Introduction to Neuroscience: Systems Neuroscience

The hippocampus in spatial navigation and memory consolidation

Nachum Ulanovsky

Outline of today's lecture

- **Hippocampus: Introduction and early discoveries**
- **Spatial maps in the hippocampus and related regions:**
  - **Place cells**
  - **Head direction cells**
  - **Grid cells**
- ***Intermezzo*: Structure-function relations in the hippocampus**
- **Beyond the cognitive map: Hippocampus and memory**
- **Open questions**

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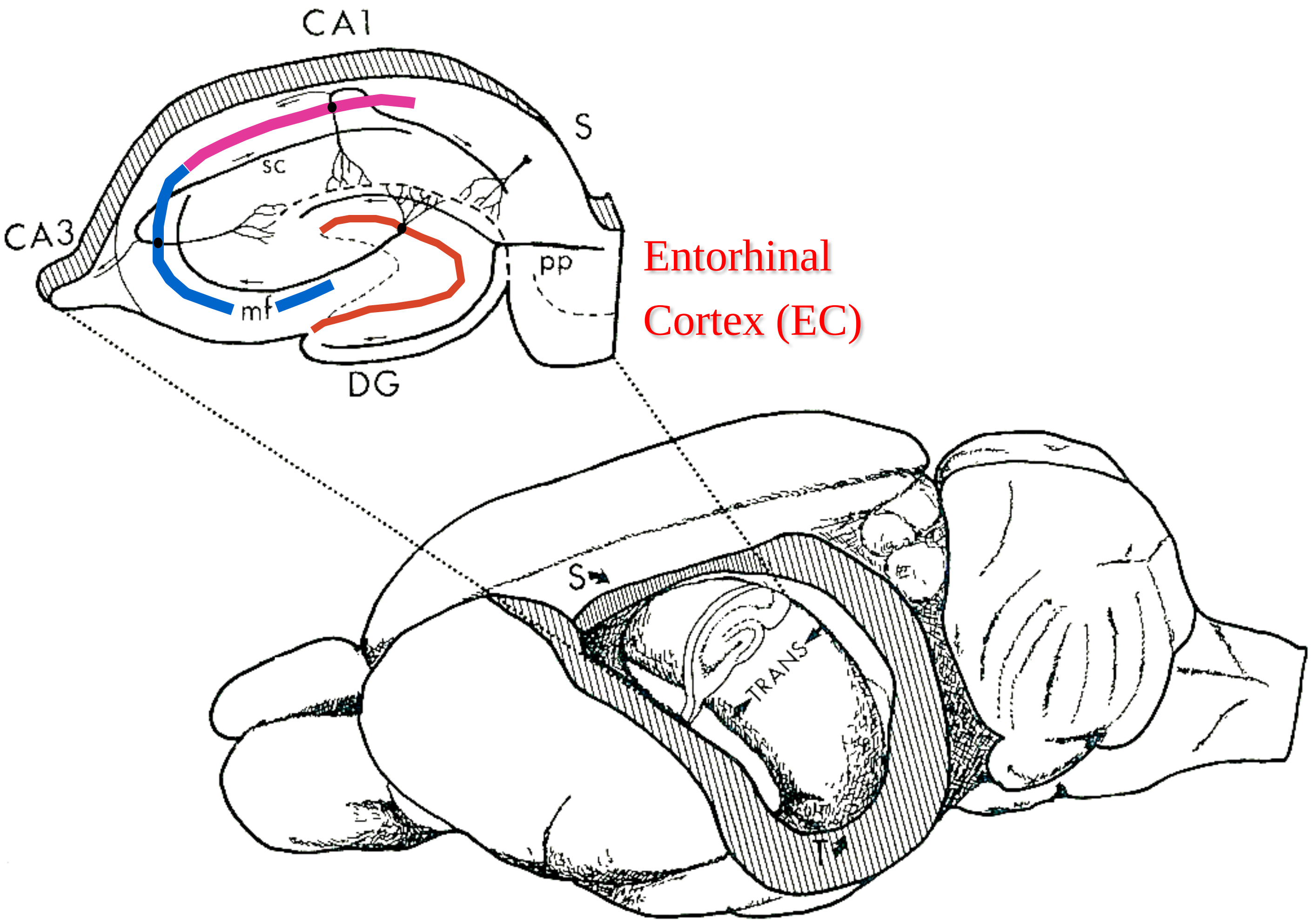
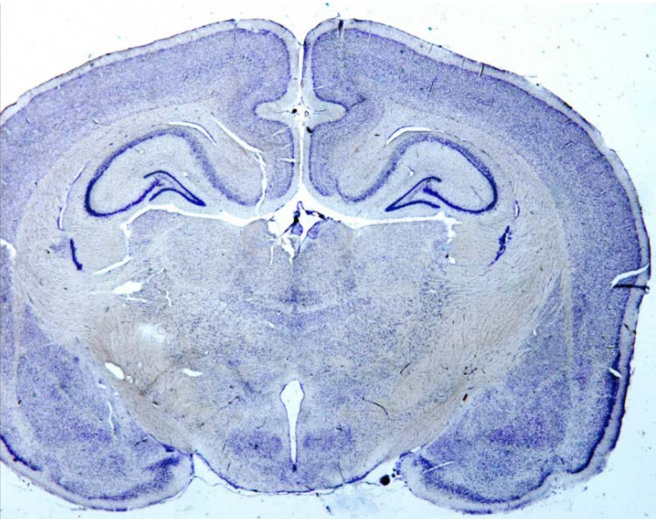
The hippocampus



