Nobel Prize Lecture,
Stockholm, 10th December, 2014

Grid cells, place cells and memory

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NTNU
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Our vision:
Understand how cognition is generated in the brain

"As humans, we can identify galaxies light years away, we can study particles smaller than an atom.
- But we still haven't unlocked the mystery of the three pounds of matter that sits between our ears."
—President Obama, April 2, 2013
(announcing the BRAIN Initiative)

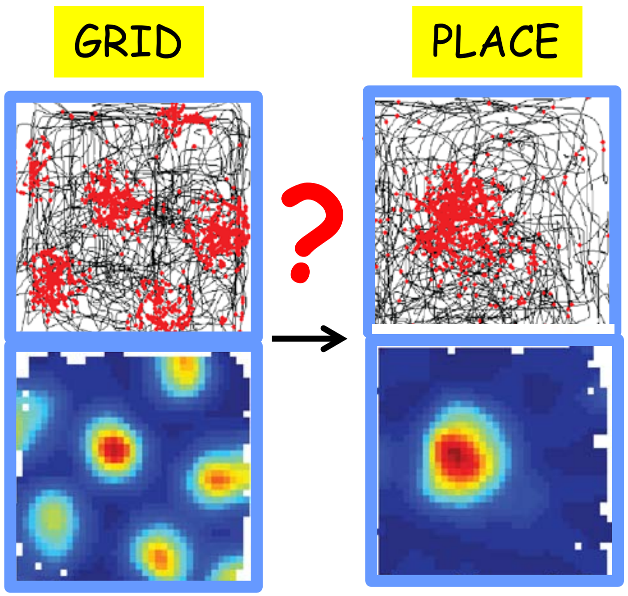
Can we?

Make the impossible possible- crack the brain´s code!

http://www.youtube.com/watch?v=kQsBrO8IbNY

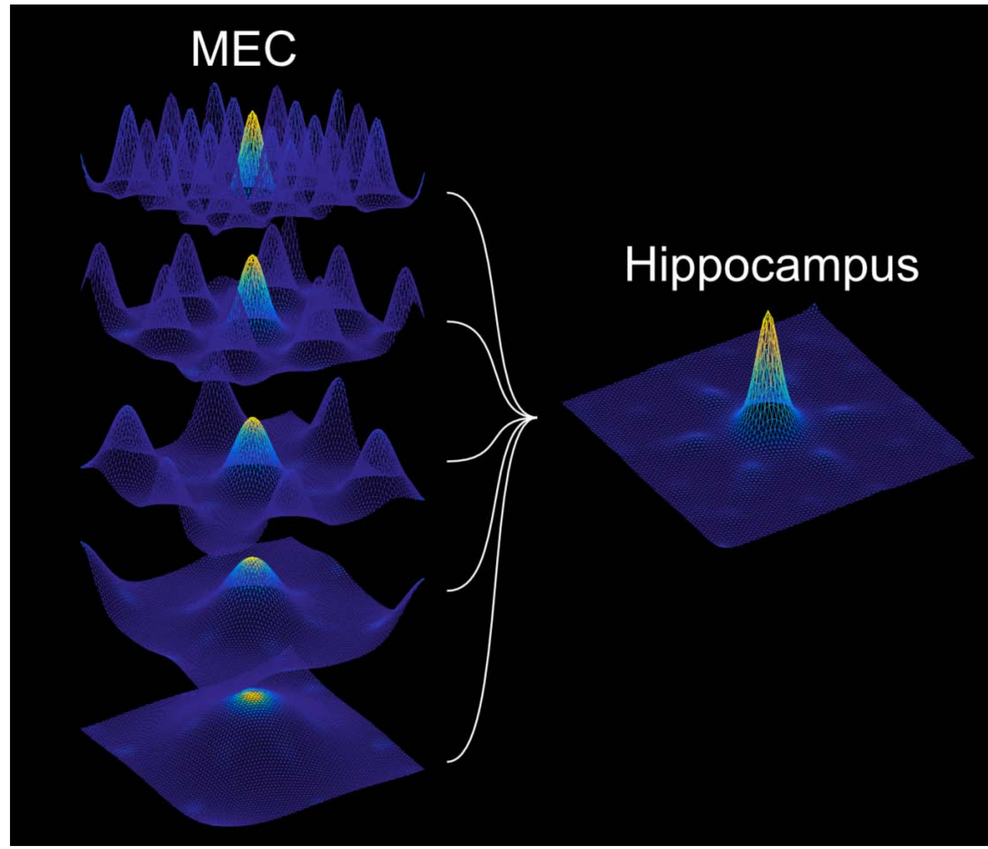
Transformation of neural codes:

Do grid cells give rise to place cells?



Grid activity can be transformed to place cell activity by linear summation of signals from grid cells with different scales …

Early models (2006):



Artwork: Tor Stensola, CNC/Kavli Institute

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

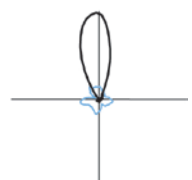
However:

In the entorhinal cortex grid cells co-exist with several other spatial cell types such as head direction cells and border cells
– do all of these cell types project to the hippocampus?

Sargolini, Fyhn, Hafting, McNaughton, Witter, Moser & Moser (2006), *Science*

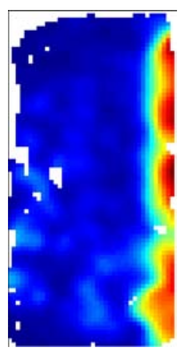
Solstad, Boccara, Kropff, Moser and Moser (2008), *Science*

Head direction cells



2006

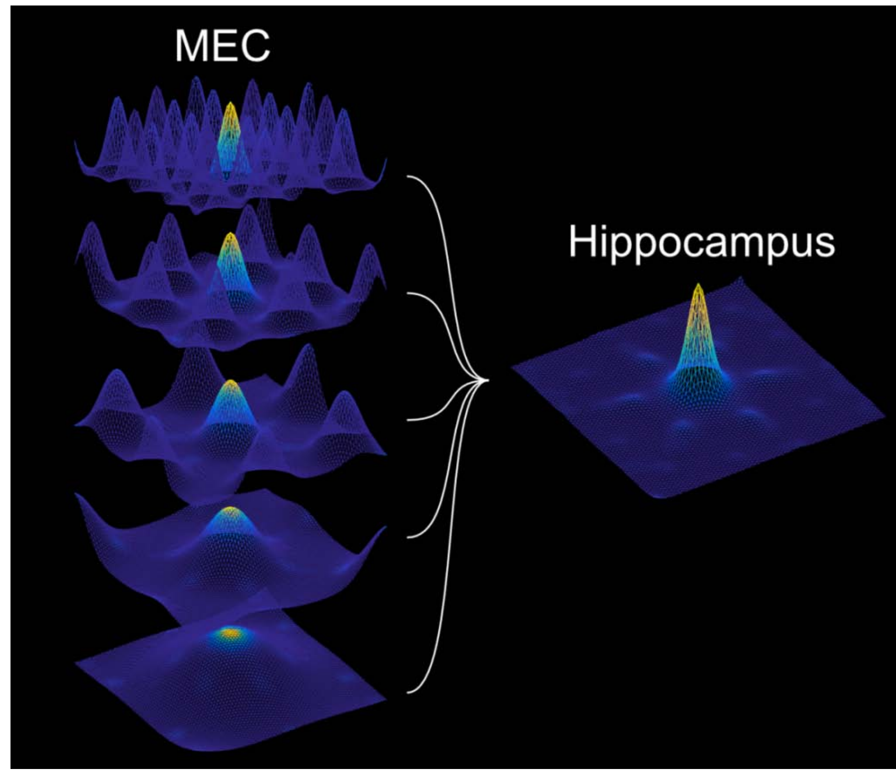
Border cells



2008

?

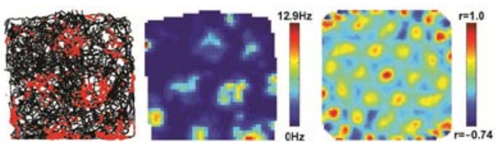
+

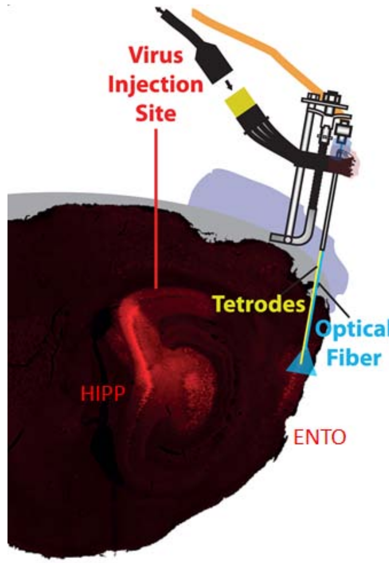


Artwork: Tor Stensola, CNC/Kavli Institute

We identified hippocampus-projecting cells in medial entorhinal cortex by using optogenetics

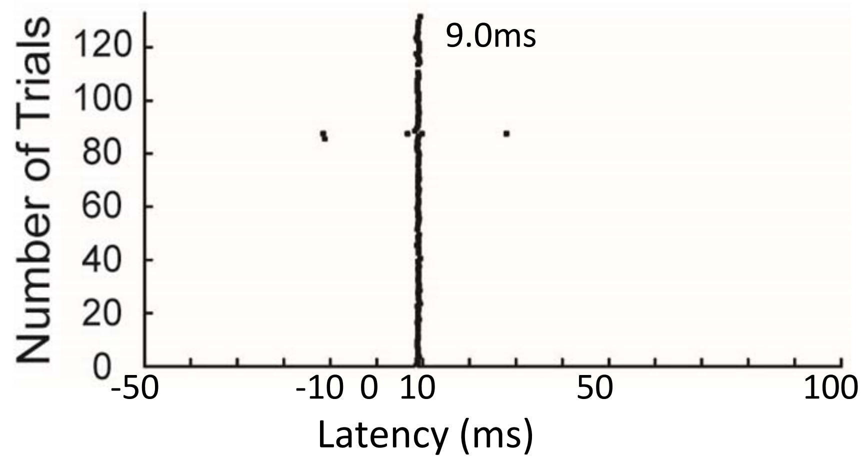
Cells identified by single unit recording:





Zhang, Ye, Miao, Tsao, Cerniauskas, Ledergerber, Moser & Moser, Science, 2013

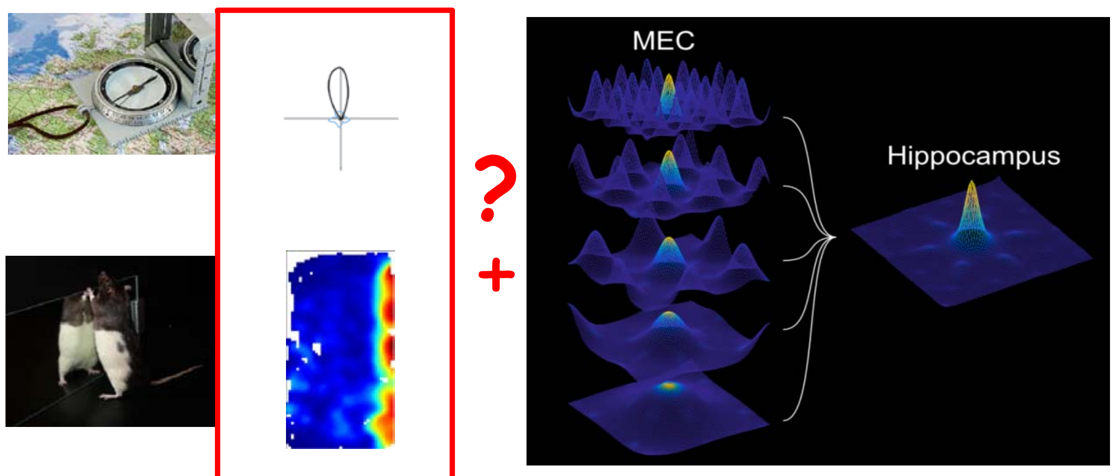
Raster plots show that infected cells fire at a fixed minimal latency after photostimulation:



Grid cells, head direction cells, border cells and non-spatial cells responded at fixed minimal latencies to the photo-stimulation, suggesting they all project to the hippocampus!

