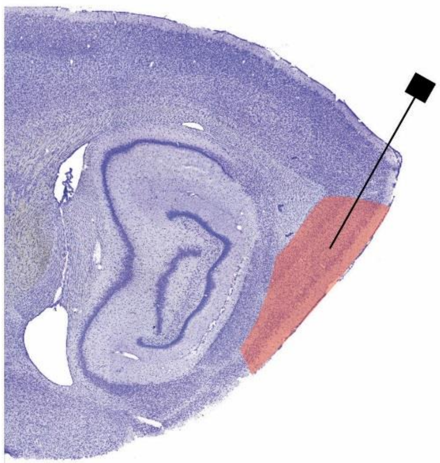
Stensola et al. *Nature*, 492, 72-78 (2012)

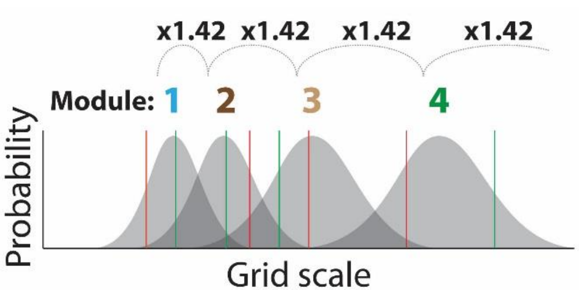
The spacing of the grid cells has a topograhical organization, with an increase in grid scale from dorsal (top) to ventral (bottom)…



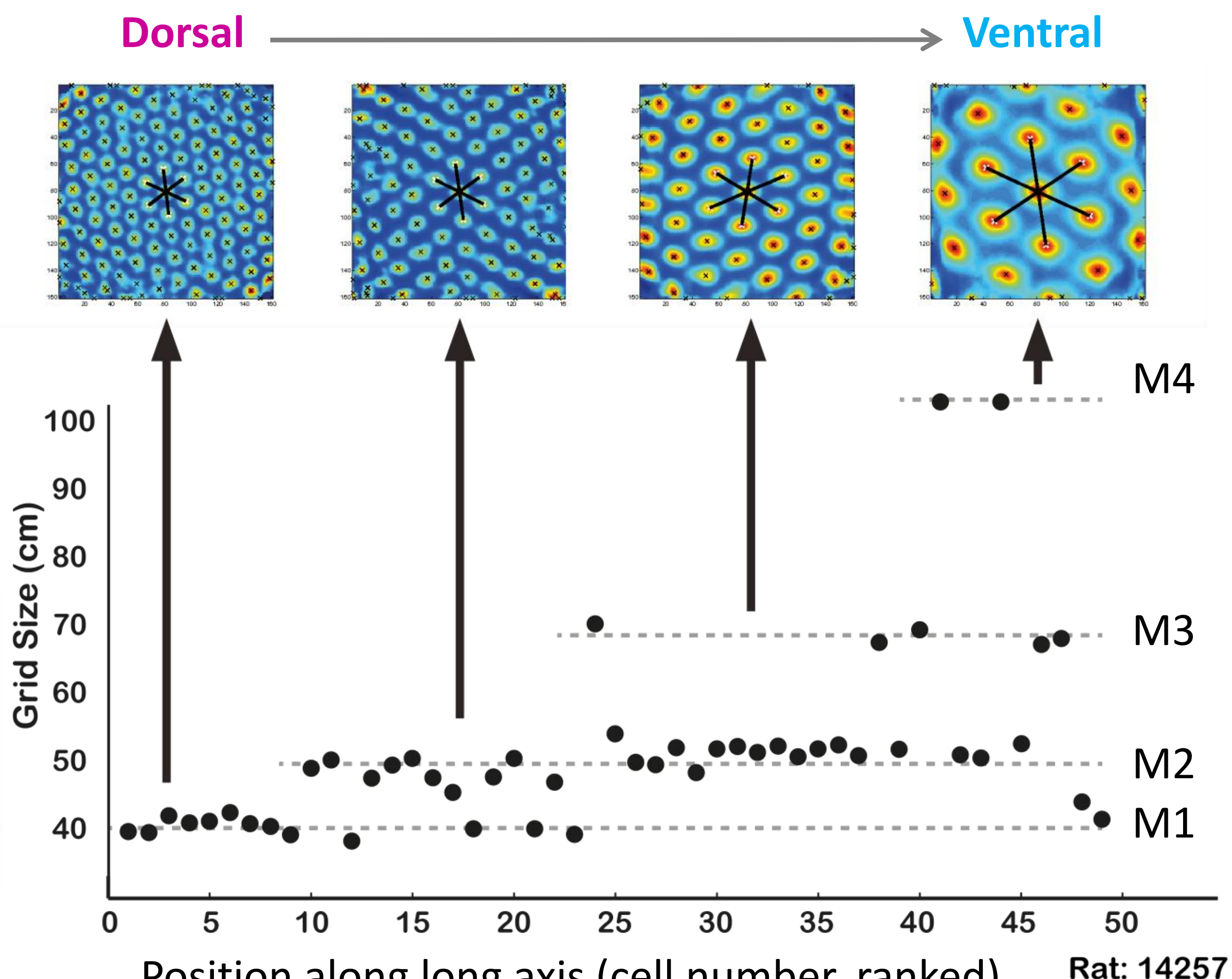
Hafting et al. (2005). *Nature* 436:801-806

…but the steps in grid spacing are discrete, suggesting that grid cells are organized in modules



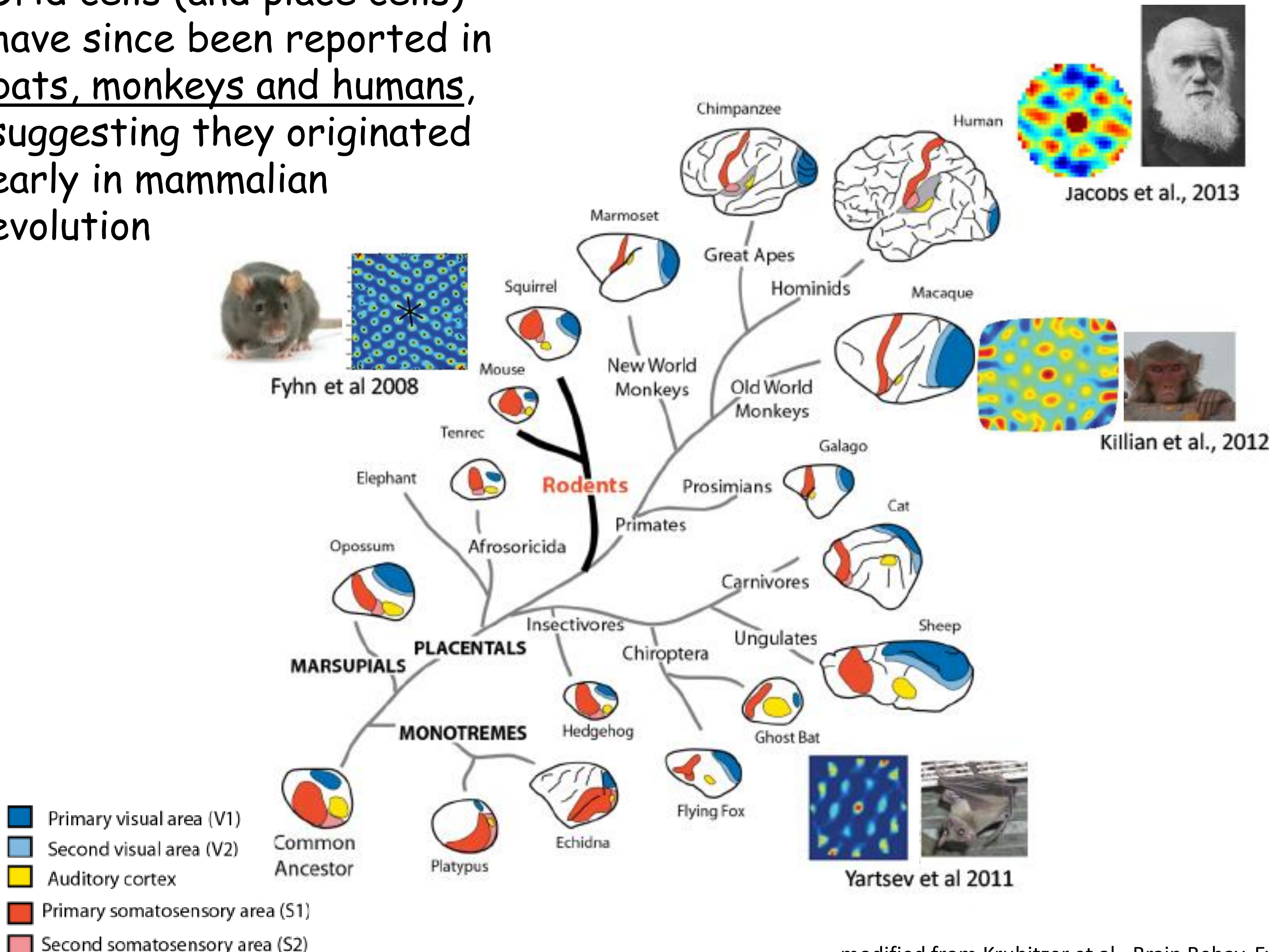


The scale ratio is constant, as in a geometric progression



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

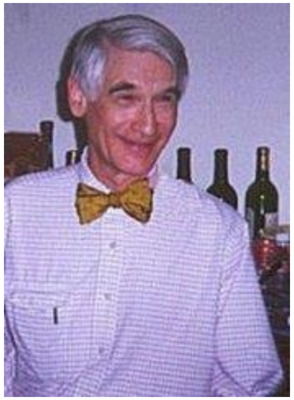
Grid cells (and place cells) have since been reported in <u>bats, monkeys and humans</u>, suggesting they originated early in mammalian evolution