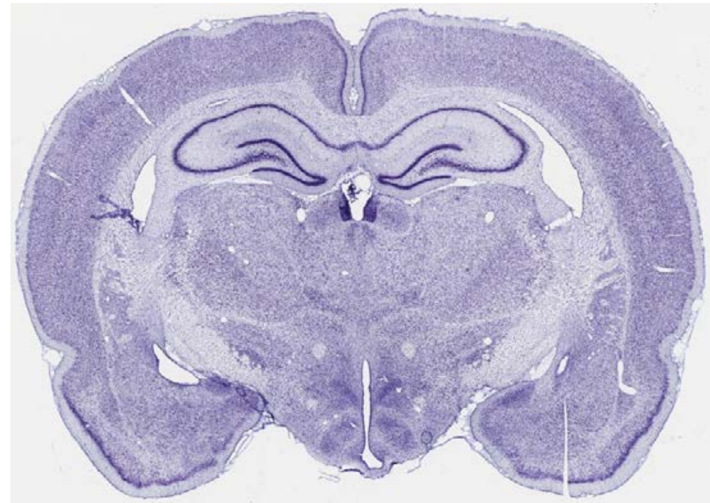
(Amaral and Witter 1989)

The hippocampus is highly conserved across mammals

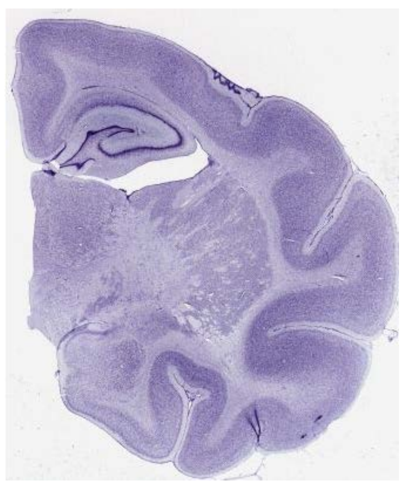
Egyptian fruit bat



Rat

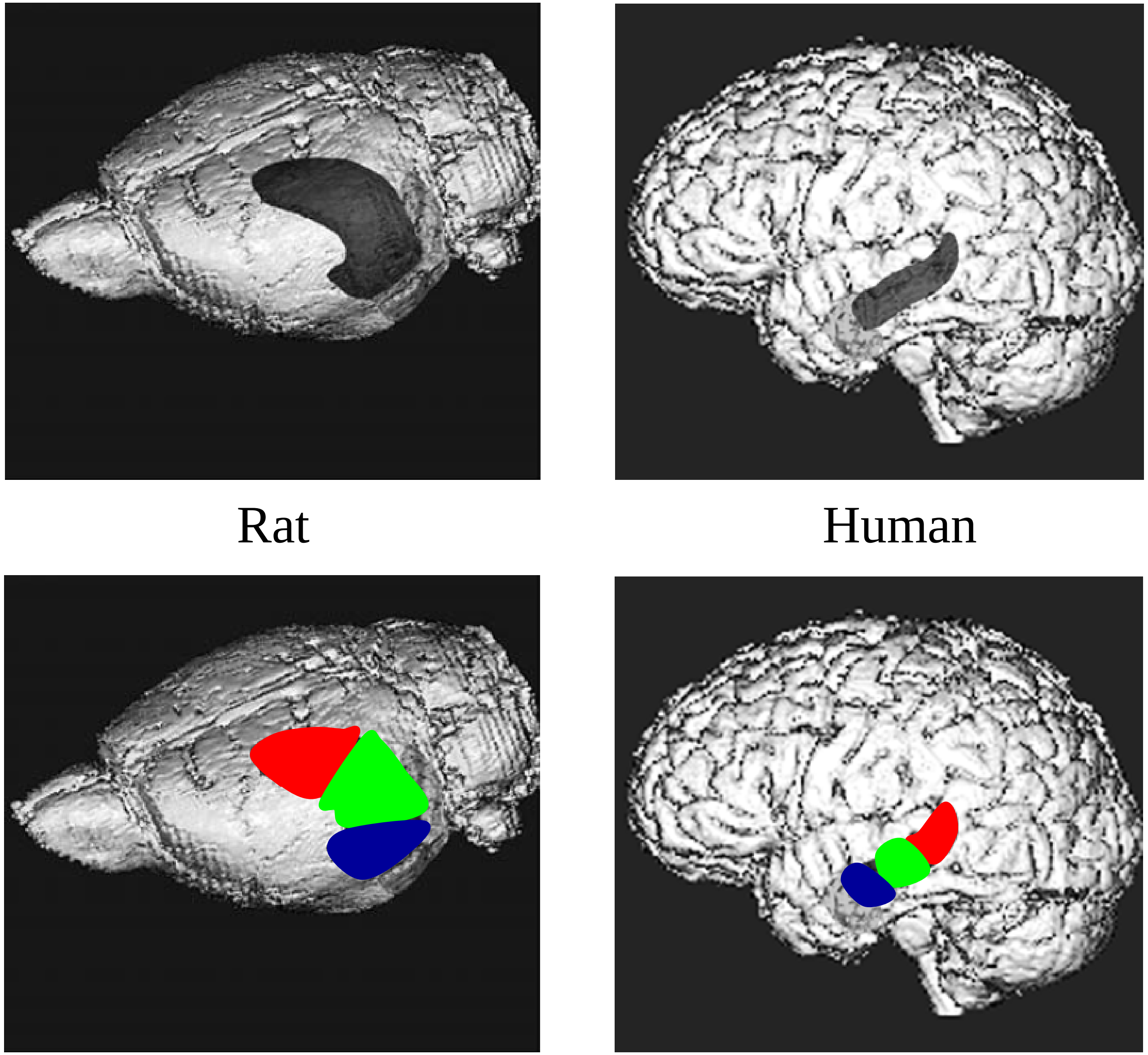


Echidna