Questions to be addressed in future experiments:

- Does a specific place cell get mixed input from several functional cell types in the medial entorhinal cortex?
- Or do different place cells receive different types of input e.g. grid or border input?
- Is there an intrinsic gating function in the hippocampus? Does the hippocampus select different inputs at different times?

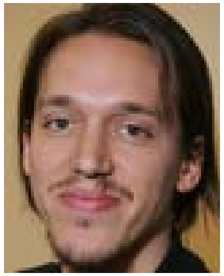


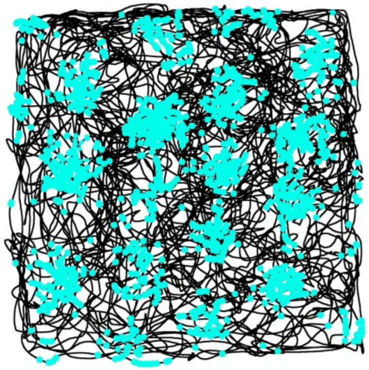
Artwork: Tor Stensola, CNC/Kavli Institute

How does a grid cell “know” where to be active and where to be silent?

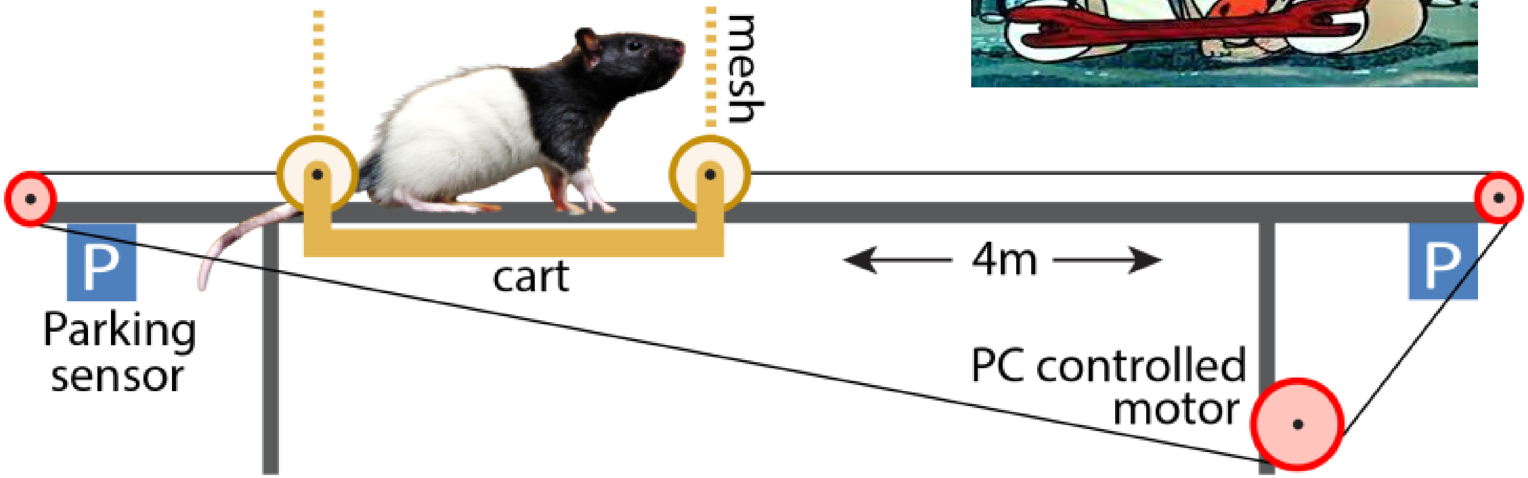
Since animals move with different speeds, the spatial representation may need a speedometer

The entorhinal network has speed cells



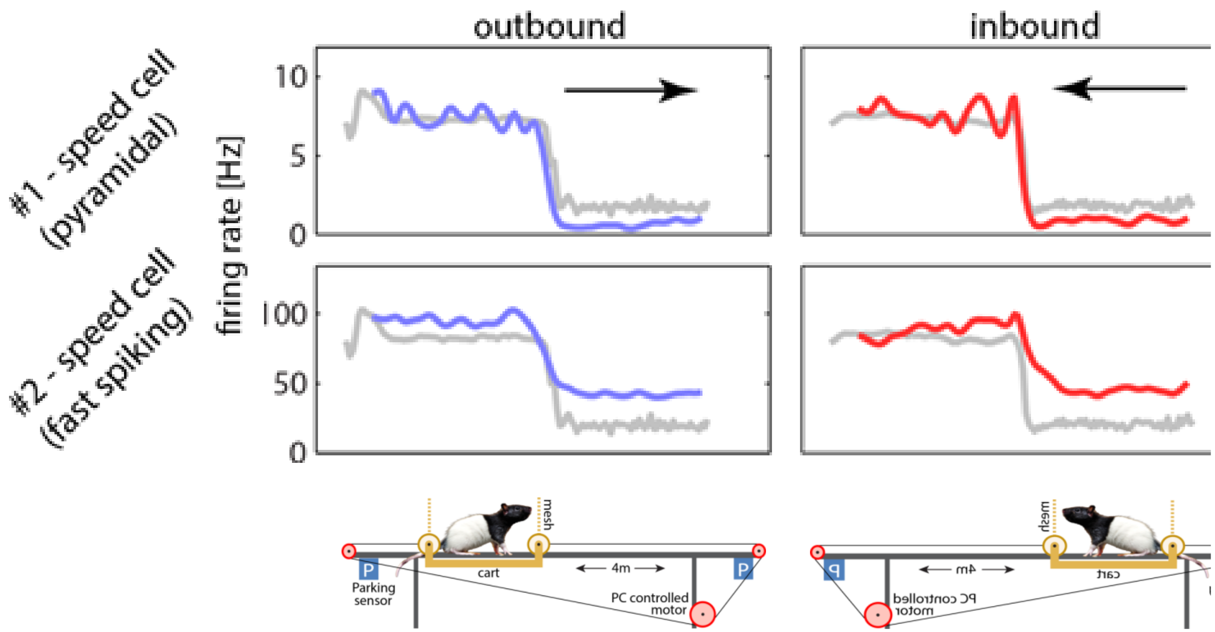


Speed cells are necessary for updating the grid pattern in accordance with the animal's movement (distance=speed x time)



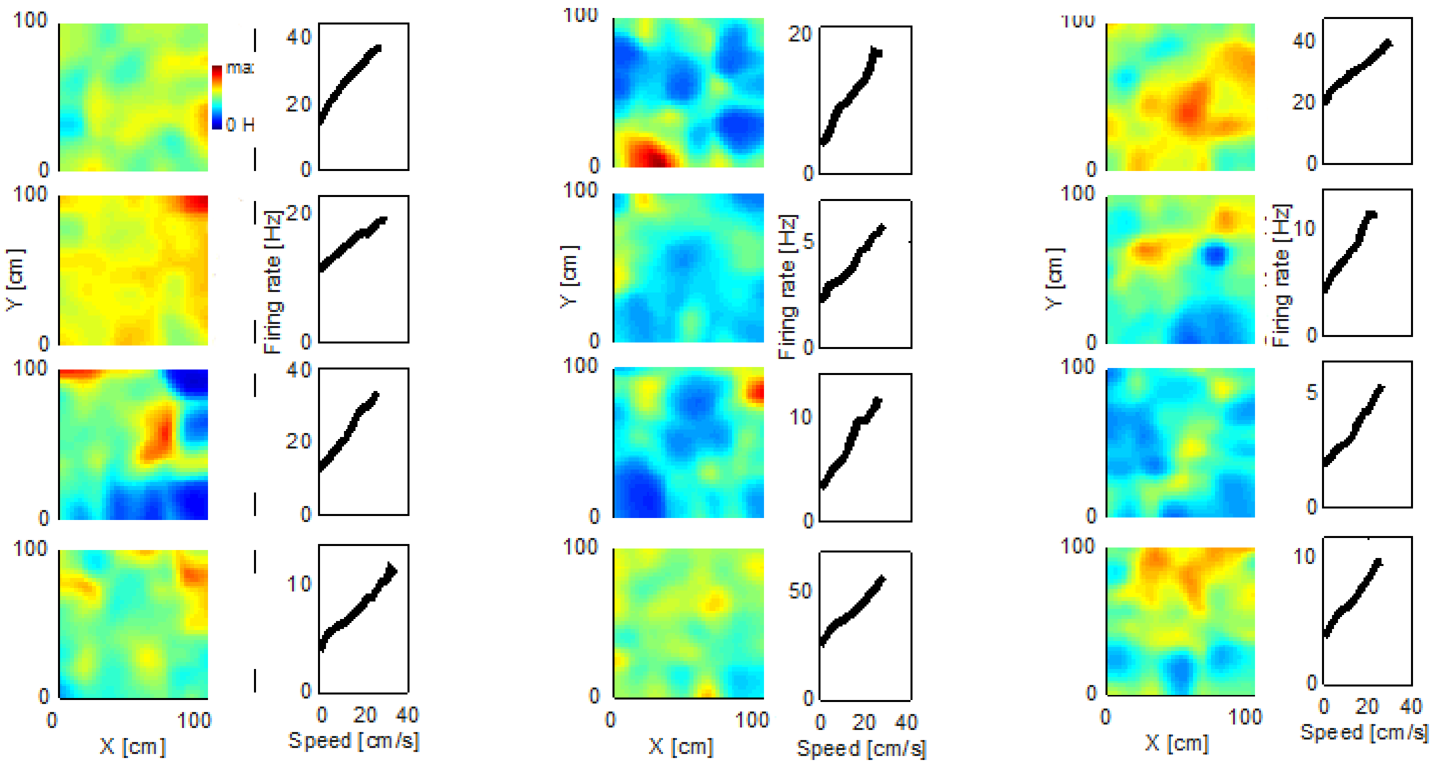
Kropff, Carmichael, Moser and Moser, unpublished

Speed cells have firing rates that follow the animal's running speed



Kropff, Carmichael, Moser and Moser, unpublished

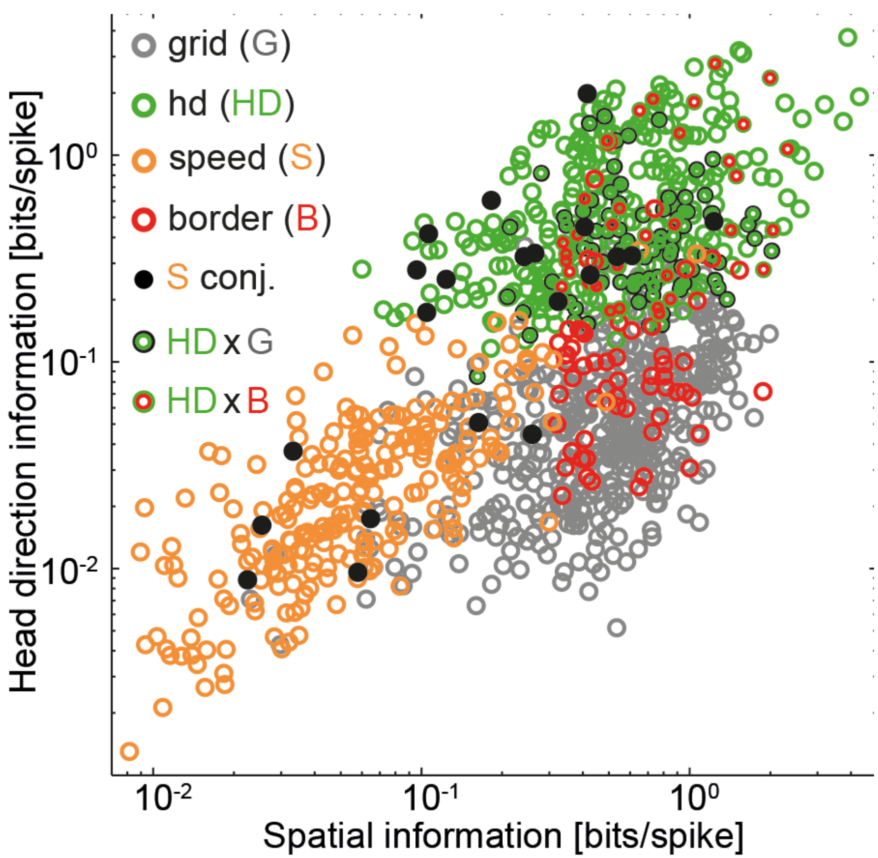
256 neurons in the open environment satisfy the criteria for speed cells