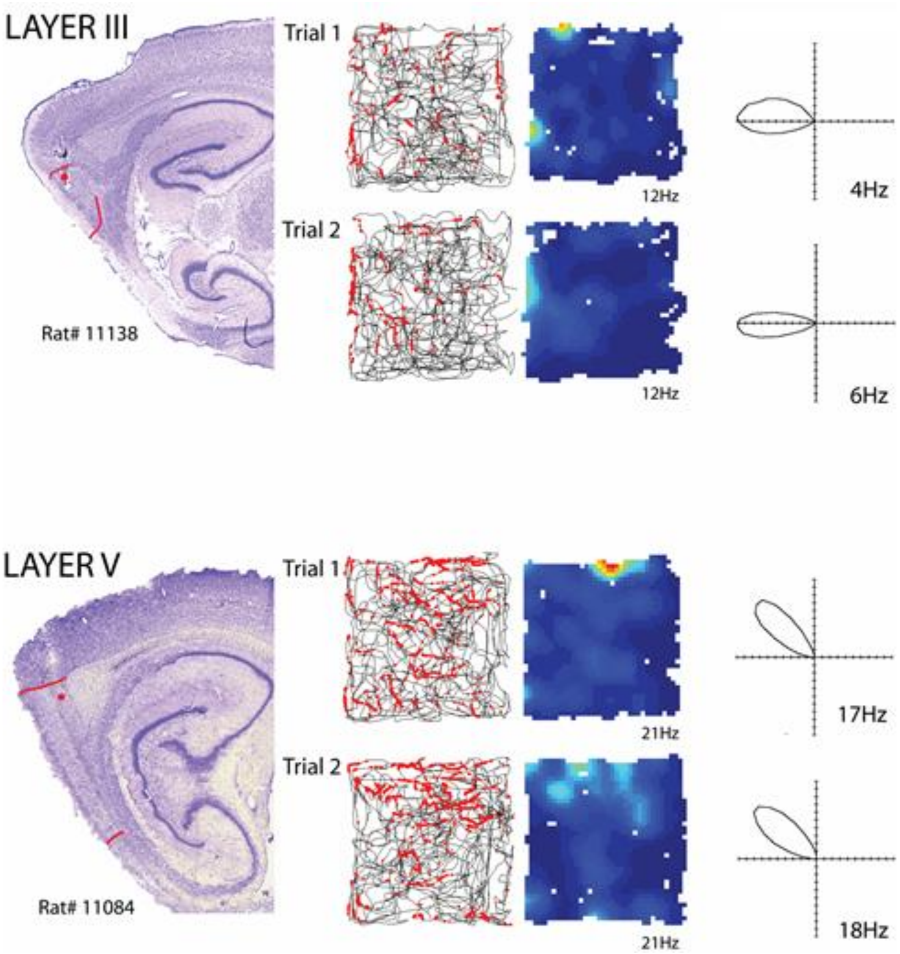
modified from Krubitzer et al., Brain Behav. Evol., 2011

Grid cells are not alone

Grid cells were not alone in the entorhinal system:
they coexist with entorhinal **head-direction cells** (2006),…



Ranck, 1985

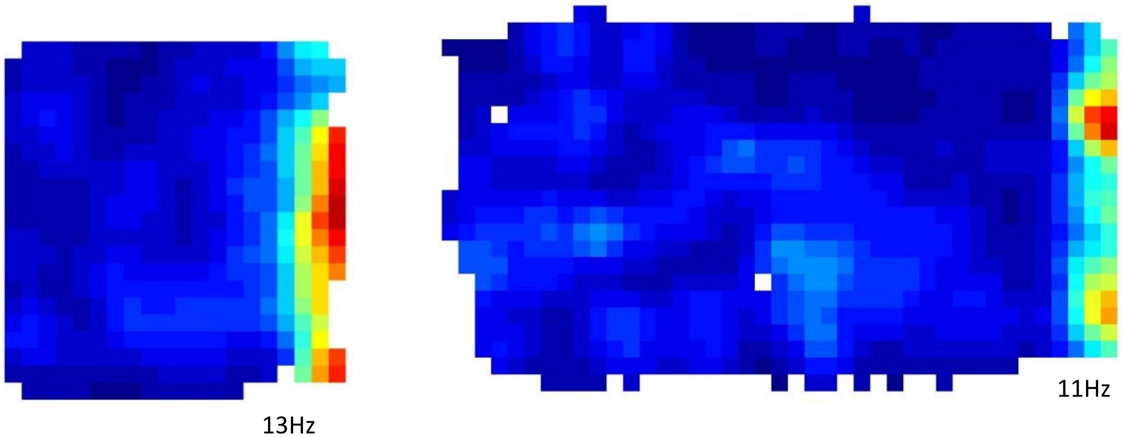


Sargolini et al., Science 312, 754-758 (2006).

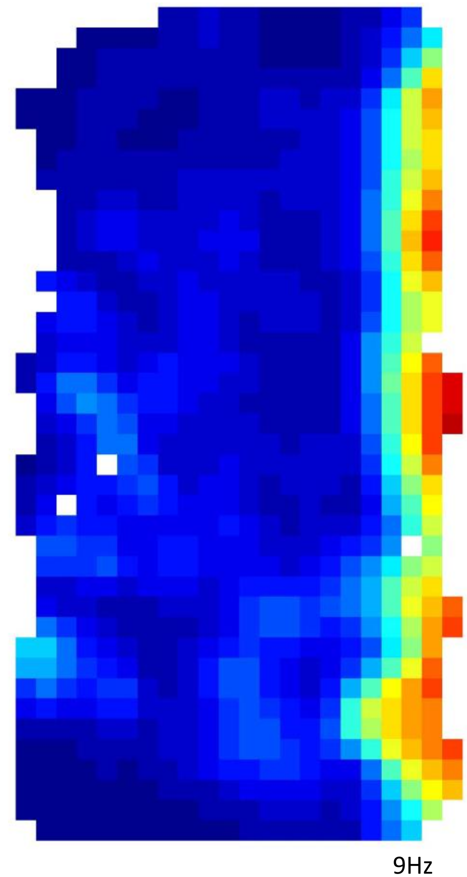
…with **border cells** that fire specifically along local borders (2008),…

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

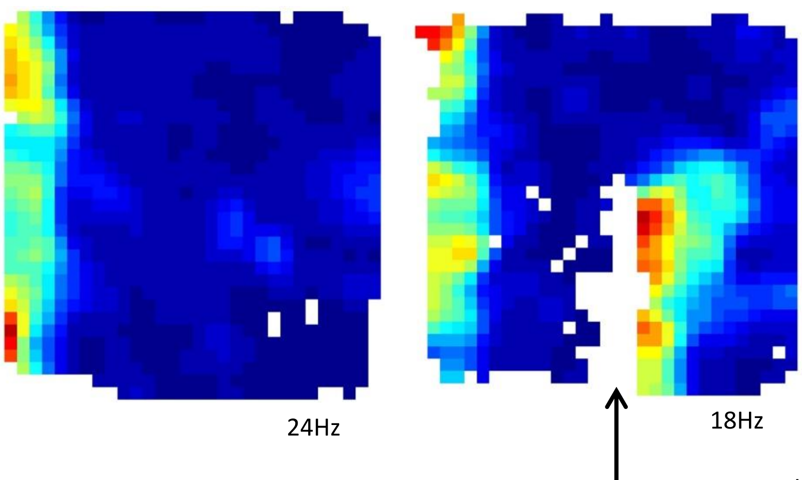
….in the *x* direction:

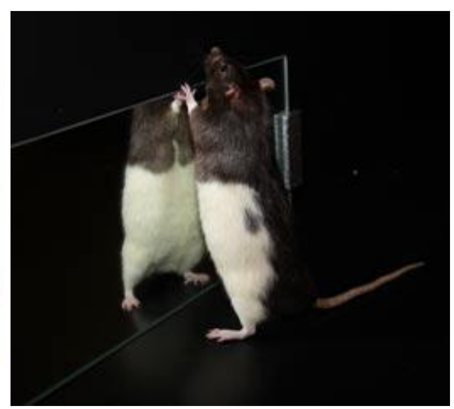


….and in the *y* direction:



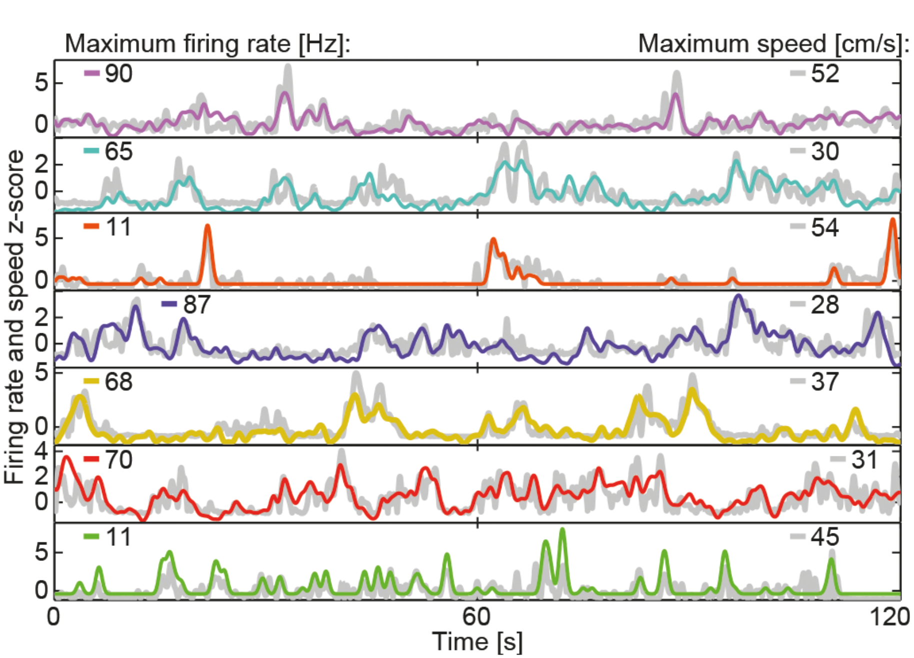
Introducing a barrier duplicates the firing field:

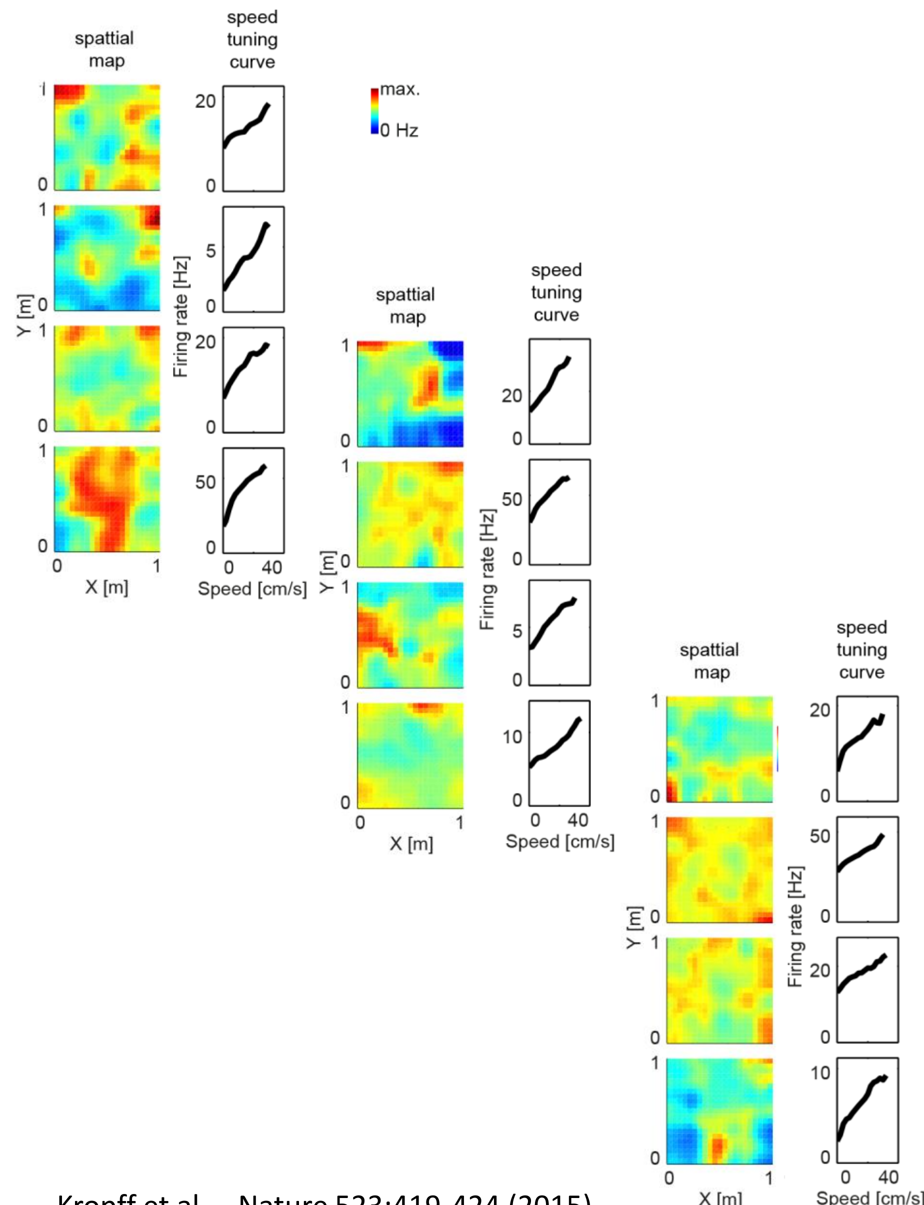




Solstad et al., Science 322, 1865-1868 (2008).

… and with speed cells whose firing rates increase proportionally with running speed (2015)…

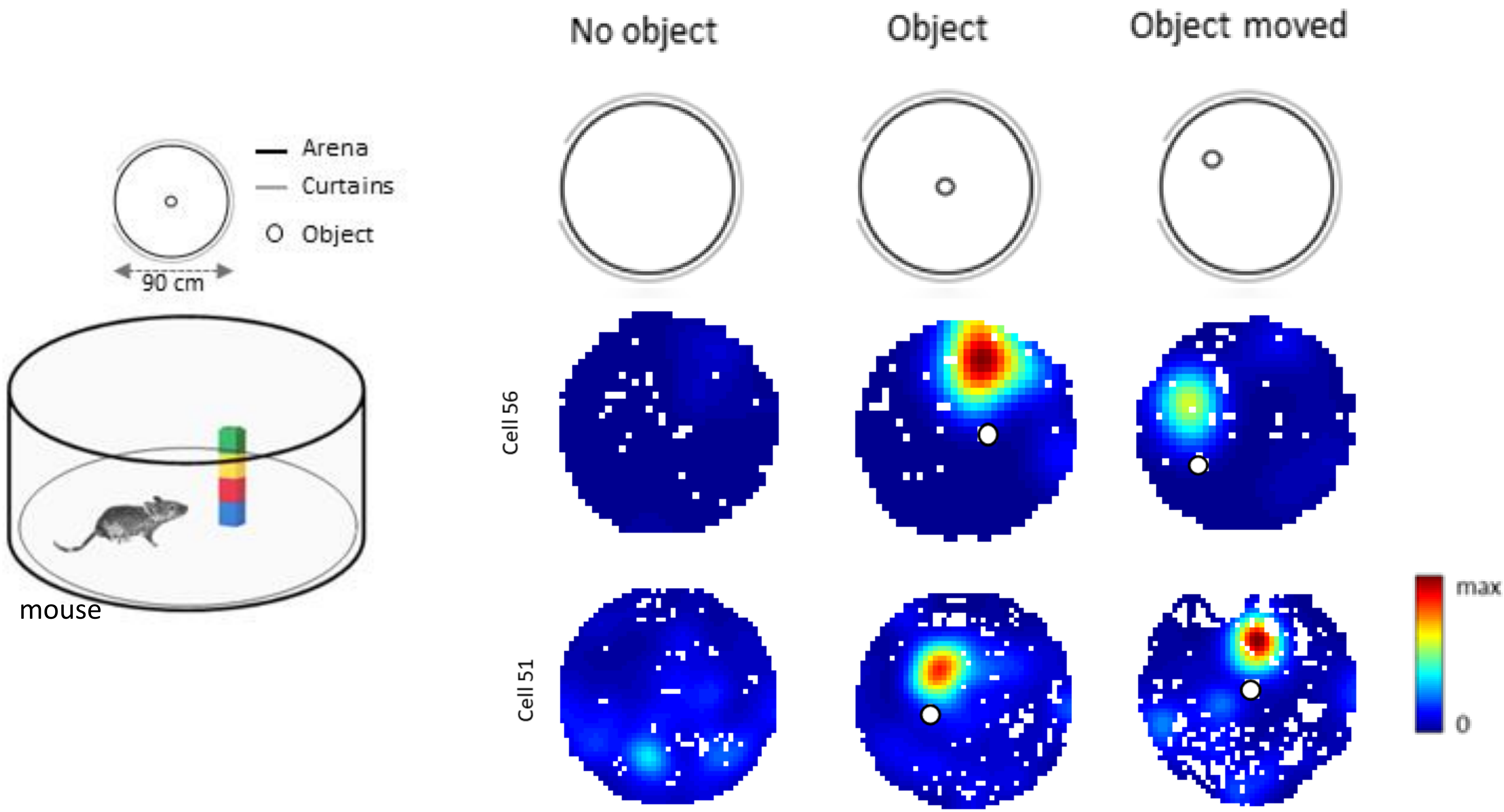




These speed cells may be required for using self-motion to construct grid patterns!

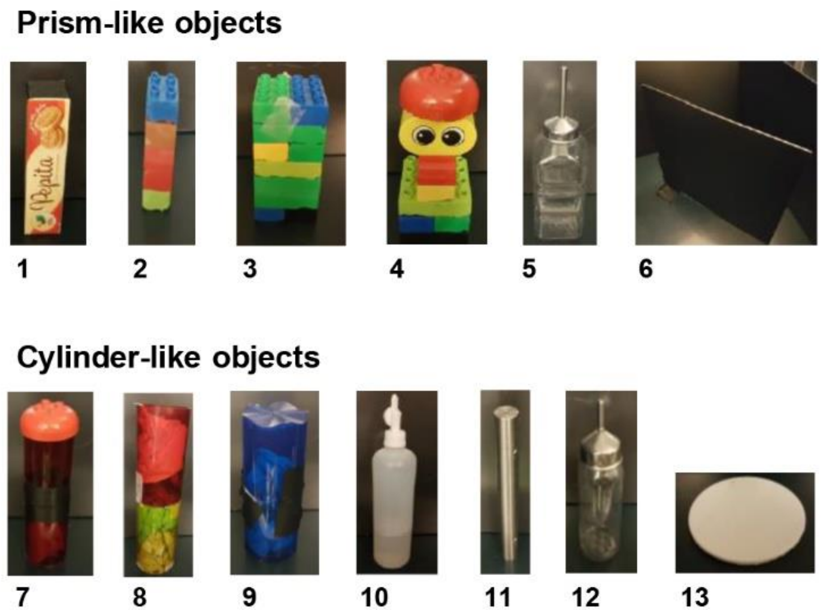
Kropff et al., , Nature 523:419-424 (2015)

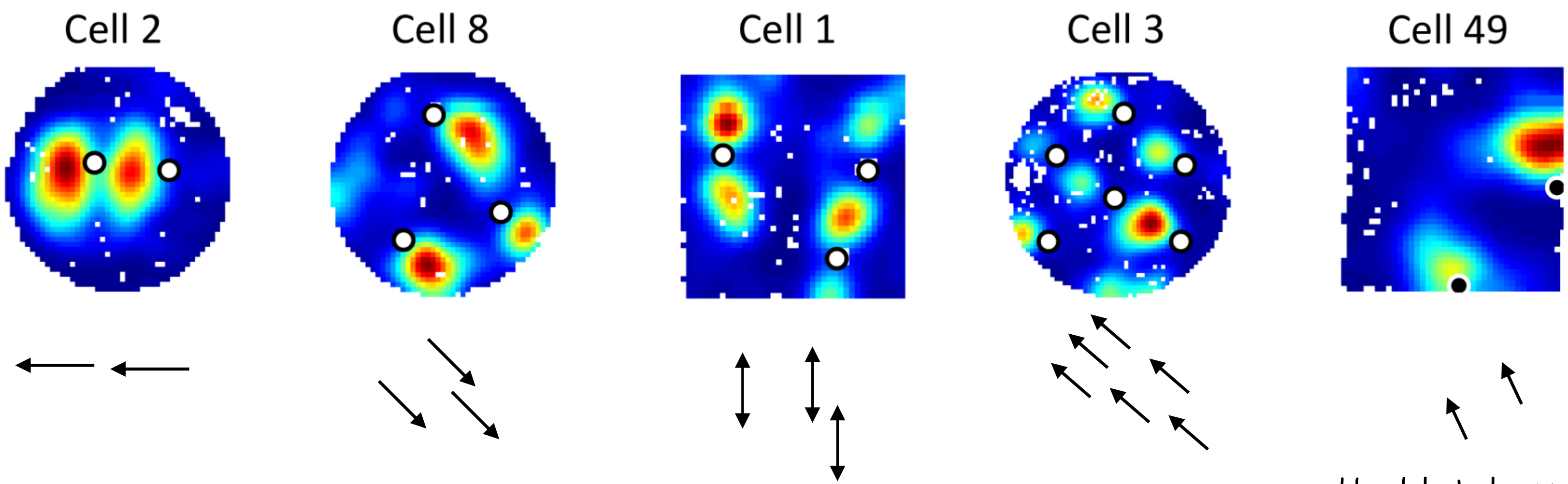
... and with cells that encode vectors to discrete landmarks (object-vector cells; ca. 15%):



Øyvind Høydal et al., unpublished

Directional tuning preferences are maintained with different objects and object locations….