(ancient egg-laying mammal)



Highly conserved brain structure across all mammals, including humans (exists also in birds, but looks quite different)

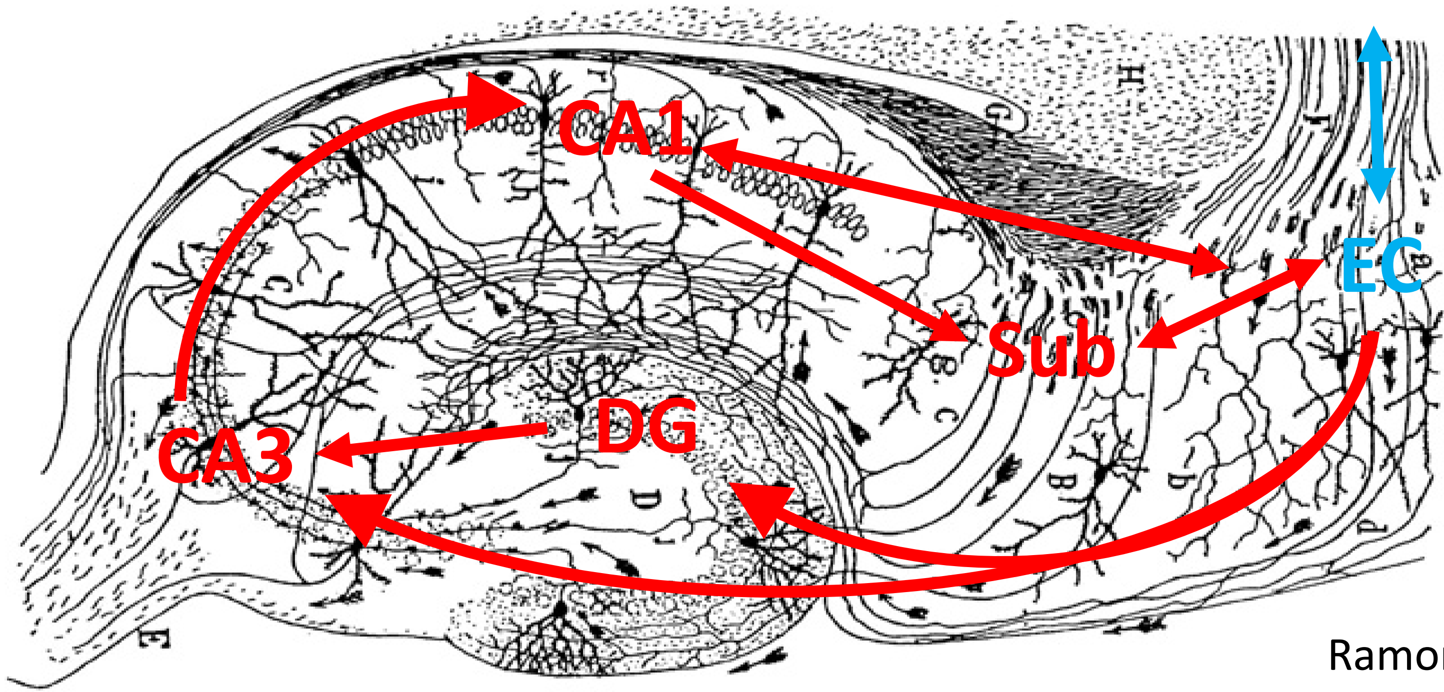
The hippocampus is highly conserved across mammals