Kropff, Carmichael, Moser and Moser, unpublished

All of these cells had a linear speed-rate relationship

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



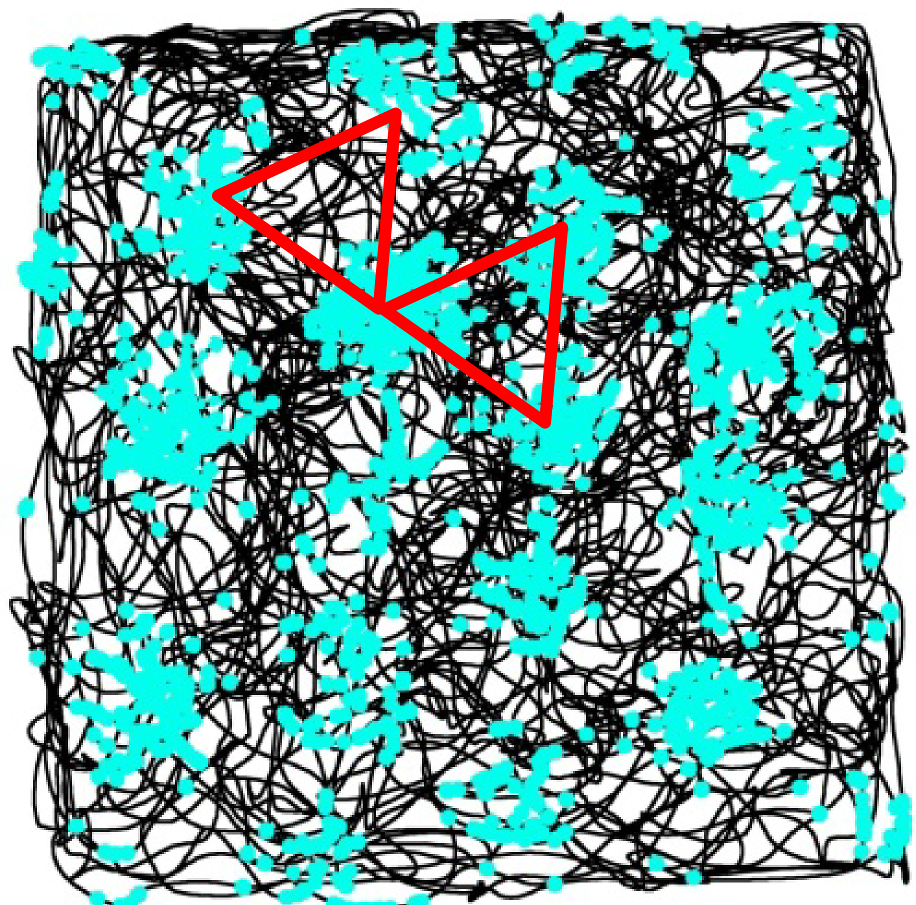
Speed cells are found in all layers and 32% were fast-spiking cells (in contrast to 0.5% in the other cell groups)

Kropff, Carmichael, Moser and Moser, unpublished

Integration of speed and head direction inputs enables grid cells to fire at precise locations:

+

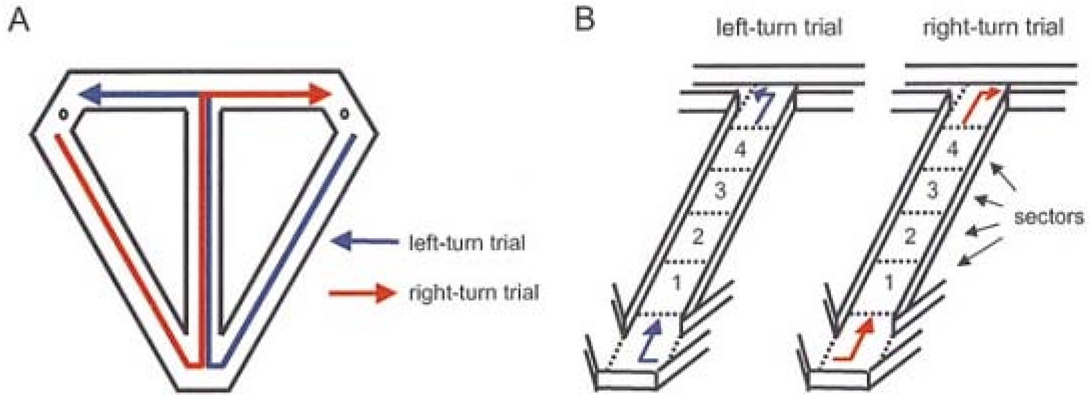
Distance = speed x time

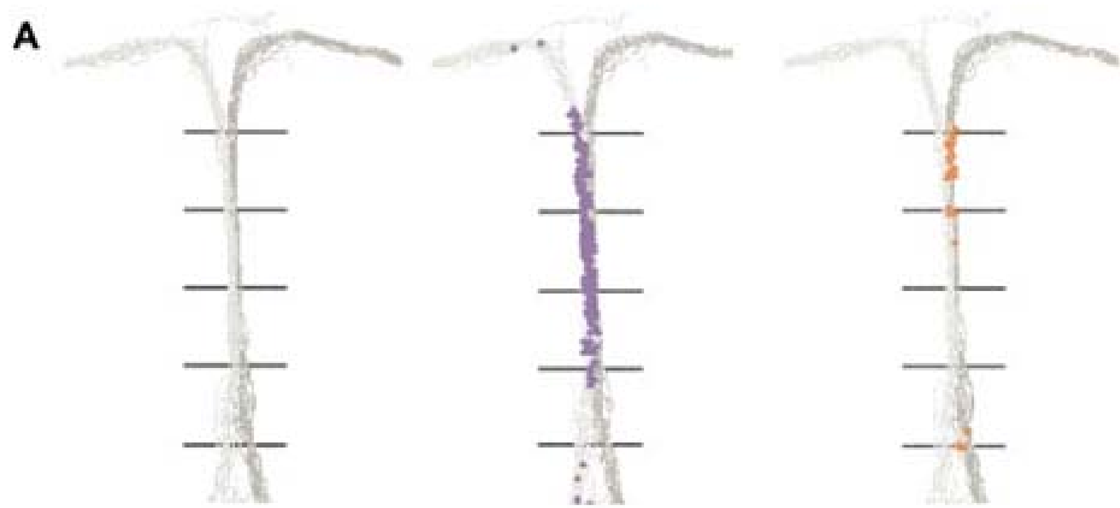


Speed cells are necessary for updating the grid pattern in accordance with the animal's movement

During spatial navigation, animals move from one place to another – how is the route between the places represented?

Does a cell's activity reflect any relationship between future and current positions?



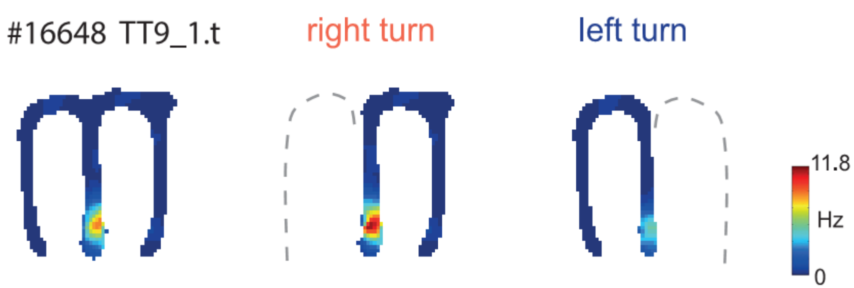


They tested this in a continous alternation task (left-right) while recording the acitvity of hippocampal CA1 cells:

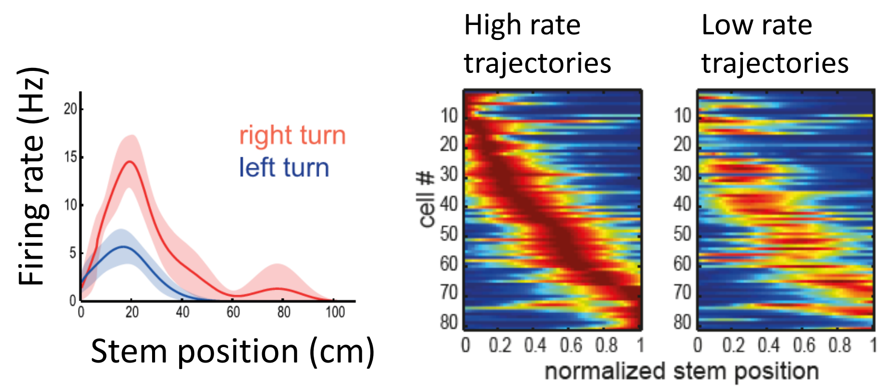
Wood, Dudchenko, Robitsek and Eichenbaum (2000)

Trajectory-dependent rate changes are much stronger in CA1 than in CA3

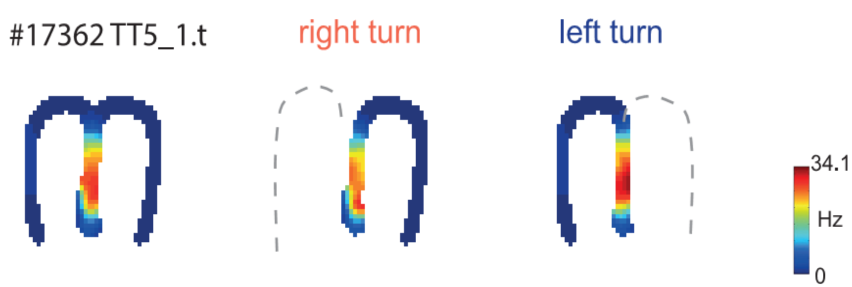
CA1 place cell



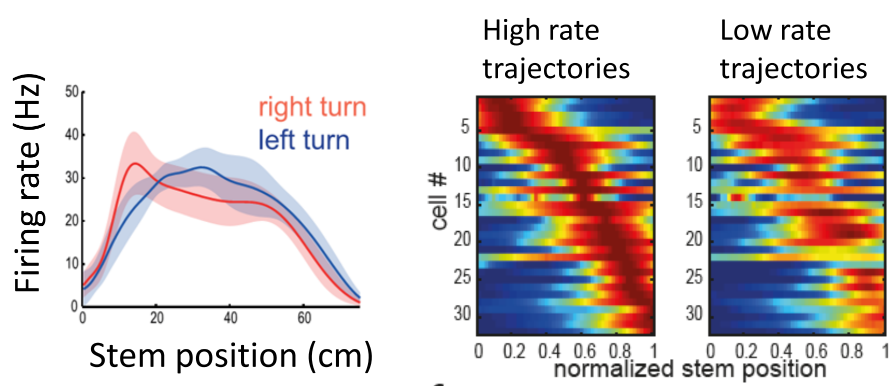
53% of cells show significant rate change on the stem



CA3 place cell



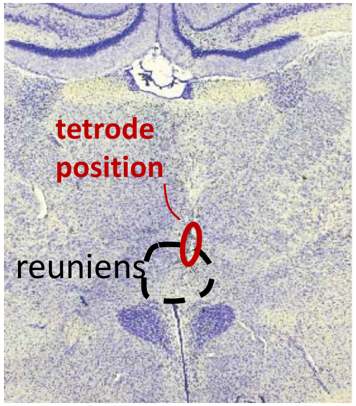
19% of cells show significant rate change on the stem