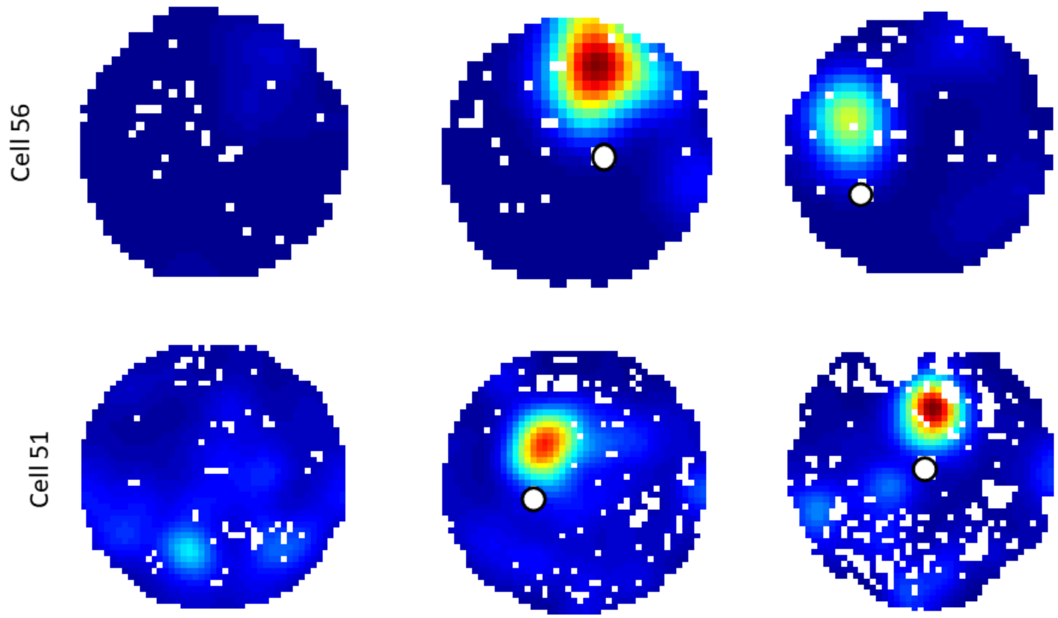




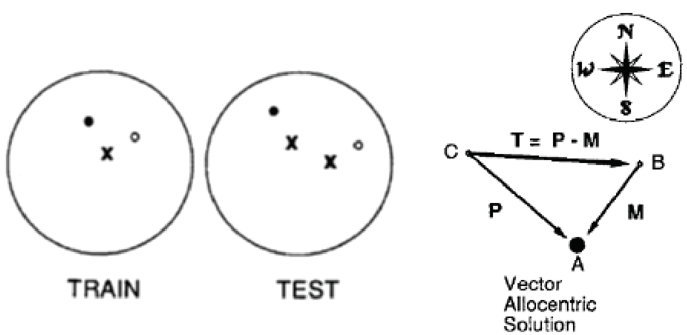
Høydal et al., unpublished

… suggesting that these cells represent direction and distance from any prominent local object (i.e. they do not care about content)

These observations suggest that objects or their locations are included in the metric representation of the MEC,



and that a major proportion of cells in MEC (similar to grid cells) specifically devoted to encoding position in relation to those objects.



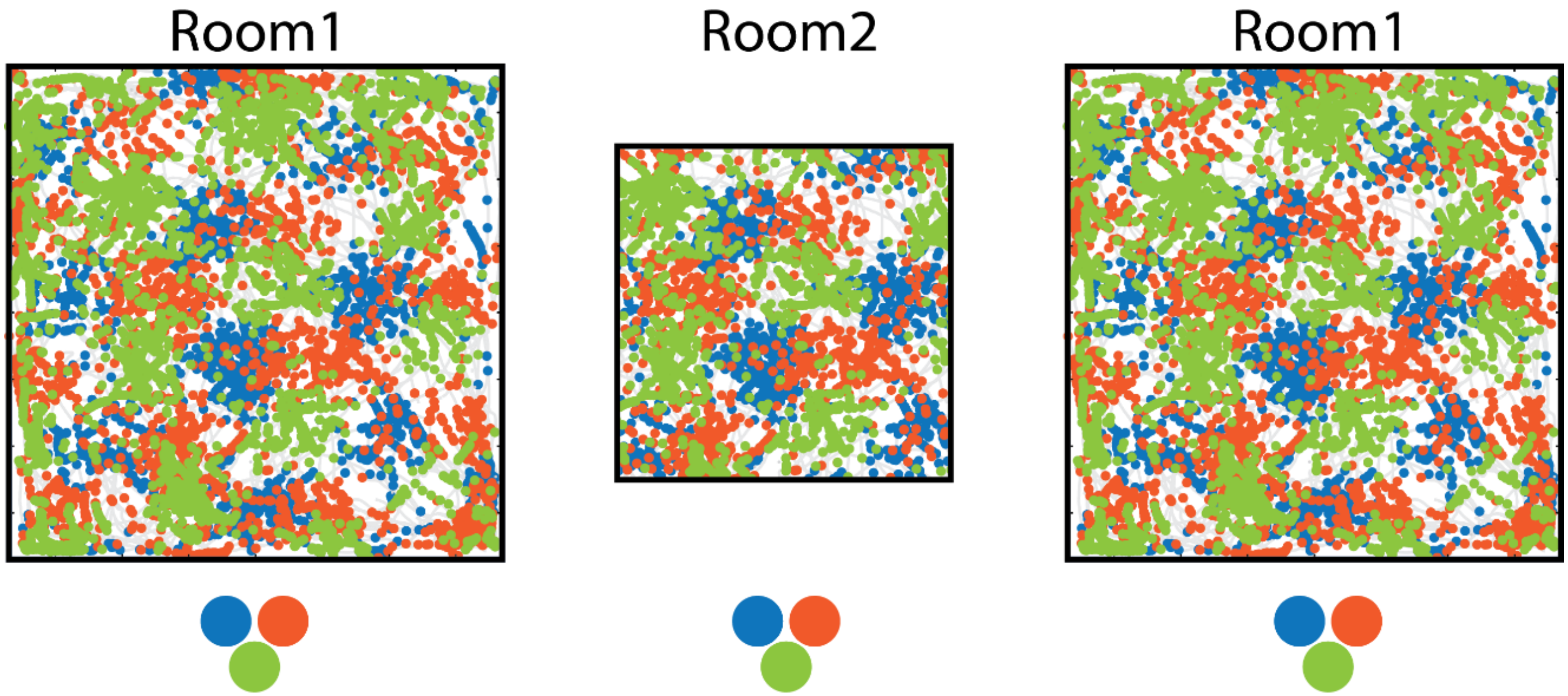
Collet et al. 1986

McNaughton et al. 1995

The spatial map in entorhinal cortex is fundamentally different from the place-cell map in the hippocampus:

The grid-cell map is low-dimensional, the place-cell map high-dimensional

The grid map is rigid and universal:
Scale, orientation and phase relationships are preserved....



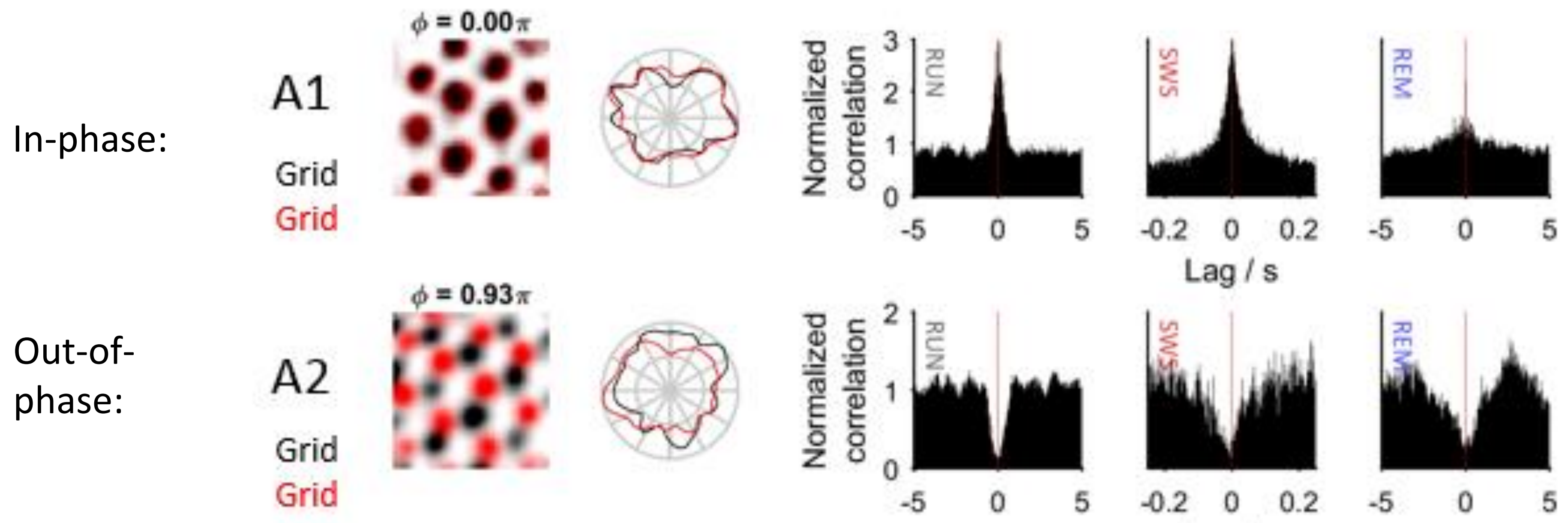
... i.e. the same map is used over and over again
(«low dimensionality»)

The intrinsic structure of the entorhinal grid map is maintained during sleep (SWS and REM):

Those cells that fire together during running, fire together during sleep

Example cell pair:

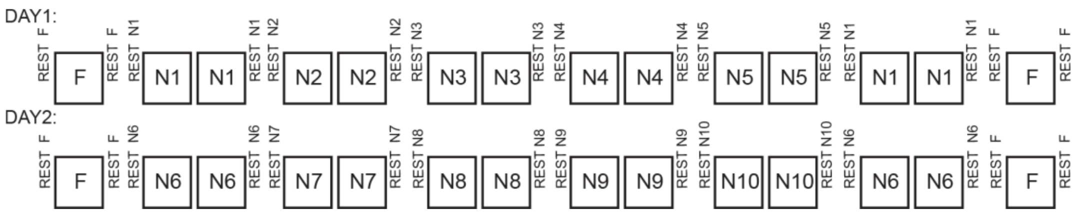
Spike-time crosscorrelograms:



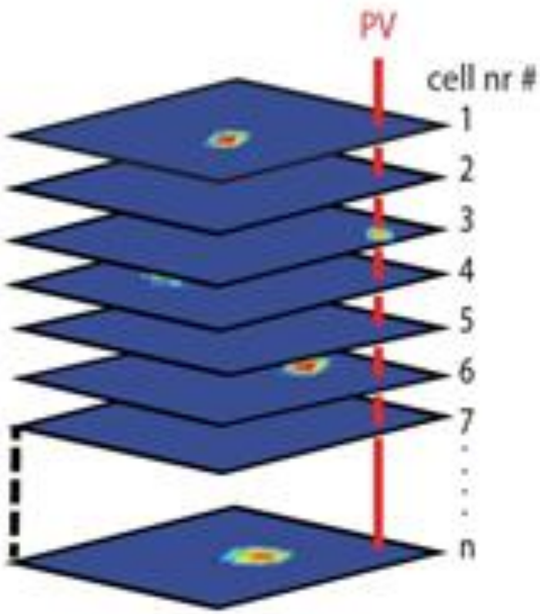
Grid cells with similar grid fields (high crosscorrelation) maintain correlated firing during slow-wave sleep (although with faster dynamics)

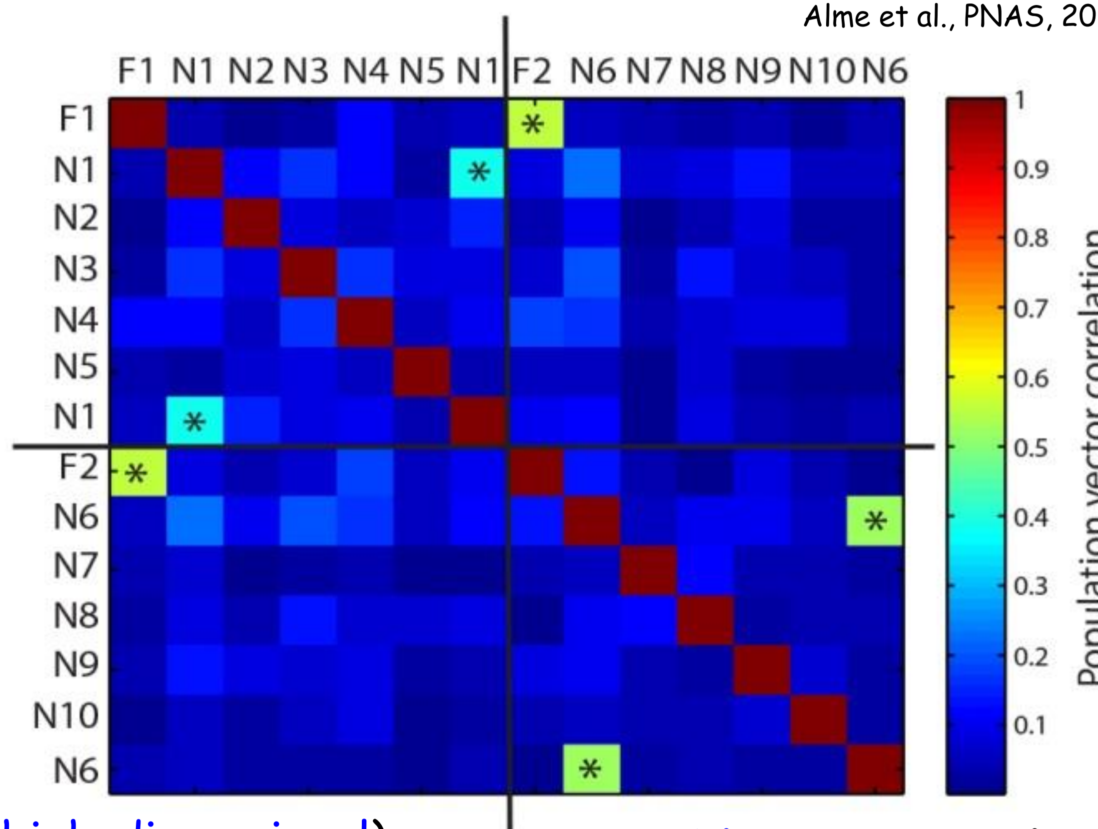
Gardner et al., (& Trettel et al.), unpublished

<u>Place cells</u> are totally different: In place cells, activity is uncorrelated across pairs of 11 rooms (but correlated between repeated exposures to the same room (*)):



Alme et al., PNAS, 2014



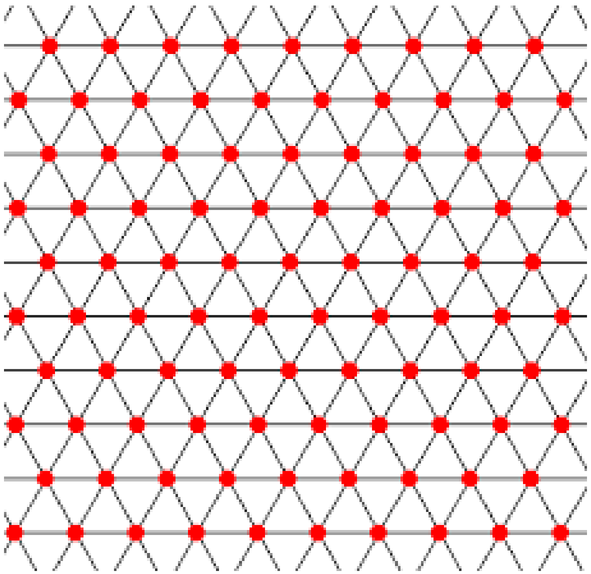


Place cells 're-map' completely (high-dimensional)

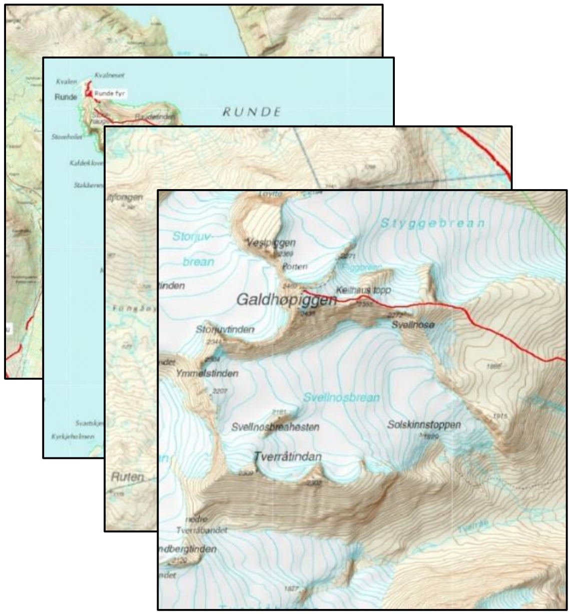
blue = uncorrelated

Thus the positioning system has two components: a rigid map of grid cells and a multifaceted map of place cells

GRID CELLS



PLACE CELLS



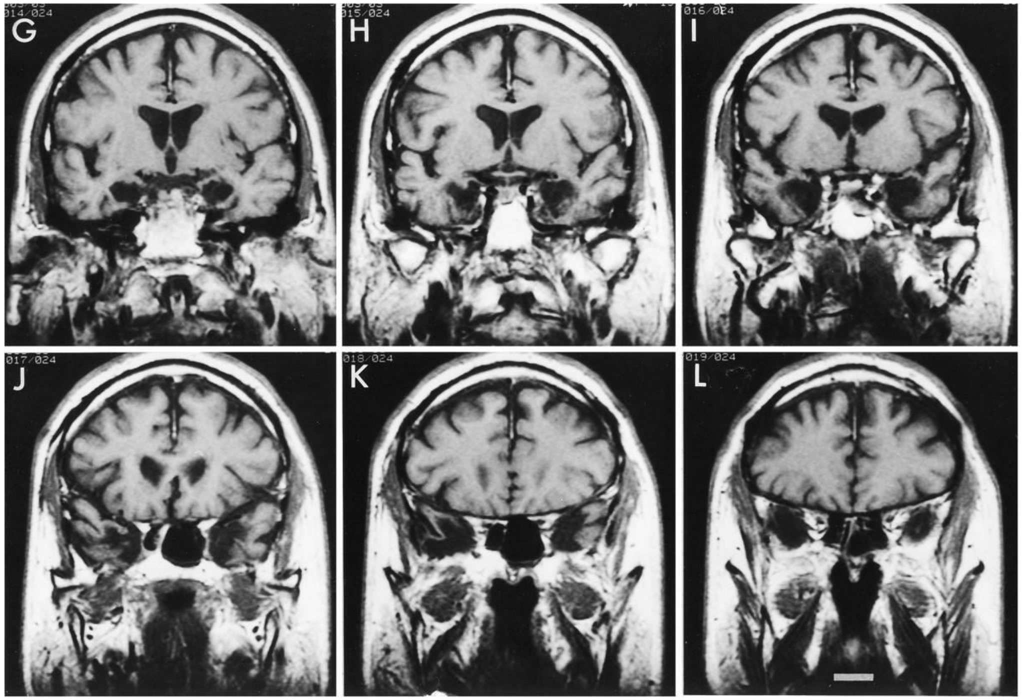
The rigid system of grid cells is good for measuring position (you do not want your ruler to change from one house to the next).

The many uncorrelated maps of place cells enable storage of distinct memories (they may store thousands of places and experiences at these places)…

The multiplicity of the place-cell maps is consistent with the known role of the hippocampus in memory:

Henry Molaison
(1926-2008)

In the mid 1950s, patient H.M. received an experimental surgery where the hippocampus was removed (Scoville and Milner, 1957). He lost all episodic memory, in addition to his sense of space...