In primates: The hippocampus is at the bottom of the brain and rotated 90° backwards compared to rats, but otherwise is very similar.

Posterior hippocampus in humans is equivalent to *dorsal (septal) hippocampus* in rats (red).

The hippocampus is part of a primarily uni-directional processing loop: entorhinal cortex → hippocampus → entorhinal cortex

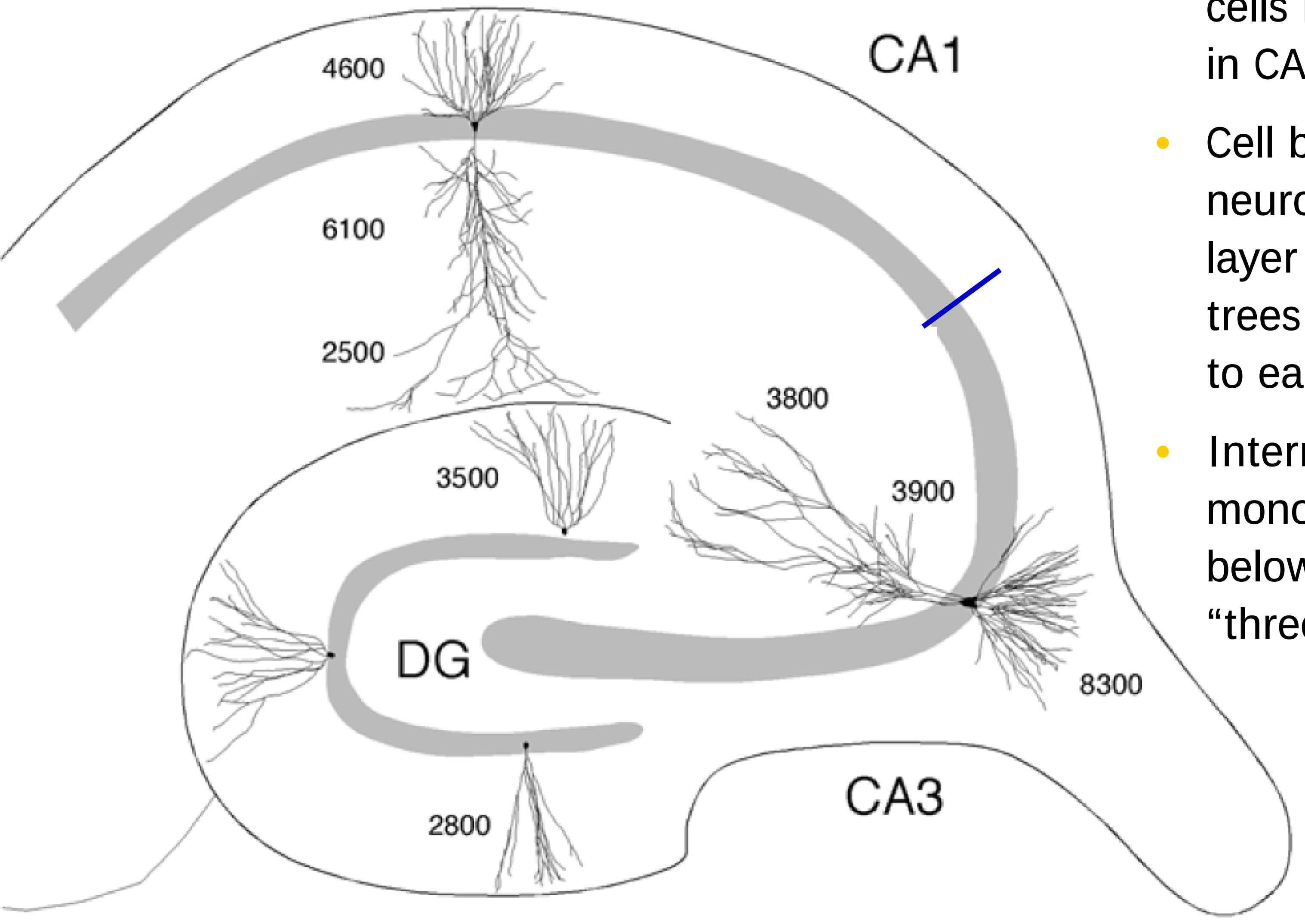


Ramon y Cajal

EC	Entorhinal Cortex
CA1	Cornu Ammonis 1
CA3	Cornu Ammonis 3
DG	Dentate Gyrus
Sub	Subiculum

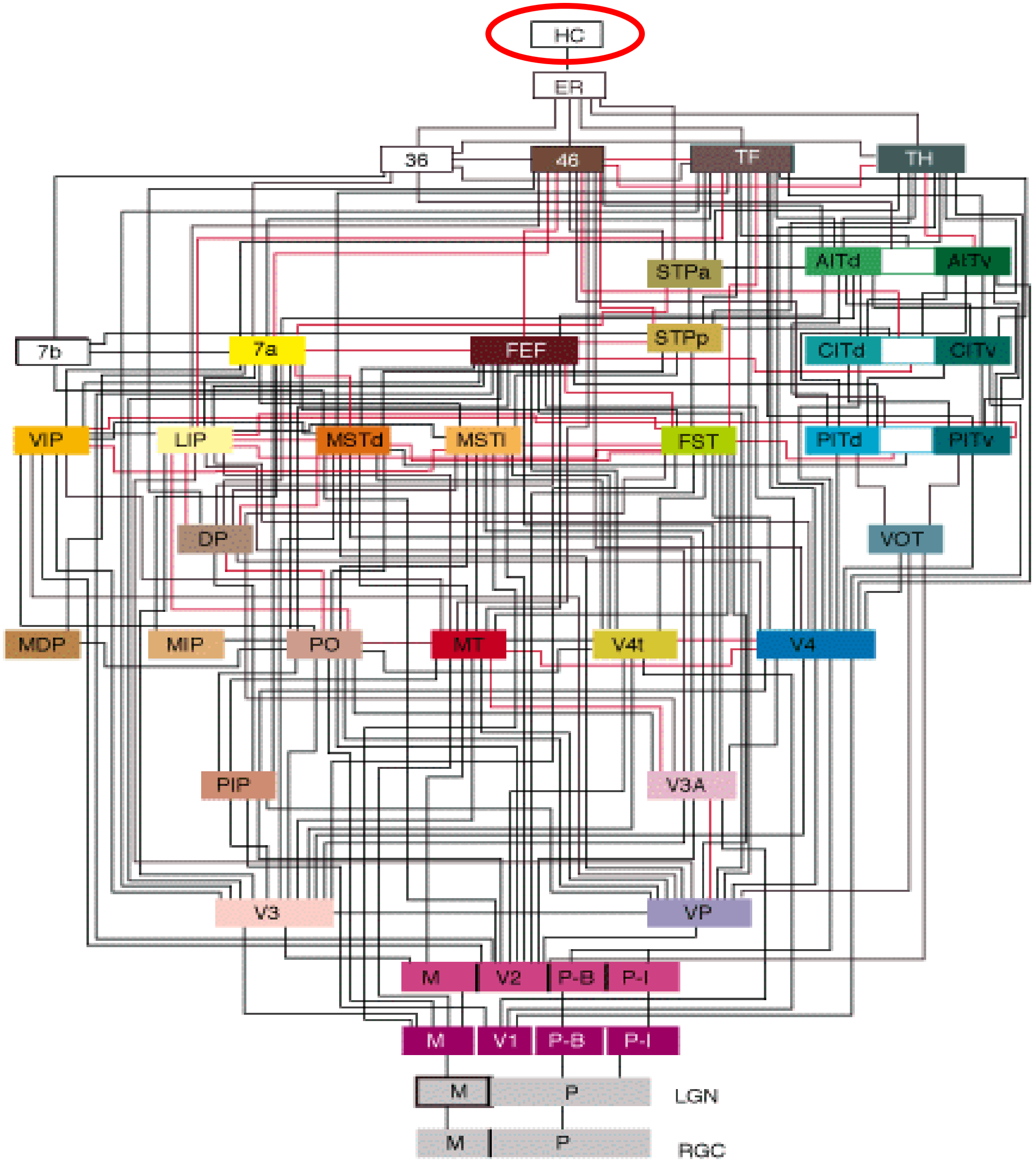
- This uni-directional connectivity is quite different than what is typically found in neocortex, where connectivity is usually bi-directional (i.e., if area A projects to B, then B also projects to A).