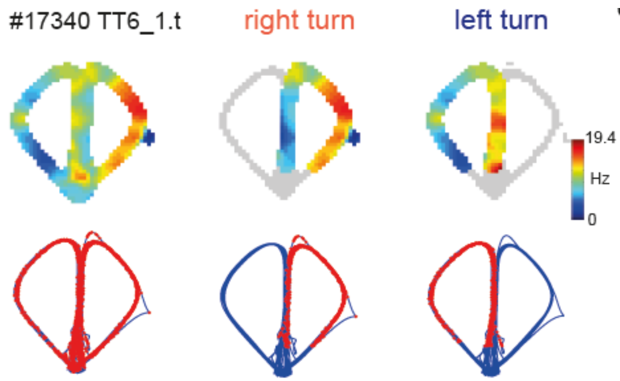


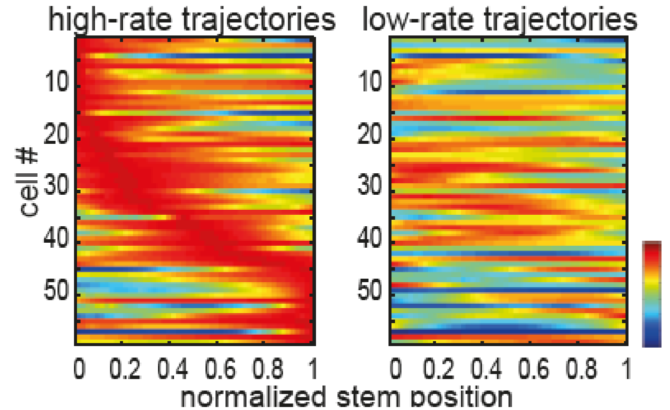
Why? Only CA1 receives direct input from nucleus reuniens

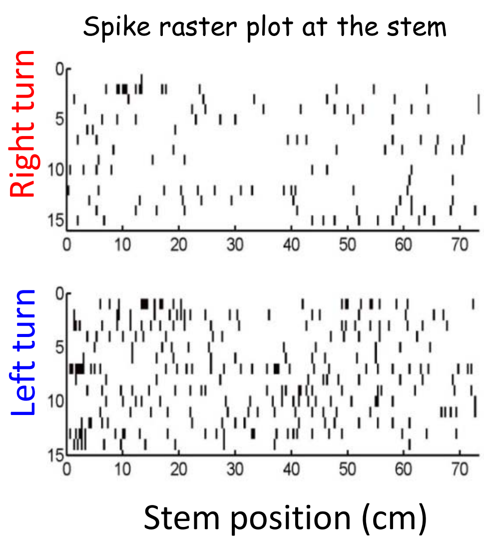
Ito, Zhang, Witter, Moser and Moser, unpublished

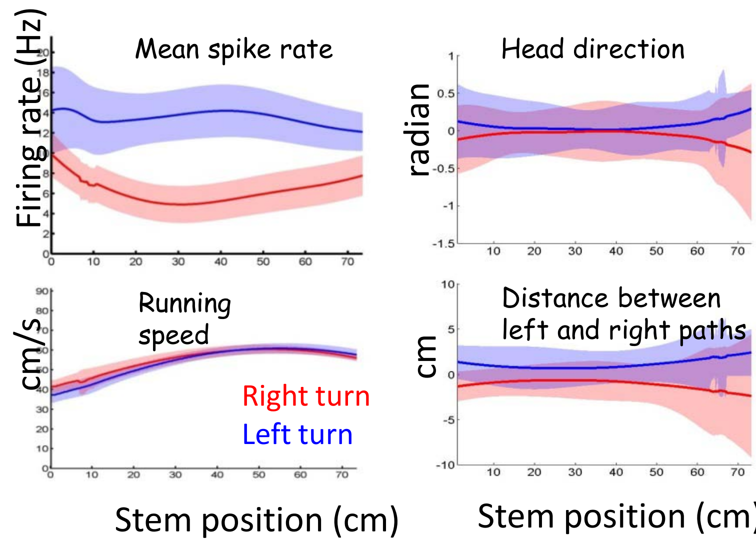
Nucleus reuniens neurons also show trajectory-dependent rate change







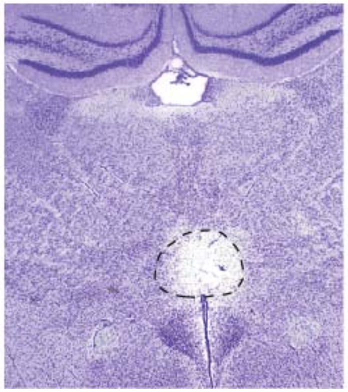




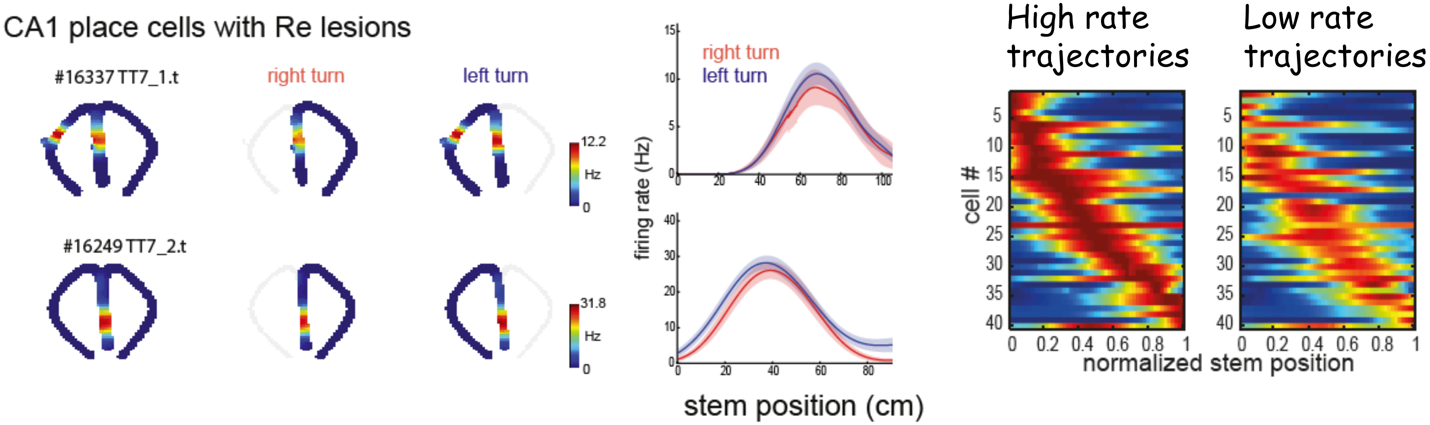
25/60 reuniens cells (42%) showed significant trajectory-dependent rate change

Reuniens lesions reduced trajectory-dependent rate change in CA1 neurons

Example of Re lesion (#16337)



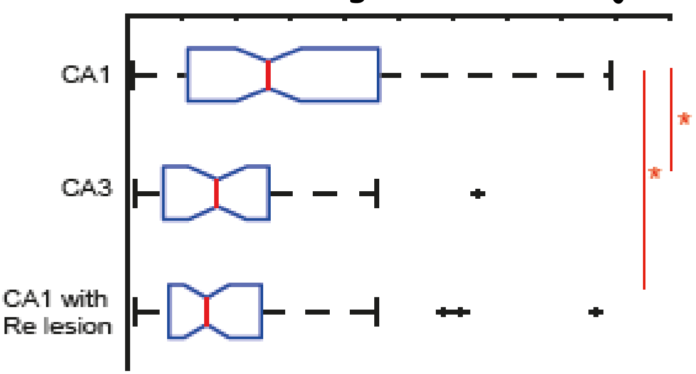
ibotenic acid injection



Now only 7/43 cells (16%) showed significant trajectory-dependent rate change

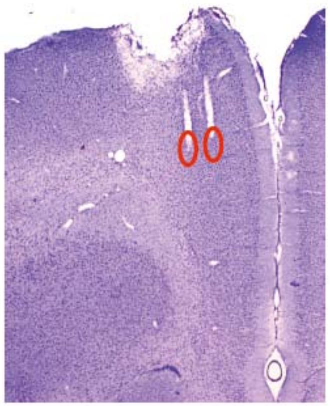
(53% of cells show significant rate change on the stem – in the normal rats)

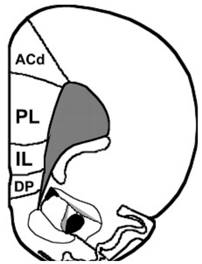
Peak rate change between trajectories

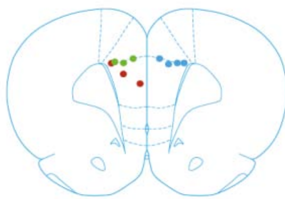


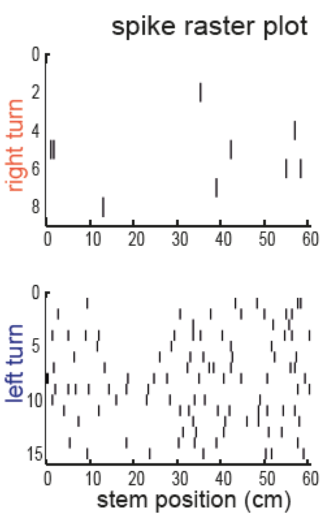
Neurons in the medial prefrontal cortex (prelimbic area) also showed trajectory-dependent activity