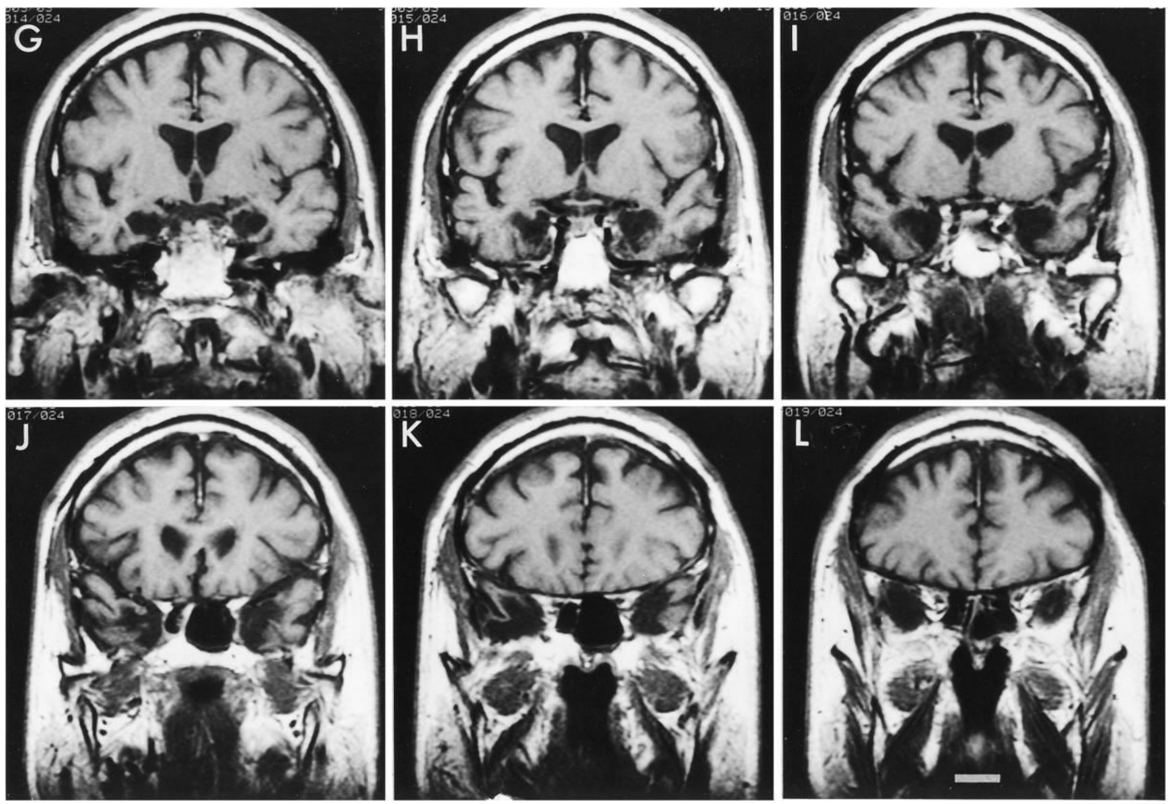


... suggesting that the same cells of the hippocampal system are used both for space and memory. Space may be a framework for memory.

But in episodic memories, there is also an element of time – our understanding of which is in a much more nascent stage.

Henry Molaison
(1926-2008)

Scoville & Milner, 1957



Corkin et al., J. Neurosci. 1997

Encoding of time in the entorhinal cortex

Albert Tsao

Embargoed until August 29, 7.00 pm

ARTICLE

https://doi.org/10.1038/s41586-018-0459-6

Integrating time from experience in the lateral entorhinal cortex

Albert Tsao[1,3]*, Jørgen Sugar[1], Li Lu[1,4], Cheng Wang[2], James J. Knierim[2], May-Britt Moser[1] & Edvard I. Moser[1]*

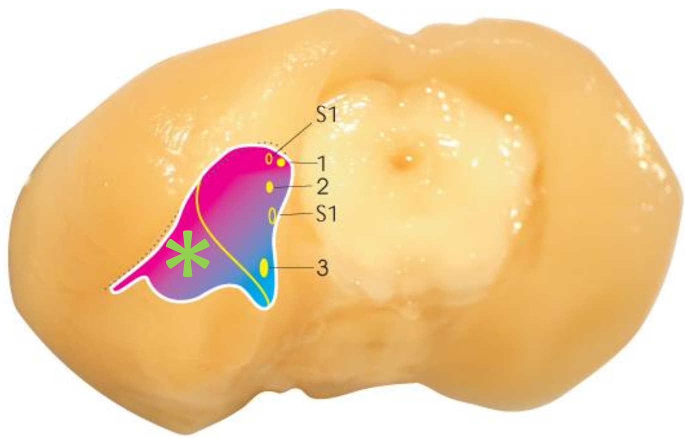
The encoding of time and its binding to events are crucial for episodic memory, but how these processes are carried out in hippocampal–entorhinal circuits is unclear. Here we show in freely foraging rats that temporal information is robustly encoded across time scales from seconds to hours within the overall population state of the lateral entorhinal cortex. Similarly pronounced encoding of time was not present in the medial entorhinal cortex or in hippocampal areas CA3–CA1. When animals' experiences were constrained by behavioural tasks to become similar across repeated trials, the encoding of temporal flow across trials was reduced, whereas the encoding of time relative to the start of trials was improved. The findings suggest that populations of lateral entorhinal cortex neurons represent time inherently through the encoding of experience. This representation of episodic time may be integrated with spatial inputs from the medial entorhinal cortex in the hippocampus, allowing the hippocampus to store a unified representation of what, where and when.

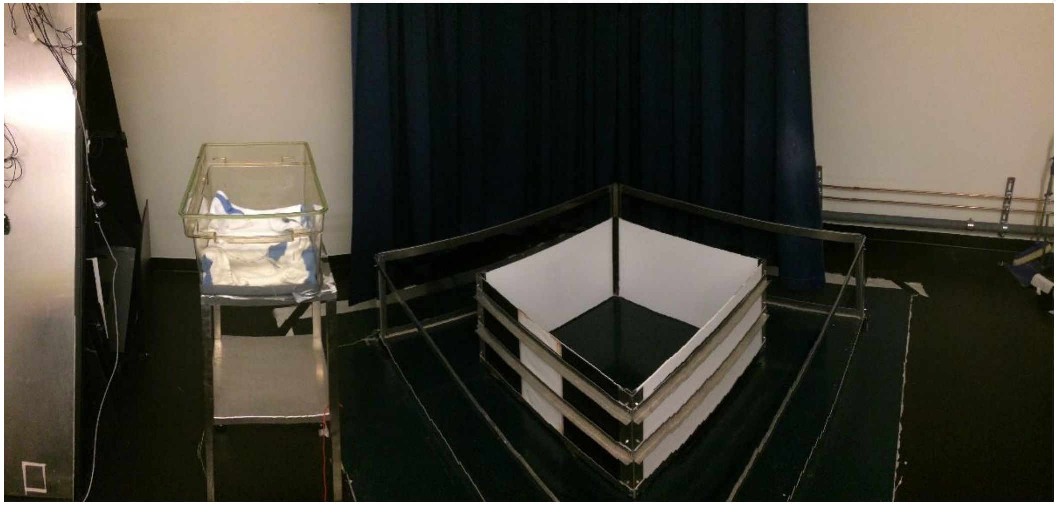
The representation of time is a crucial component of episodic memory[1–3]. Although a considerable body of work has now demonstrated that the hippocampus has an essential role in generating a representation of time[4–11], our understanding of how the brain represents time for episodic memory (episodic time) is still in a nascent stage. The primary function of episodic time is to record the order of events within experience, which does not require a precise representation of metric time, differentiating it from interval and circadian timing[12–14]. Rather than being able to keep precise metric time, the neural code for episodic time should have the following two fundamental properties: 1) the code should arise automatically without any behavioural training, to support one-shot formation of episodic memory, and 2) the code should be able to capture the different scales of time at which experience may occur. Recently, two types of representation of time have been observed in the hippocampus and medial entorhinal cortex (MEC): time cells, which fire at specific points in time as an animal performs a task[15–19], and the decorrelation of place cell activity across hours to days[20–25]. However, neither of these representations of time has been shown to fully support one-shot formation of episodic memories in combination with variable timescales. Furthermore, how either of these representations of time

colour with progression of time. Data were also recorded from the CA3 and MEC for comparison. Examining LEC responses by eye, we noticed that some cells exhibited clear ramping activity (Fig. 1a, b), raising the possibility that the passage of time can be tracked through the firing rates of individual LEC cells. Responses to specific environmental features such as walls and cue cards[26] were also observed, consistent with the established role of the LEC in encoding environmental context[28–30].

We quantified the influence of wall colour and time on the activity of single cells using a generalized linear model (GLM) incorporating time, wall colour and position as variables for fitting the firing rates of individual neurons, which were binned temporally into blocks of 500 ms (Extended Data Fig. 2a–d). A considerable number of LEC cells were selective specifically for time (20.4% of all recorded cells), whereas only 2.0% of CA3 cells and 4.5% of MEC cells were selective for time alone (number of cells significantly influenced by at least one variable for LEC: 186 out of 451, 41.2%; CA3: 72 out of 148, 48.6%; MEC: 49 out of 133, 36.8%; Fig. 1c). The distributions of cell selectivity for the LEC, CA3 and MEC were consistent across individual animals (Fig. 1c).

Evidence for time coding in lateral entorhinal cortex (LEC)