The hippocampus is a single-layer (or three-layer) cortex



- Projections neurons: Granule cells in DG and Pyramidal cells in CA1 and CA3
- Cell bodies of projection neurons form almost a mono-layer (in the rat), and dendritic trees are very orderly parallel to each other
- Interneurons are found in the mono-layer, but also above and below it (hence the term “three-layer cortex”)

The hippocampus is a high-level brain region



Felleman & Van Essen, *Cereb Cortex 1, 1-47 (1991)*

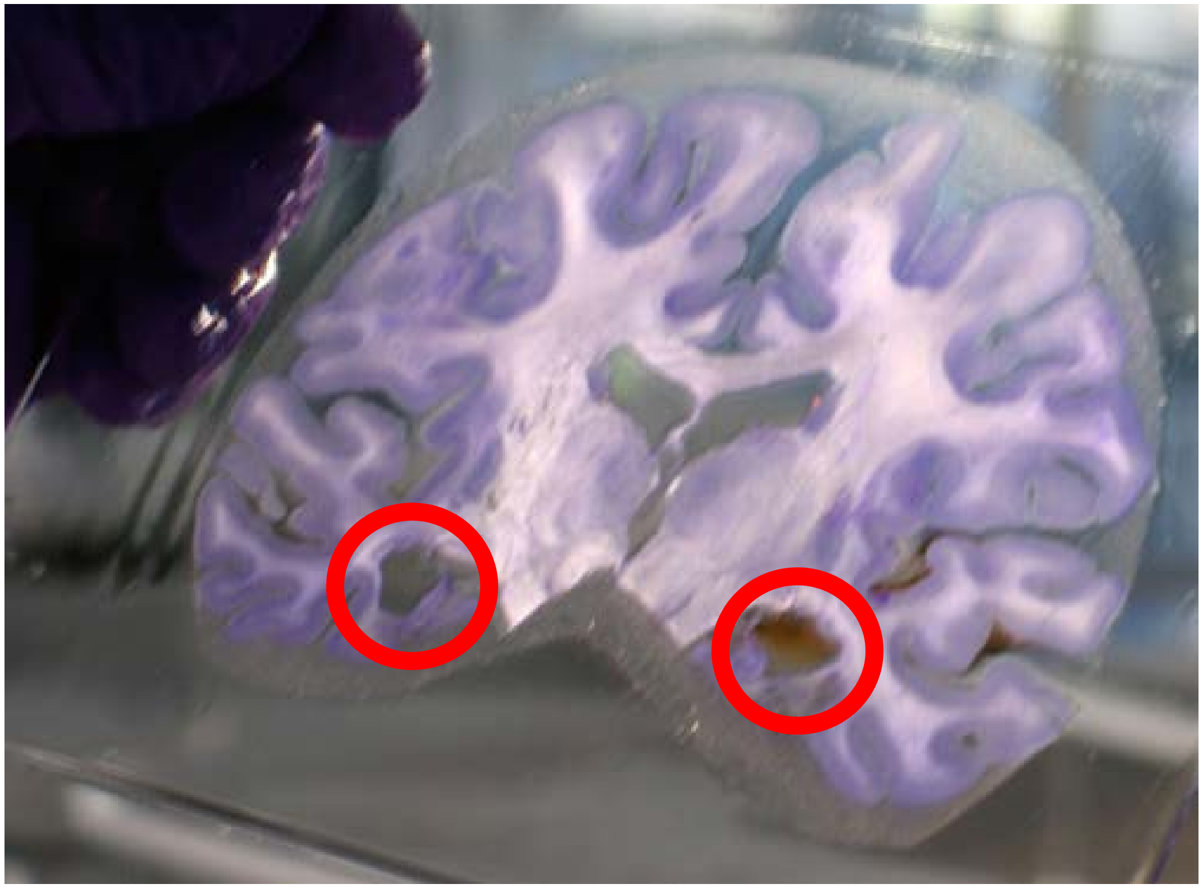
- Huge amount of visual processing until any external sensory information reaches the hippocampus
- In other senses (auditory, somatosensory) there is similarly complex processing upstream of the hippocampus – except olfactory inputs that reach the hippocampus much more directly (olfactory bulb → entorhinal cortex)
- Such high-level brain areas are expected to be notoriously difficult to understand: Presumably, responses must be extremely complex ?