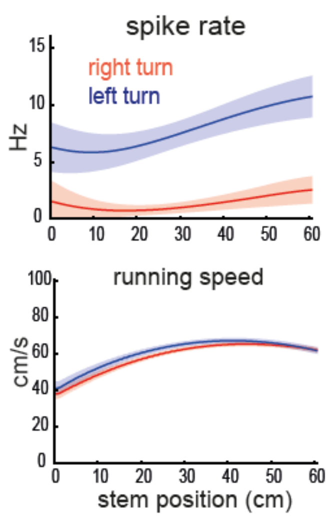
mPFC prelimbic area

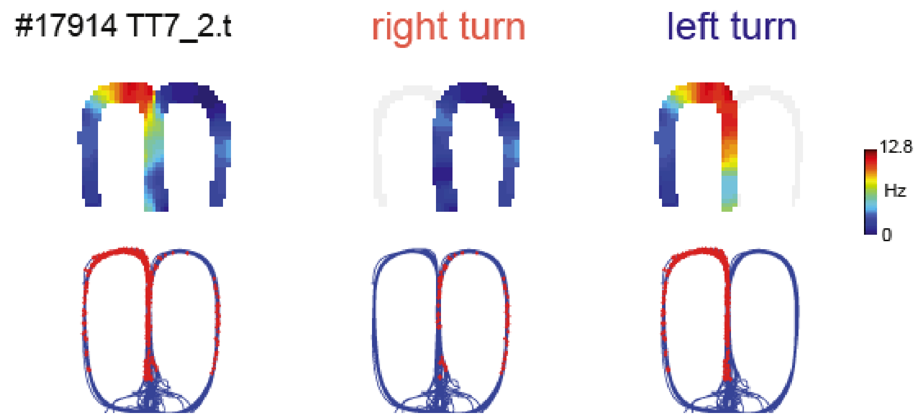






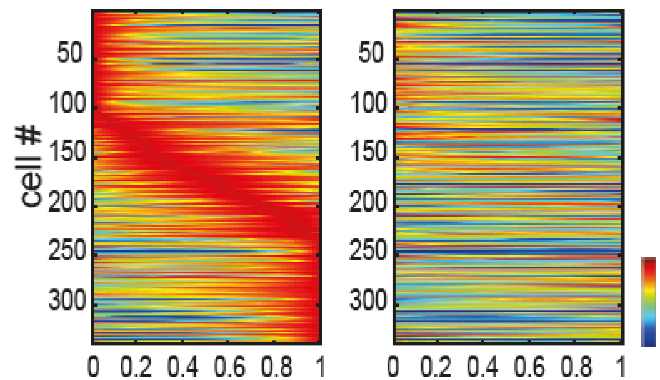






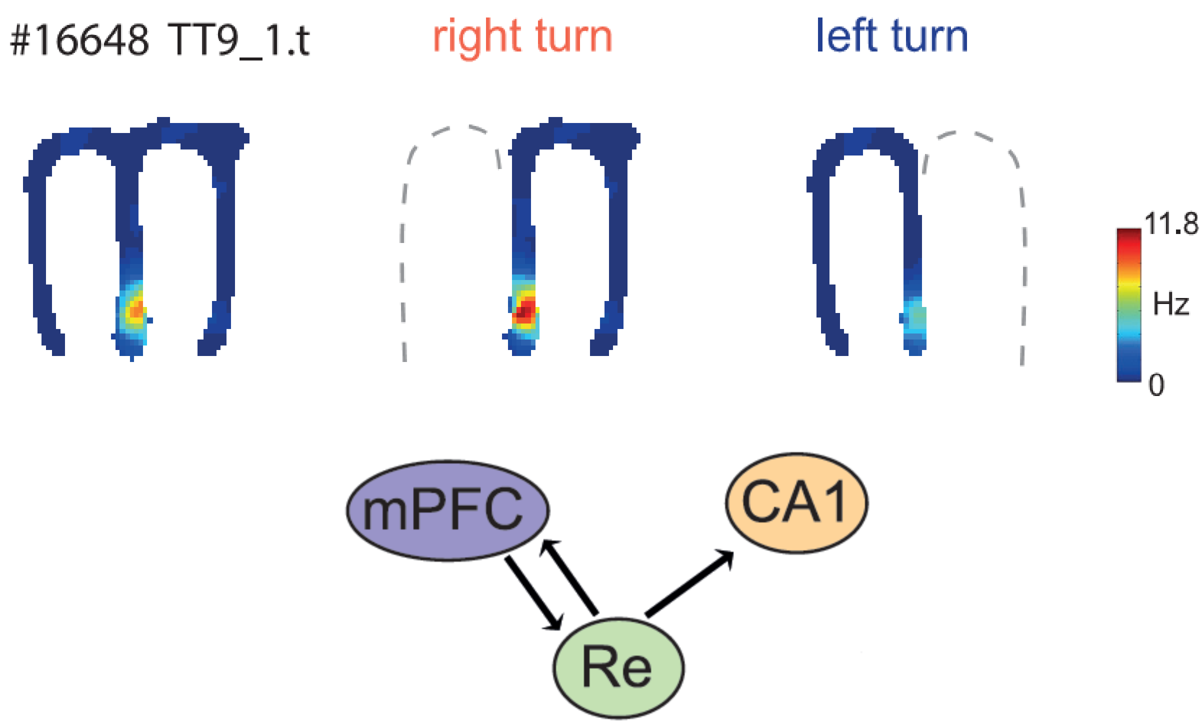
High rate trajectories

Low rate trajectories



111/339 cells (32%) showed significant trajectory-dependent rate change

In conclusion, the medial prefrontal cortex may provide route information to the CA1 of the hippocampus via the nucleus reuniens



Thus, thalamus is a key node in long-range communication between cortical regions involved in representing the future path during goal-directed behaviour

The hippocampus – memory or space?

"After operation this young man could <u>no longer recognize the hospital staff nor find his way to the bathroom</u>, and he seemed to recall nothing of the day-to-day events of his hospital life."

For the next 55 years, each time he met a friend, each time he ate a meal, each time he walked in the woods, it was as if for the first time.

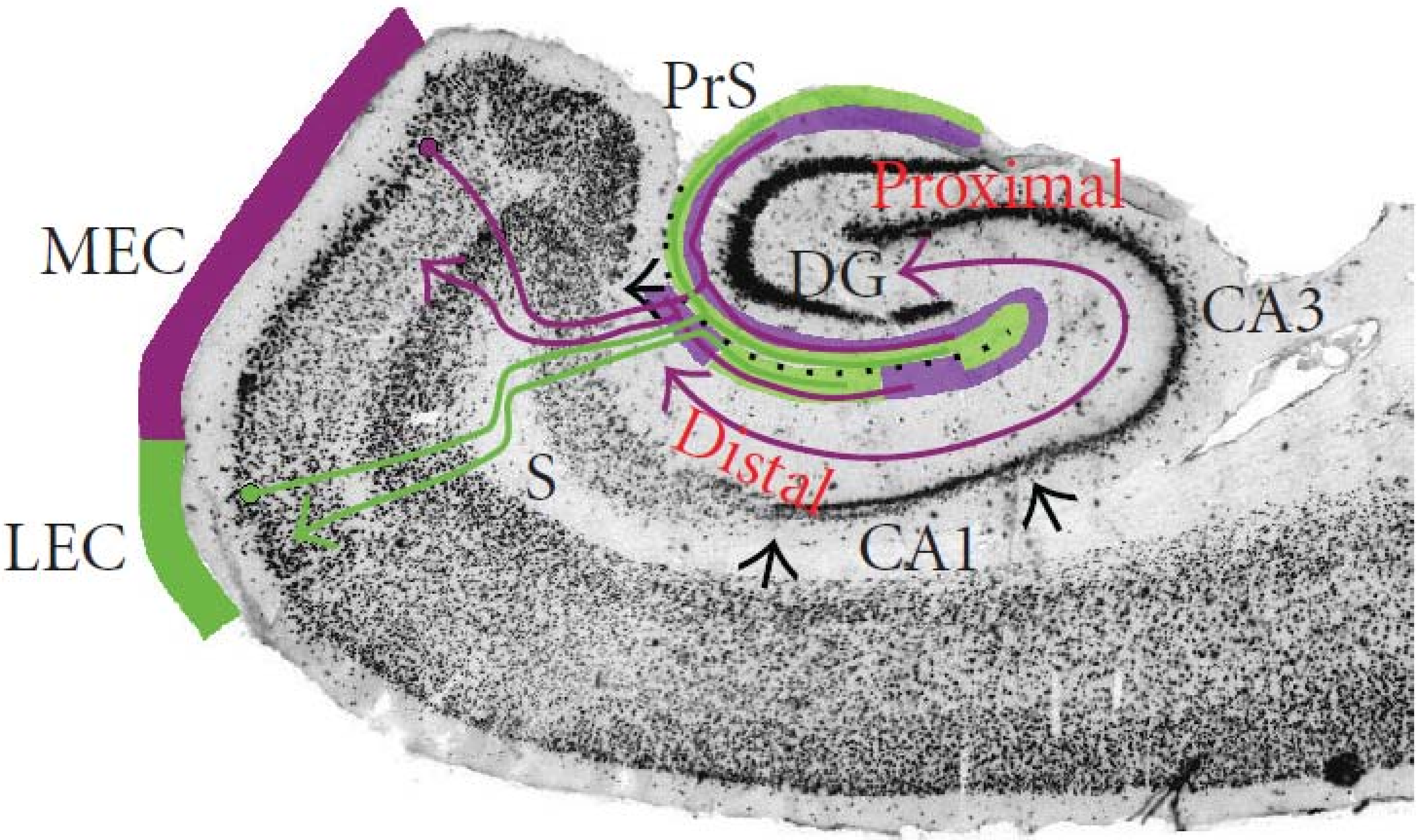
Scoville & Milner, 1957

H.M.

Method of loci:

Space is used as a framework for storing memories

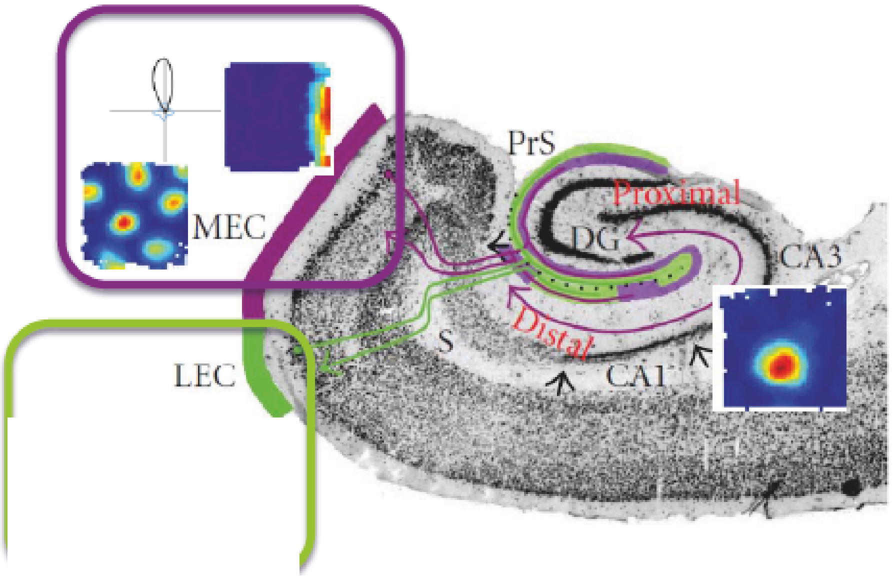
Hippocampus receives cortical inputs from both the medial entorhinal cortex (MEC) and the lateral entorhinal cortex (LEC)

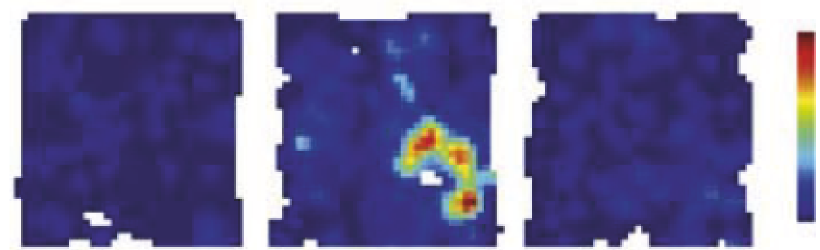


Modified from Canto and Witter, 2008

LEC cells provide information about the non-spatial content of the environment (Deshmukh and Knierim, 2011):

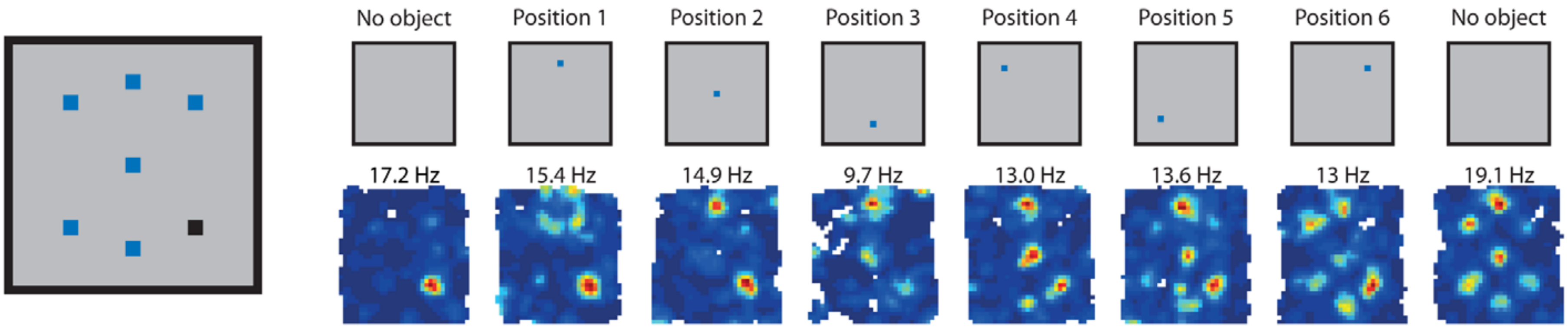
LEC cells respond to objects:





Tsao, Moser, Moser (2013). Curr Biol 23:399-405

Moving the object leaves memory-trace fields in LEC cells



In each location, trace fields emerge one trial after the presentation of the object.
Note that trace fields accumulate across trials.