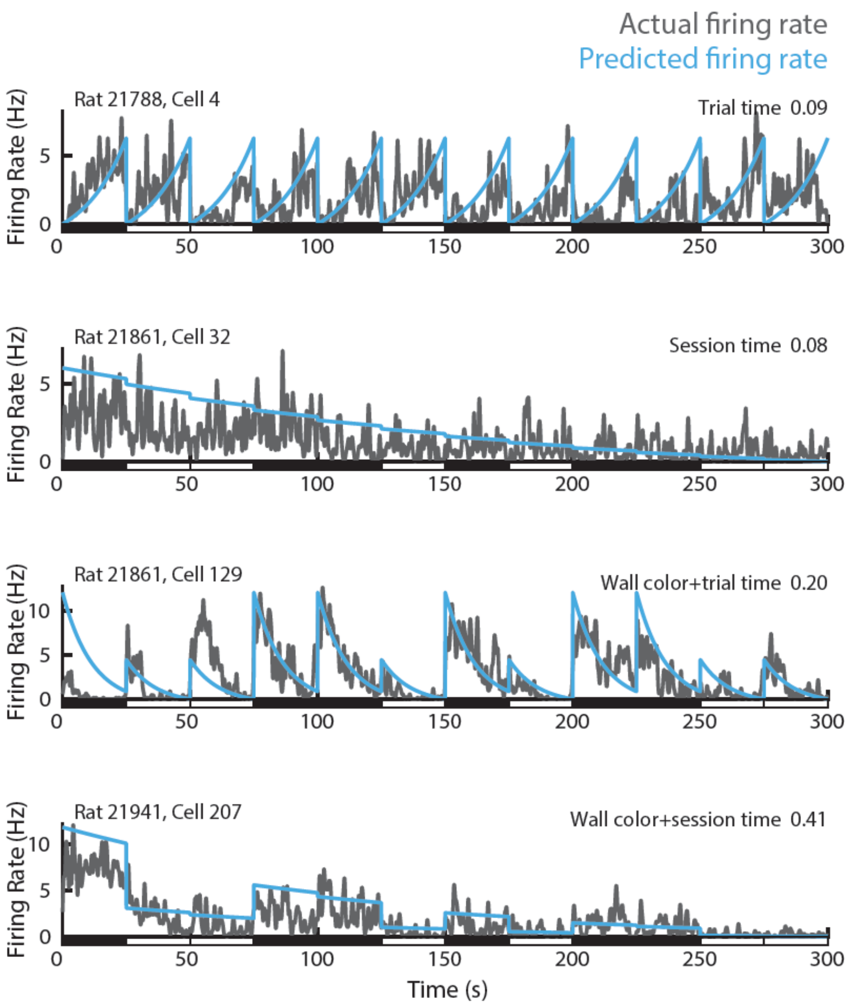




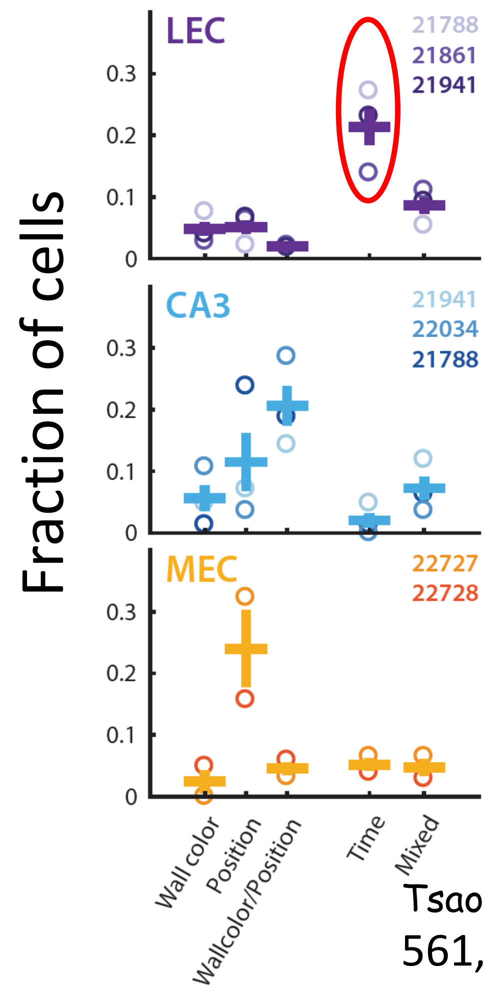
Tsao et al., Nature
561, 57-62 , 2018

Time is expressed in the activity of <u>individual</u> LEC cells

Some LEC cells are strongly modulated by time, at multiple time scales:



Influences of wall colour, position and time were determined using GLM



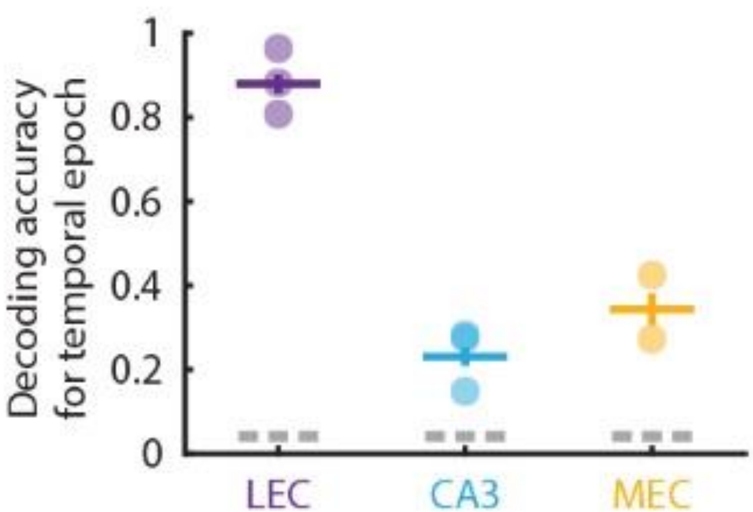
Tsao et al., Nature 561, 57-62 , 2018

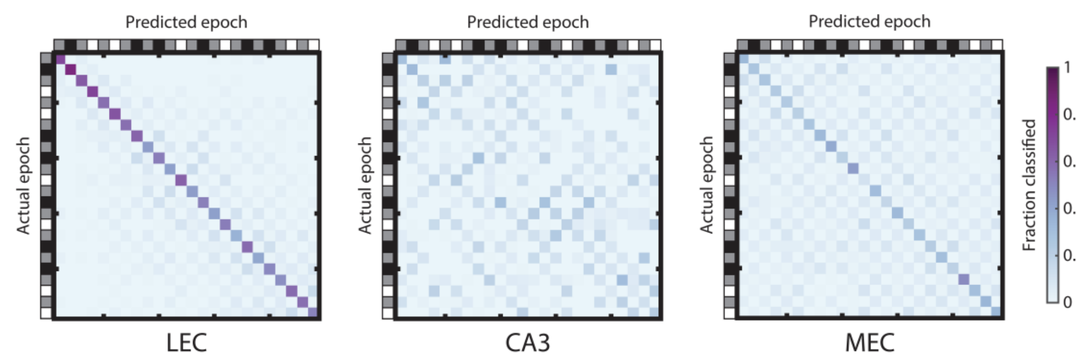
Decoding of temporal epochs from LEC neural population activity is accurate at multiple time scales (and by far exceeds that of other regions)

MACHINE LEARNING:

We trained a linear support vector machine (SVM) on 10-s trial bins, using a leave.one-out procedure. Decoding of epoch (=trial/intertrial):

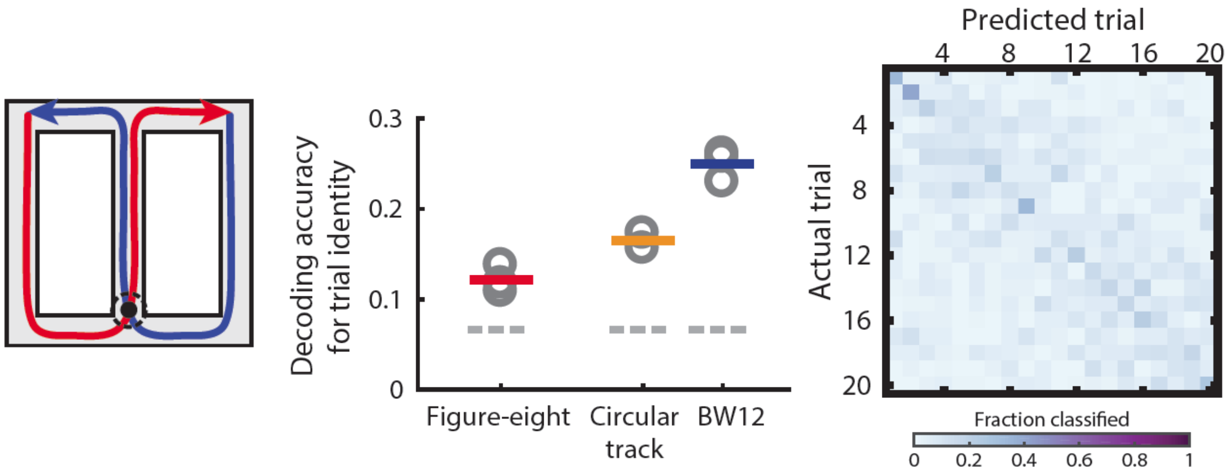
PREDICTION VS ACTUAL:



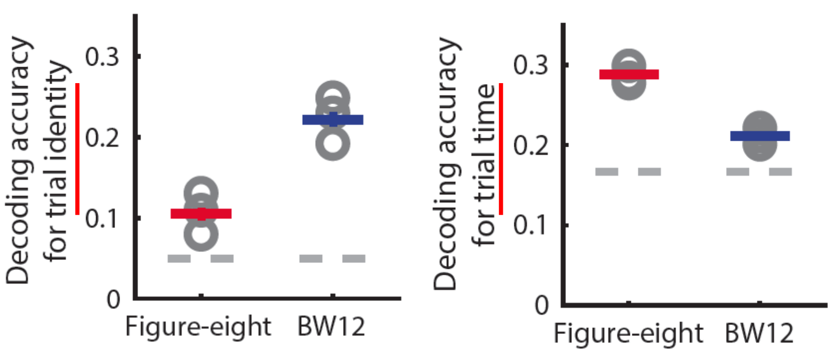


Tsao et al., Nature 561, 57-62 , 2018

But the nature of the time code is changed by experience – in a structured learning task:



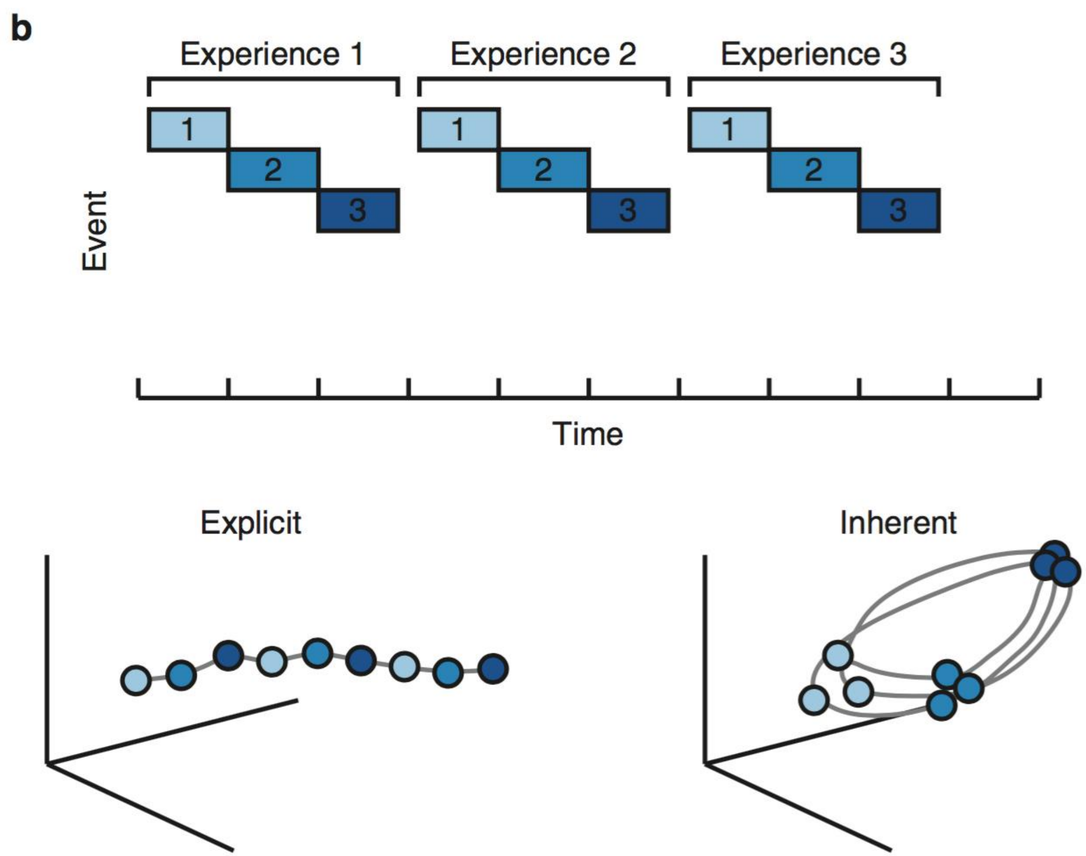
While time across trials (´trial identity´) is reduced, accuracy within trials - time since each trial start ("trial time") - is increased,..