Early ideas about hippocampal function (1920's, 30's, 40's)

- The hippocampus as part of the olfactory system (1920's) (rationale: there are strong *direct* inputs from the olfactory bulb to the entorhinal cortex, in both rat and monkey)
  - NOT TRUE: (i) Hippocampus receives multi-modal information; (ii) hippocampus exists also in anosmic animals totally lacking olfactory bubs, such as dolphins
- The hippocampus and emotional processing
  - <u>Papez circuit</u> (1937)
  - Hippocampus as part of the <u>Limbic System</u> (one of the structures along the limbus, or edge of the 4th ventricle)
    - NOT TRUE: The Limbic System is not really a unitary functional "system"
    - The Amygdala is important for emotional learning, but the hippocampus much less so

The hippocampus and memory (1950's)

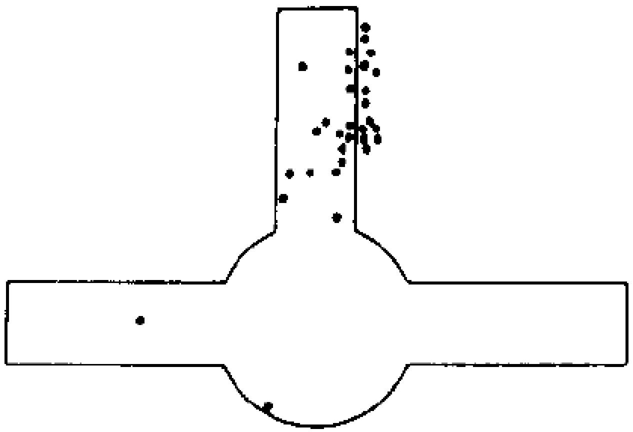
Henry Mollaison (H.M.), 1926-2008



- Patient H.M. developed severe anterograde amnesia after a surgery to treat his intractable epilepsy, during which large portions of his hippocampus, entorhinal cortex, and amygdala were removed bilaterally.
- H.M. taught the Neuroscience community that the hippocampus is crucial for memory.
- Which kind of memory? We will return to it later

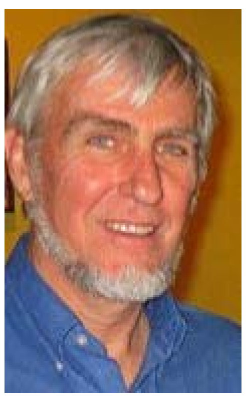
W. B. Scoville, B. Milner, *J Neurol Neurosurg Psychiatry 20, 11 (1957)*

40 years ago – A surprisingly simple discovery for such a high-level brain area: Hippocampal place cells in rats



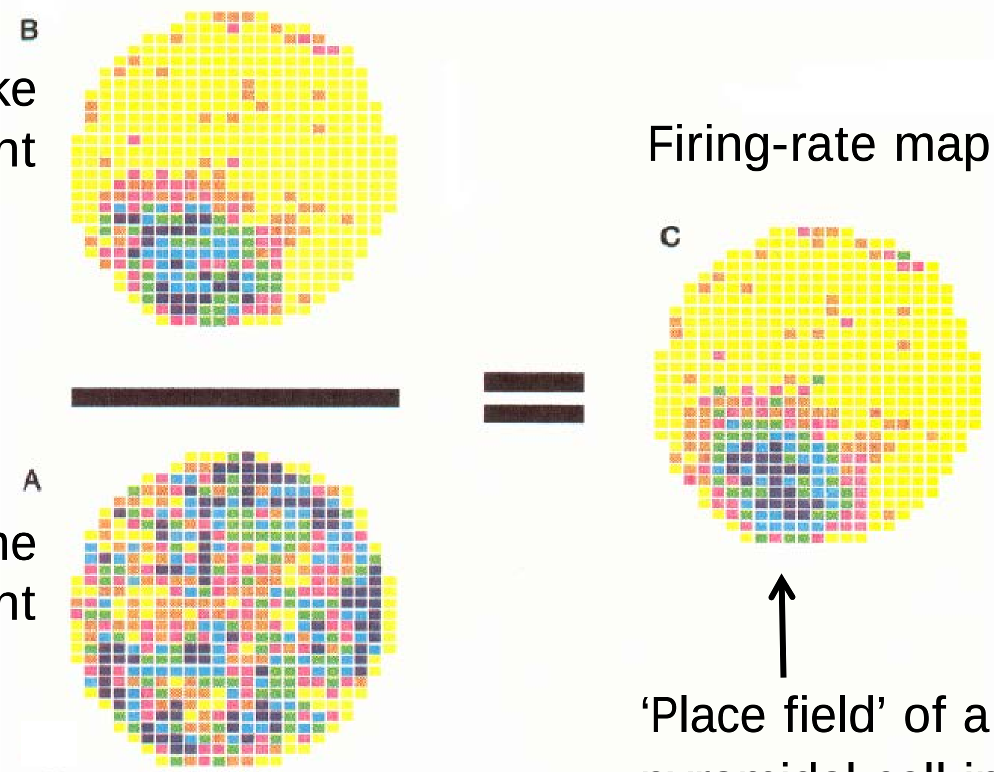
(O'Keefe & Nadel 1978)
(O'Keefe & Dostrovsky 1971)