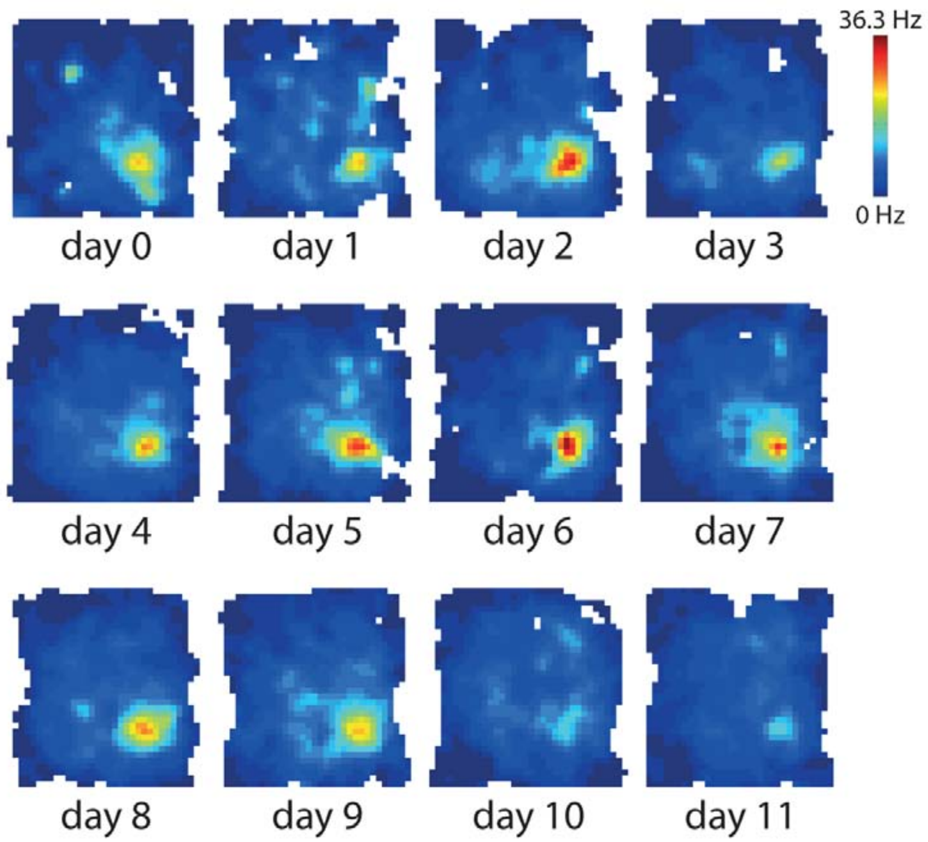
Tsao, Moser, Moser (2013). Curr Biol 23:399-405

The memory-trace of an object lasts long:

With extended training, trace fields become persistent, lasting for weeks after the last exposure to the object (before day 0),

implying that:

the trace cell activity is not a mismatch response to the absence of the object



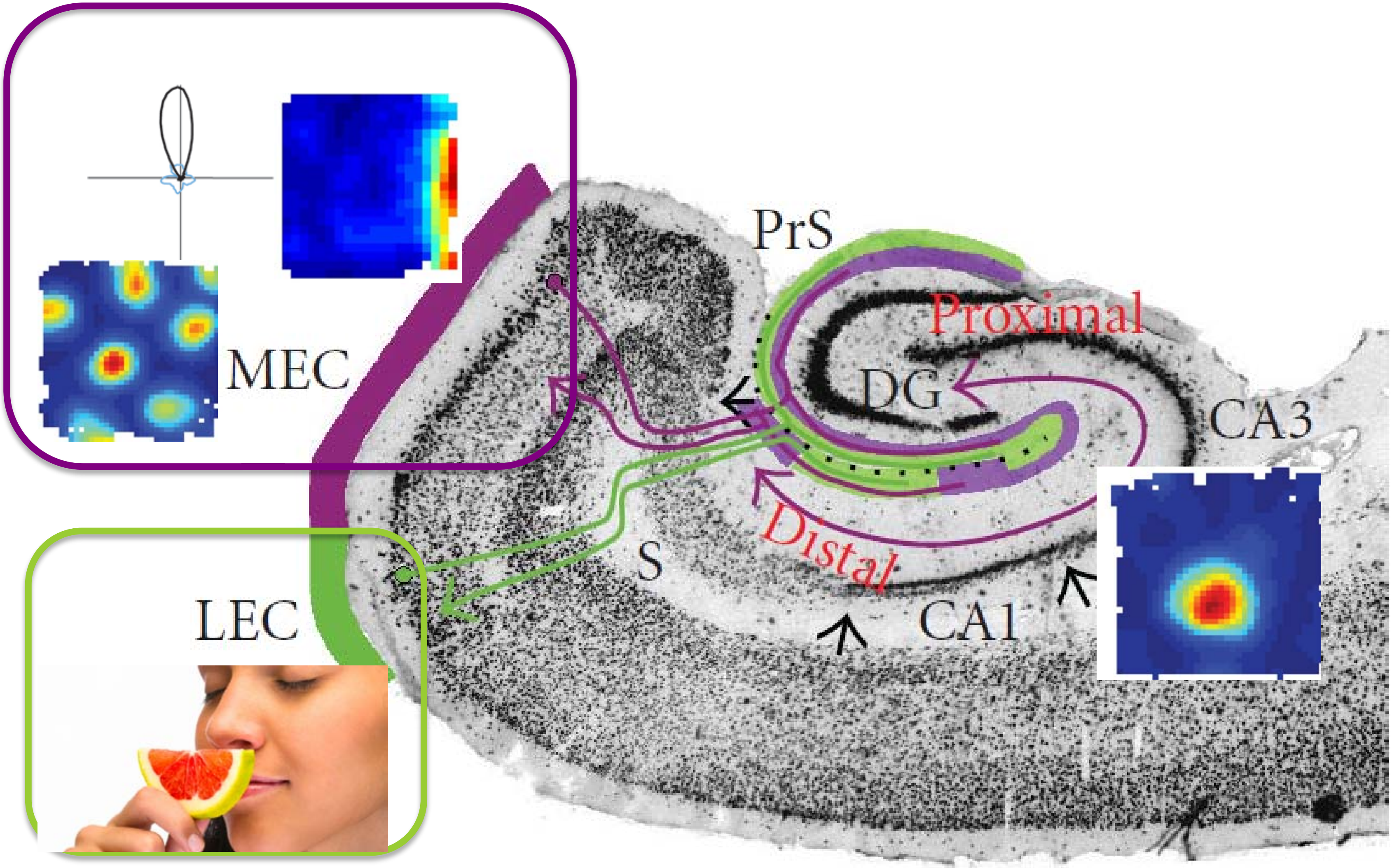
Tsao, Moser, Moser (2013). Curr Biol 23:399-405

Thus, also LEC is part of the hippocampal memory circuit

How are associations between place and episodes generated?

- Odours as an example

Hippocampus receives olfactory information through the lateral entorhinal cortex (LEC)



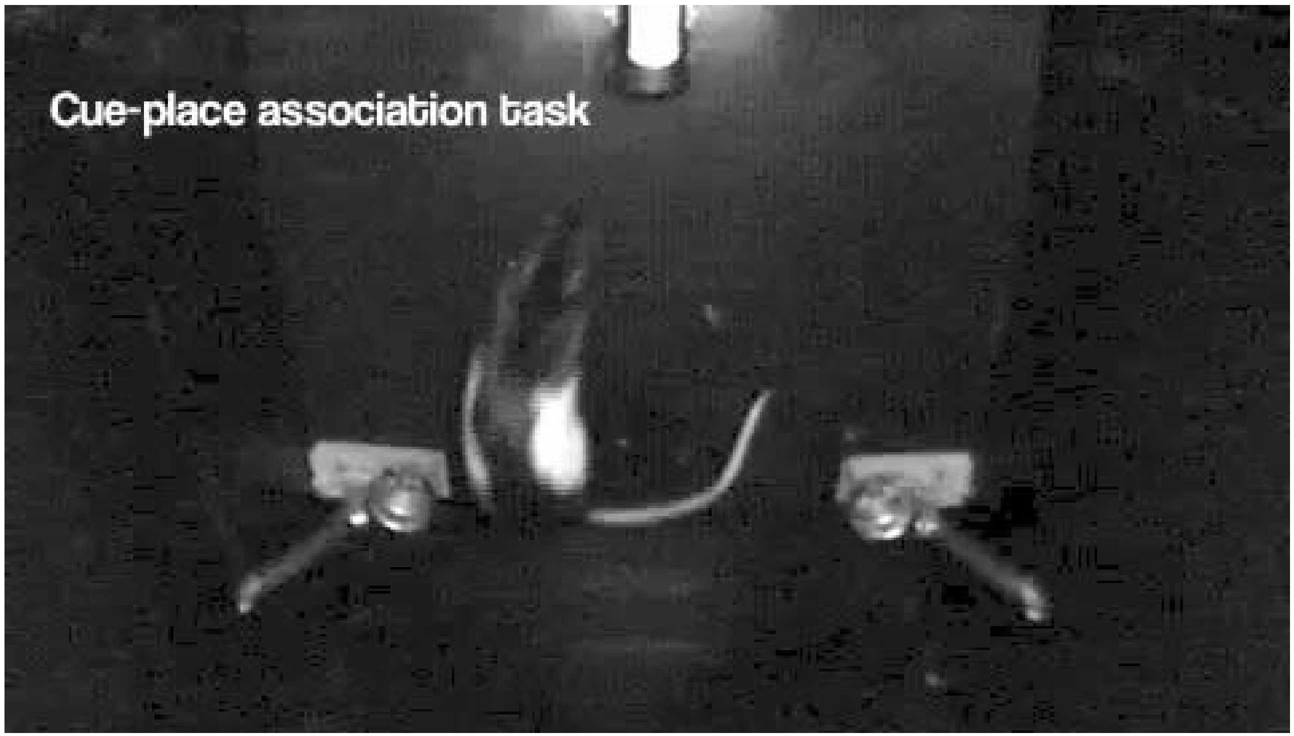
Modified from Canto and Witter, 2008

And hippocampus stores associations between odour and space

À la recherche du temps perdu – In Search of Lost Time,
Marcel Proust:

… the smell and taste of things remain poised a long time, like souls, ready to remind us, waiting and hoping for their moment …

We asked how olfactory information is encoded and retrieved in the lab

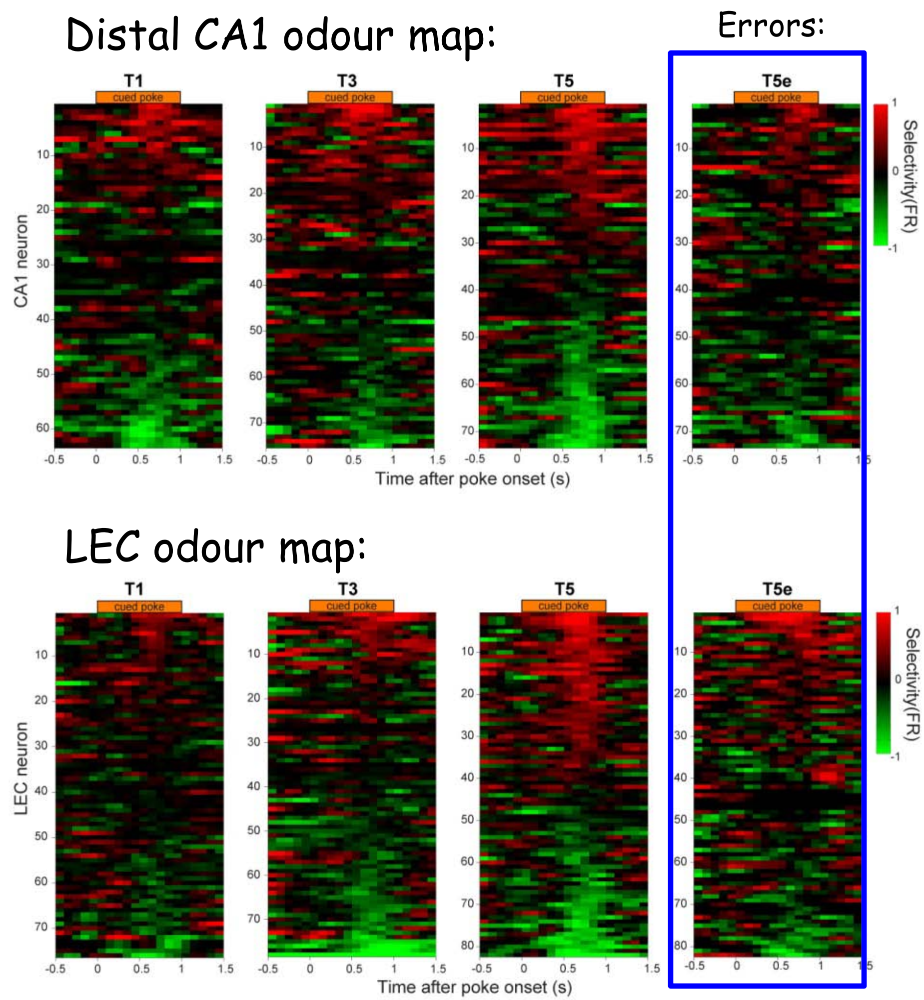


Rats were trained to asymptotic performance 85% correct (T5) in a simple odour discrimination task

Igarashi, Lu, Colgin, Moser, Moser, Nature, 2014

Odour maps developed both in dCA1 and LEC

The number of odour-selective LEC neurons during cue sampling increased with learning:



The selectivity for odours is lost on error trials...
... suggesting that the expression of an odour map during cue sampling is predictive and maybe necessary for retrieval