... suggesting that during learning, LEC fundamentally changes its organization from widely- distributed representation of 'free-running' time to a code for progression of time through event-defined individual trials.

Tsao et al., Nature 561, 57-62 , 2018

Expression of time: from free-running to repetitive:



Tsao et al., Nature
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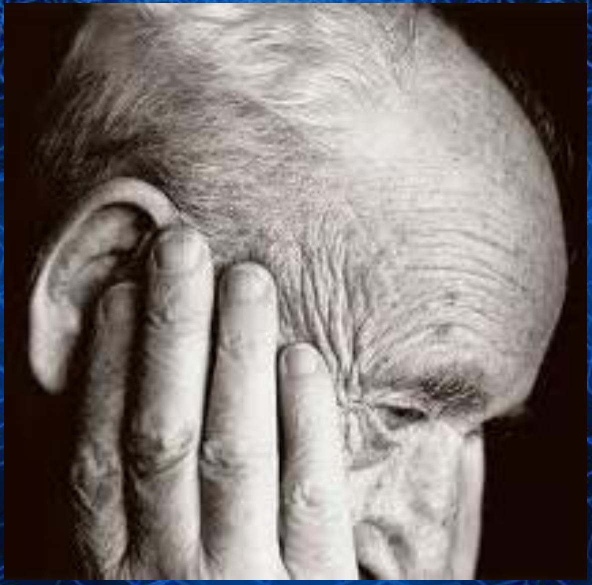
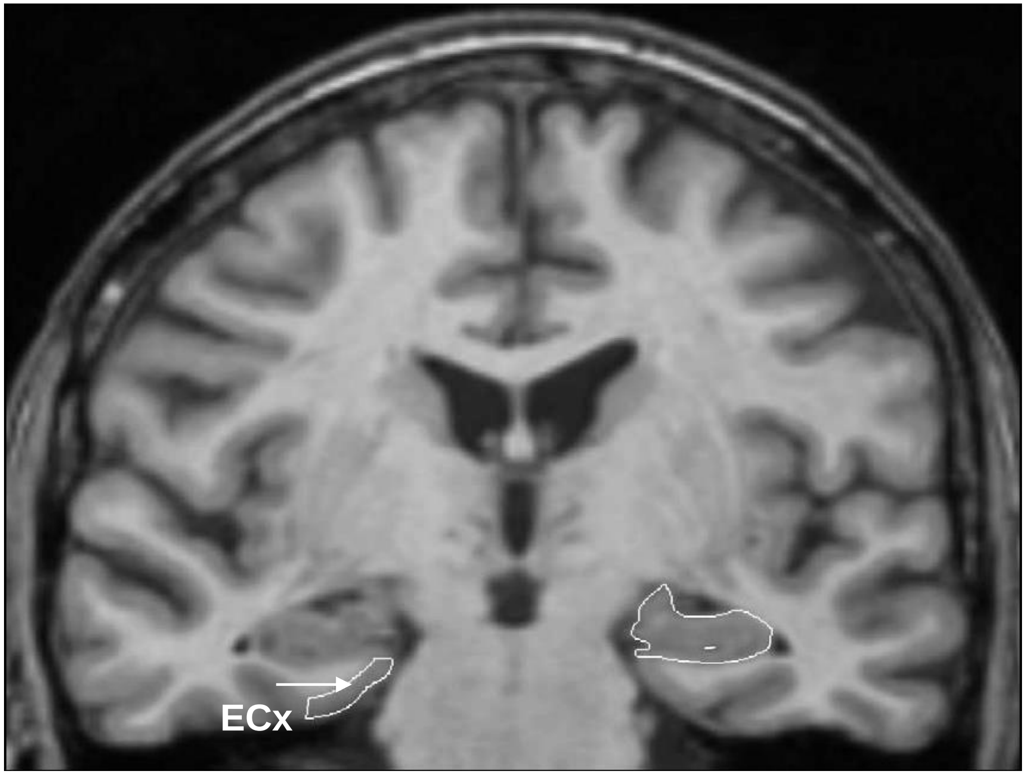
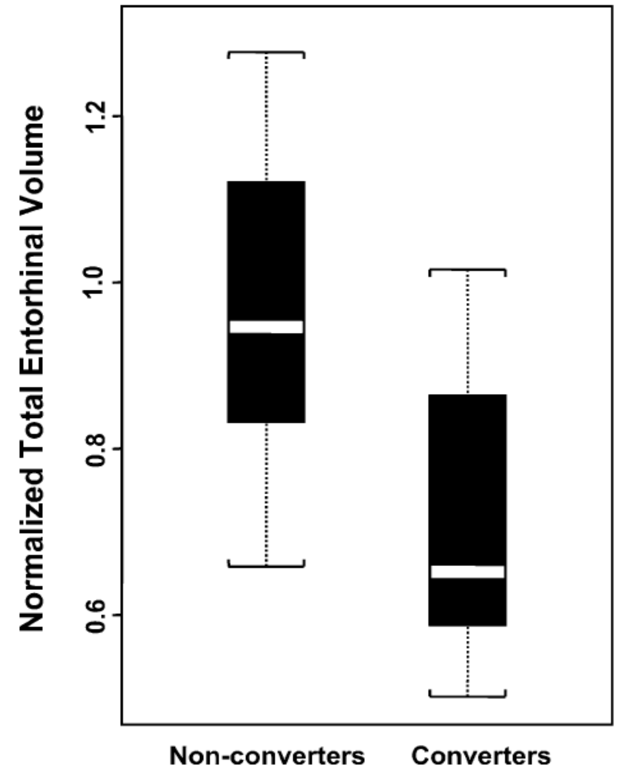
How can the new knowledge about space (and memory) in young and old rodents help us treat and understand **Alzheimer's disease**?



Impairment in grid cells may explain early stages of Alzheimer's disease.
Entorhinal cortex is often the first brain area to exhibit cell loss…

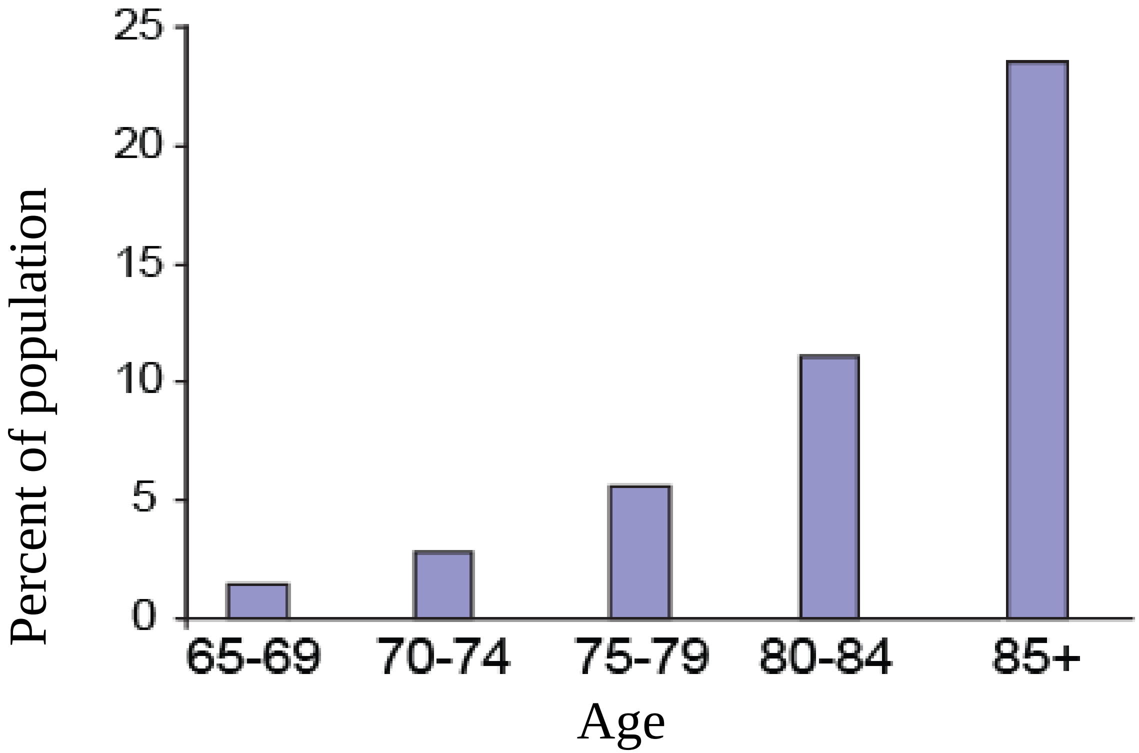


L. deToledo-Morrell et al. / Neurobiology of Aging 25 (2004)



… and this degeneration correlates with spatial disorientation and loss of memory, two of the first signs of Alzheimer's disease.

>1% of the population suffers from Alzheimer's disease. <u>The fraction increases dramatically with age</u>. Nearly every 5th person dies with Alzheimer or other forms of dementia.



… and life expectancy (LE) is increasing:

Country	2015 LE	1998 LE
Monaco	89.5	
Japan	84.7	80.0
Singapore	84.7	78.5
Macau	84.5	
San Marino	83.2	81.4
Iceland	83.0	78.8
Hong Kong	83.0	
Andorra	82.7	83.5
Switzerland	82.5	78.9
Guernsey	82.5	
Israel	82.3	78.4
Luxembourg	82.2	
Australia	82.2	
Italy	82.1	78.4
Sweden	82.0	79.2
Liechtenstein	81.8	
Jersey	81.8	78.5
Canada	81.8	79.2
France	81.8	78.5
Norway	81.7	78.2
Spain	81.6	77.6
Austria	81.4	77.3
Anguilla	81.3	

May-Britt
Moser

100s of other students, postdocs and collaborators…

Funding: NTNU, The Kavli Foundation, Pauline Braathen, The Research Council of Norway Centre of Excellence Scheme, Ministry of Education
European Commission's 7th Framework Programme, ERC Advanced Investigator Grant scheme,
Louis Jeantet Foundation, Koerber Foundation