Selective firing to one odour =

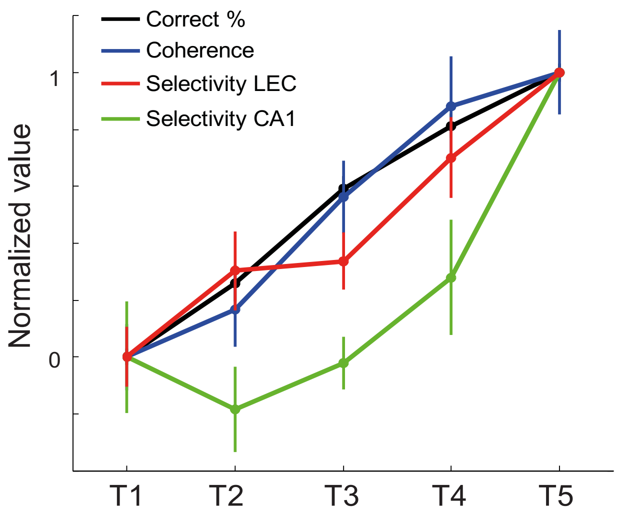
$$\frac{\text{(Firing rate to odour A – Firing rate to odour B)}}{\text{(Firing rate A + Firing rate B)}}$$

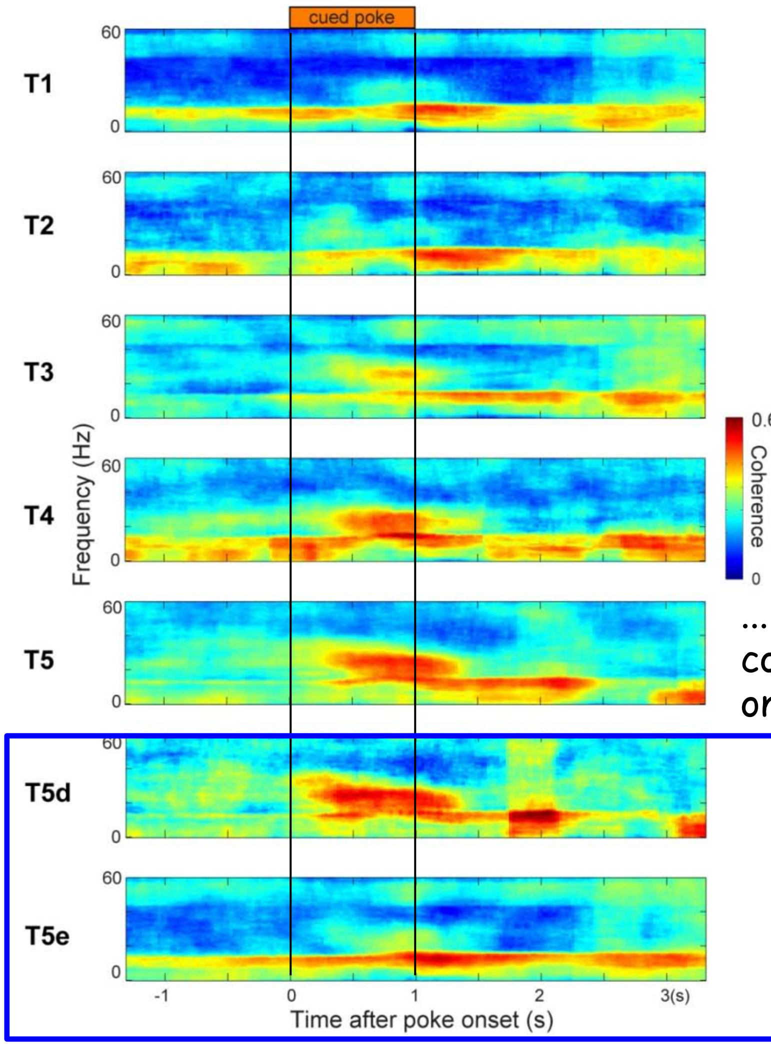
Red –more firing to odour cue A (max 1)

Green- more firing to odour cue B (max -1)

The odour maps might be the result of selective increase in 20-40 Hz coherence between dCA1 and LEC and the coherence develops with learning

... thus, LEC-dCA1 coherence may be necessary for successful discrimination





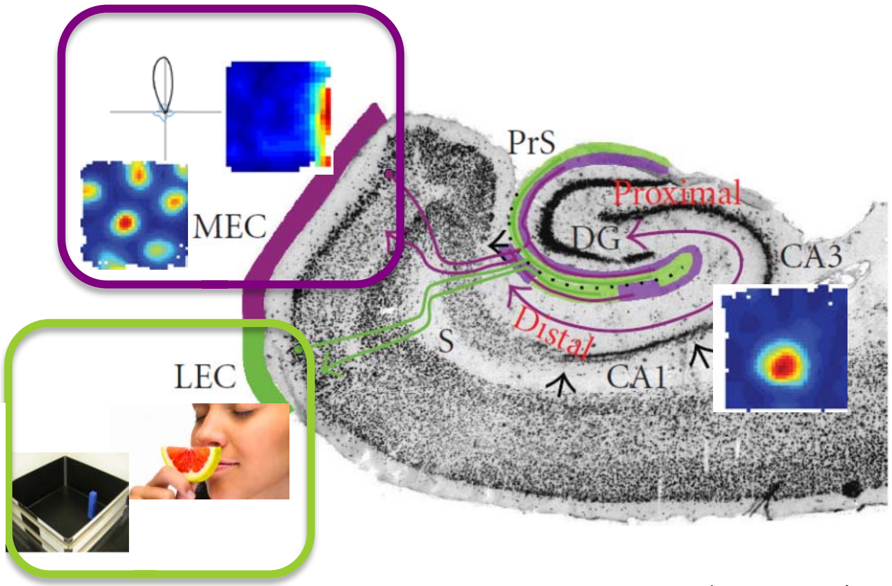
... but the coherence was lost on **error trials**:

Igarashi, Lu, Colgin, Moser, Moser, Nature (2014)

The basis of episodic memory:

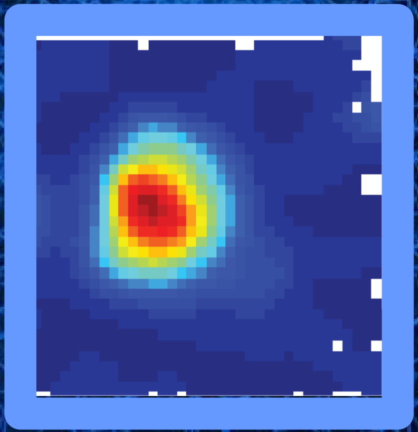
Associations between place and odours might be established through coherent oscillations between cell assemblies in hippocampus and LEC.

Development of coherent firing within dCA1 or LEC may create functional ensembles during acquisition, e.g. by enabling synaptic plasticity. Such ensembles may form the basis of odour memory.



Igarashi, Lu, Colgin, Moser, Moser, Nature (2014)

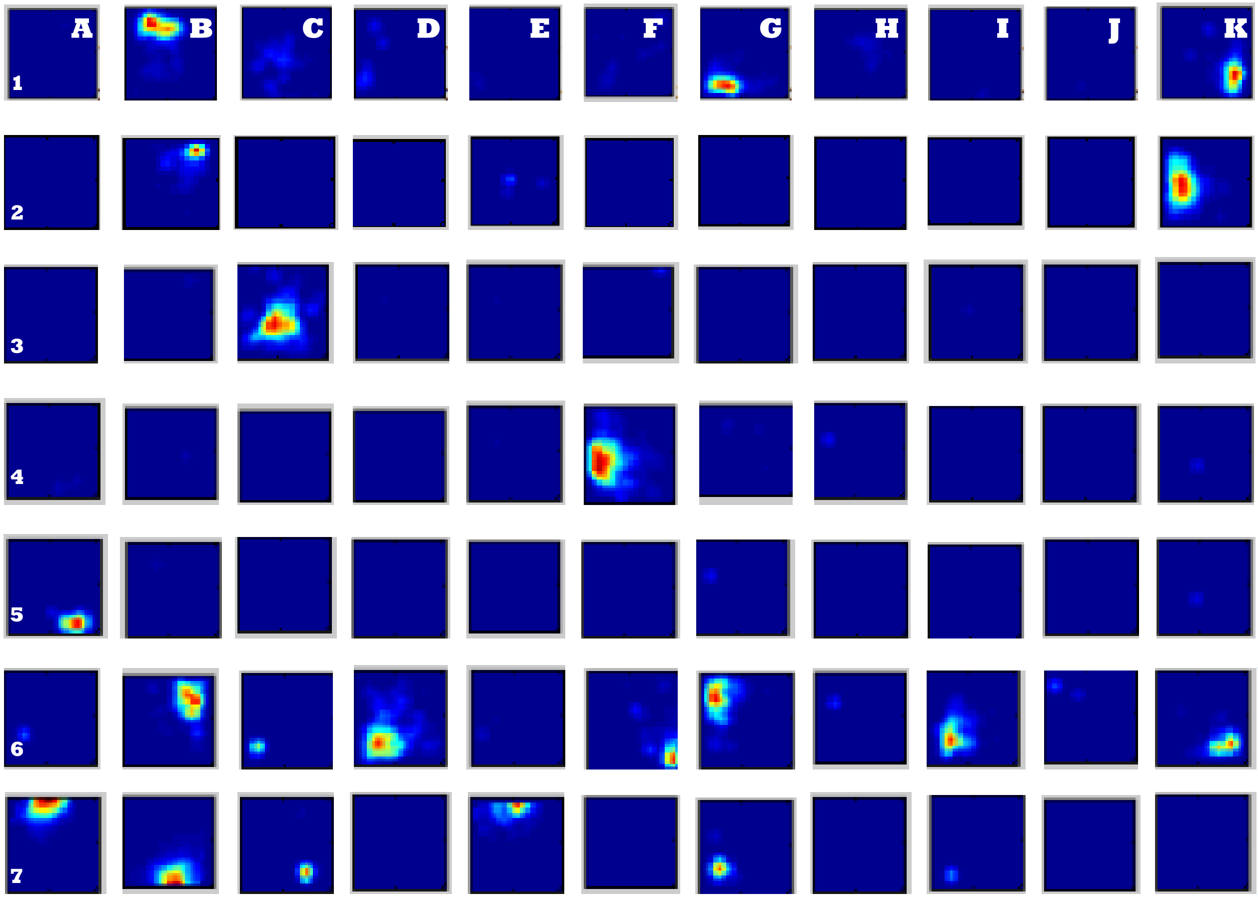
However, a big challenge for episodic memory is the risk of interference – **remapping keeps memories apart**



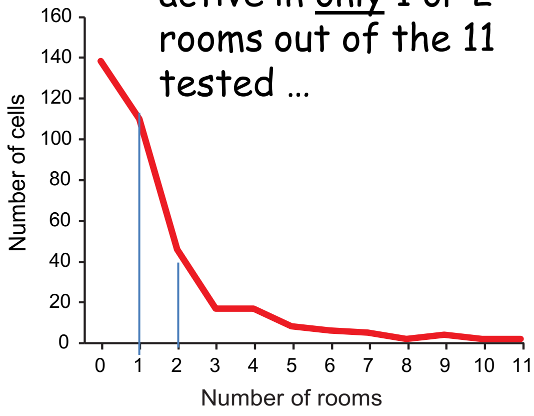
First studied by Muller and Kubie, 1987

Challenging the hippocampal remapping capacity:

CA3 cells tested in 11 rooms → 11 different maps!



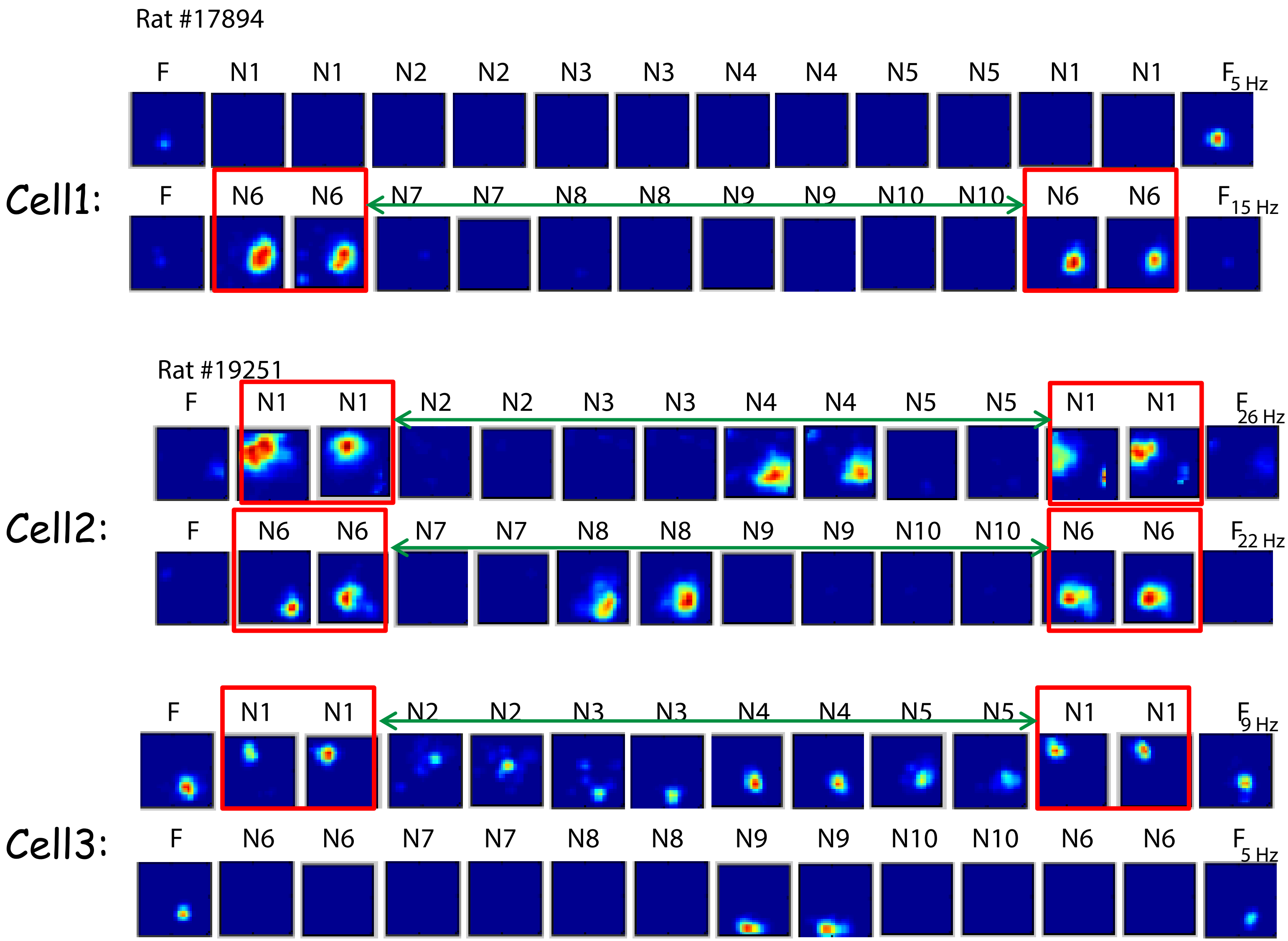
Most place cells are active in only 1 or 2 rooms out of the 11 tested …



… and if the cells are active, they have different maps in different rooms

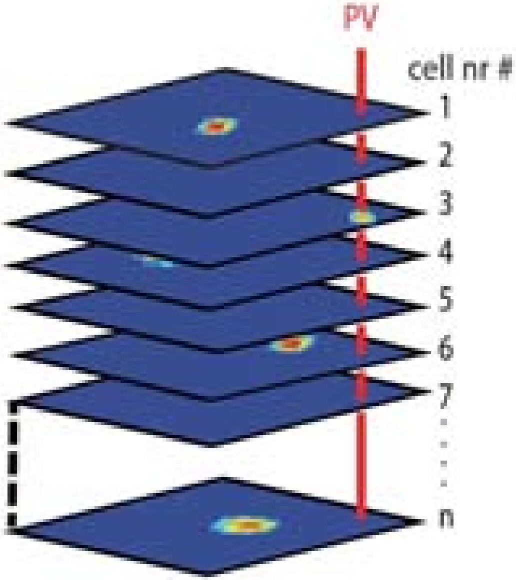
Alme, Miao, Jezek, Treves, Moser and Moser, PNAS, 8th December,2014

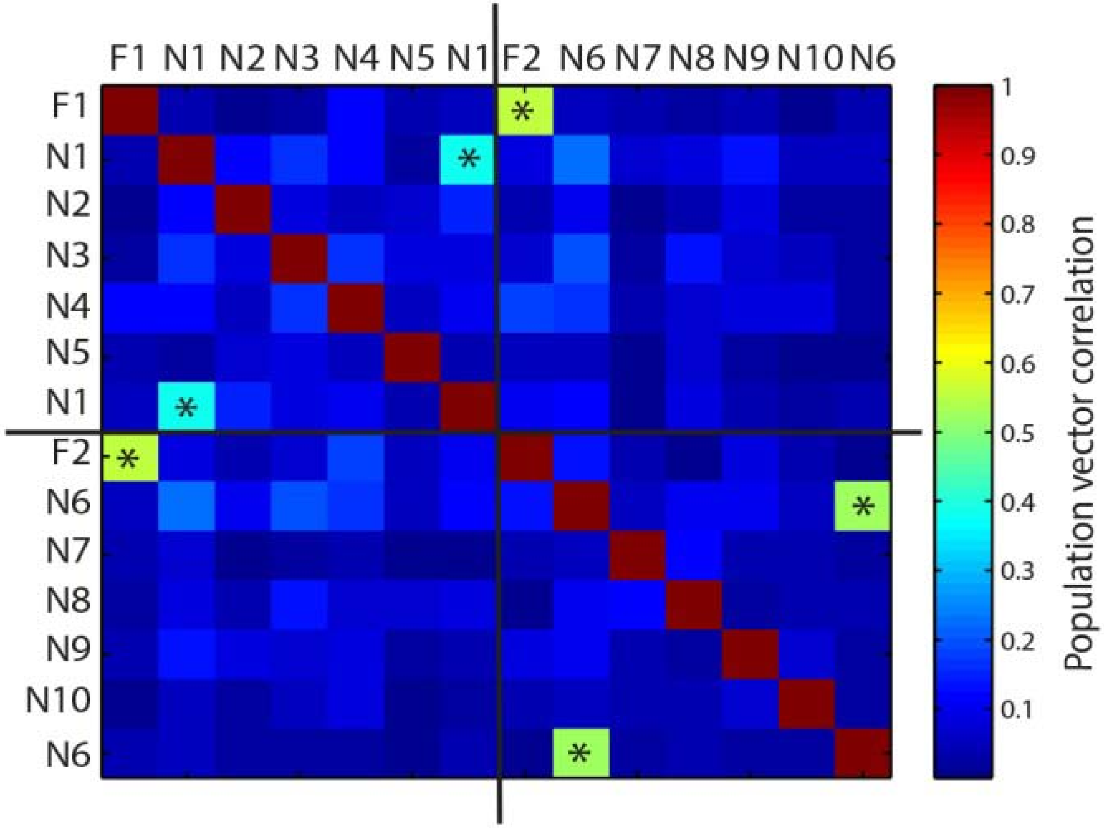
… and like episodic memory: 1 trial is sufficient to encode a map!



Alme, Miao, Jezek, Treves, Moser and Moser, PNAS, 8th December,2014

Population vector analyses confirmed that maps (representations) are uncorrelated across rooms
but correlated between repeated exposures to the same room



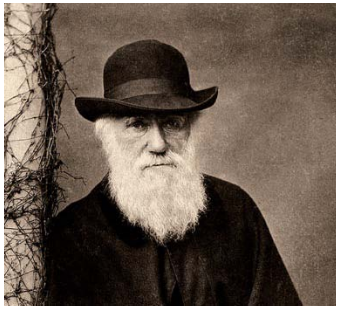


Alme, Miao, Jezek, Treves, Moser and Moser, PNAS, 8th December, 2014

Method of loci

Space is an efficient retrieval cue and keeps memories associated with each space separate

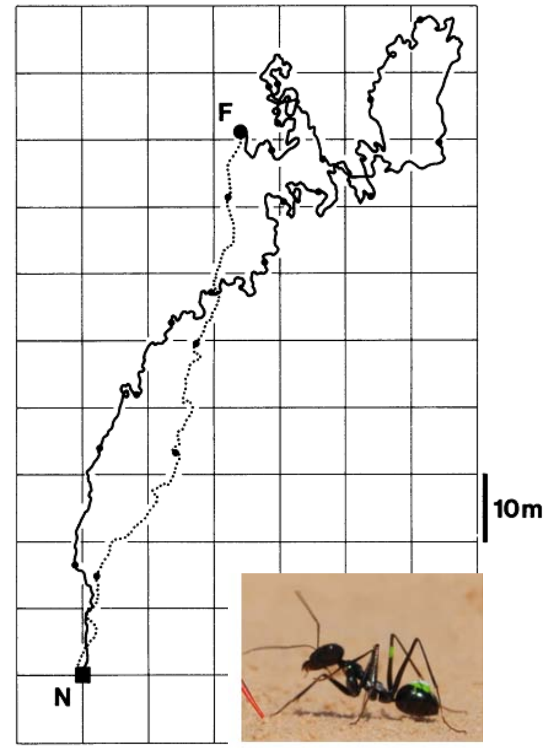
Helmet video!



Path integration – dead reckoning, originally proposed by Charles Darwin:

… neither a compass, nor the north star, nor any other such sign, suffices to guide a man to a particular spot through an intricate country …, unless the deviations are allowed for, or a sort of "dead reckoning" is kept …

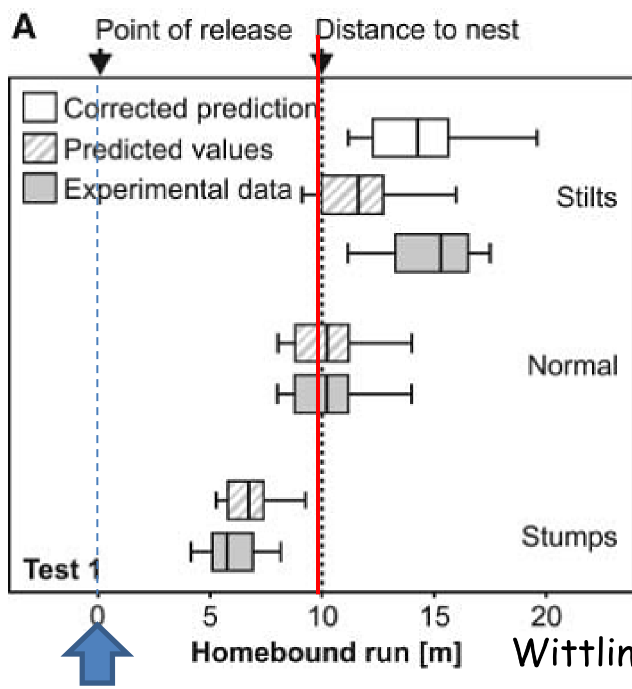
… Whether animals may not possess the faculty of keeping a dead reckoning … , I will not attempt to discuss, as I have not sufficient data.

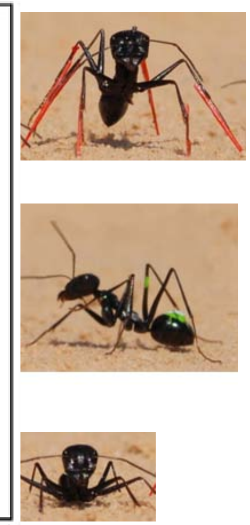


Müller and Wehner, 1988, PNAS

RECORD: Darwin, C. R. 1873. Origin of certain instincts. *Nature. A Weekly Illustrated Journal of Science* 7 (3 April): 417-418.
REVISION HISTORY: Scanned, OCRed, corrected and edited by John van Wyhe 2003-8, textual corrections by Sue Asscher 3.2007. RN3

Ants measure distance by counting steps:





Wittlinger, Wehner & Wolf, Science, 2006

Other studies have shown that path integration mechanisms apply also in mammals

Do rats have a speedometer?