John O'Keefe



Spike count

Time spent



Firing-rate map

'Place field' of a pyramidal cell in rat hippocampus

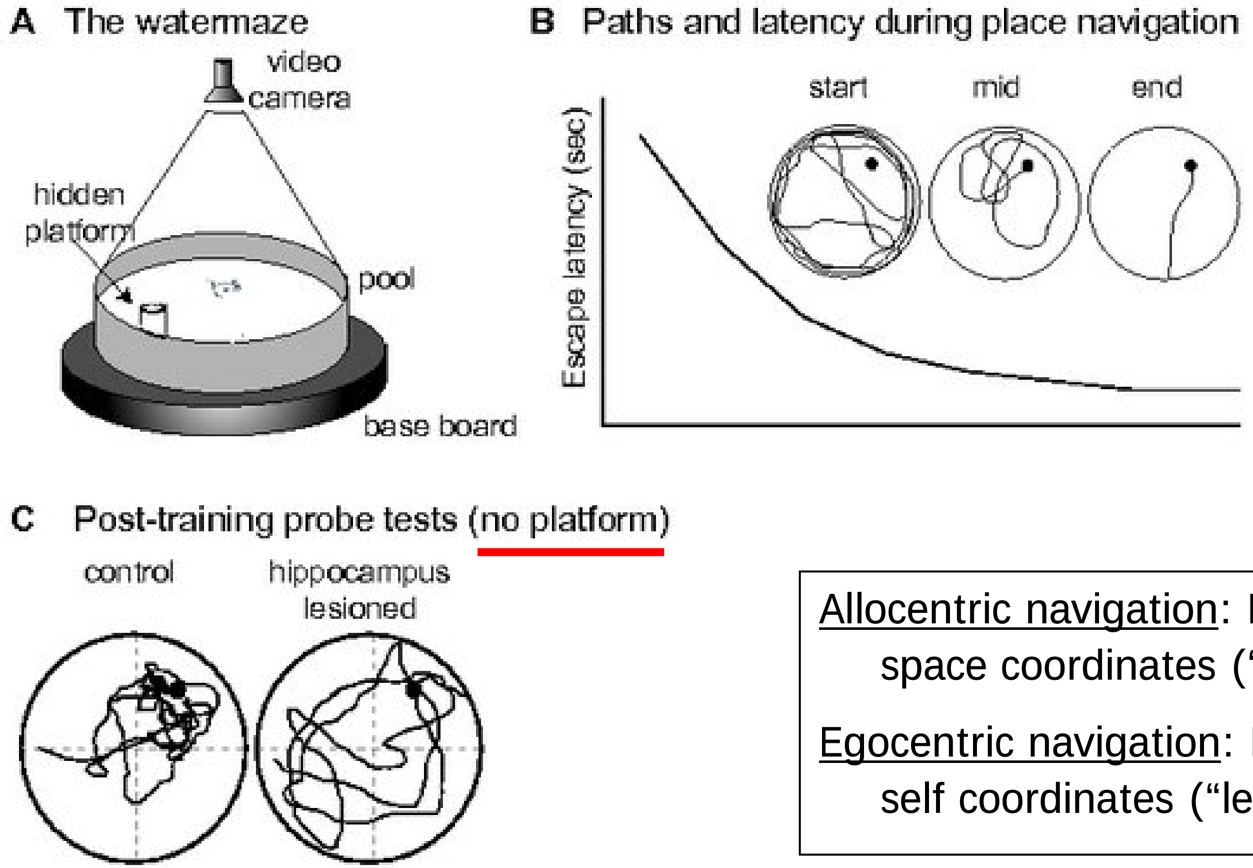
(Muller et al. 1987)

Movie of a rat hippocampal place cell in action

(Courtesy of Colgin, Moser & Moser)

Bilateral hippocampal lesions impair allocentric navigation

Richard Morris
(original finding: 1982)

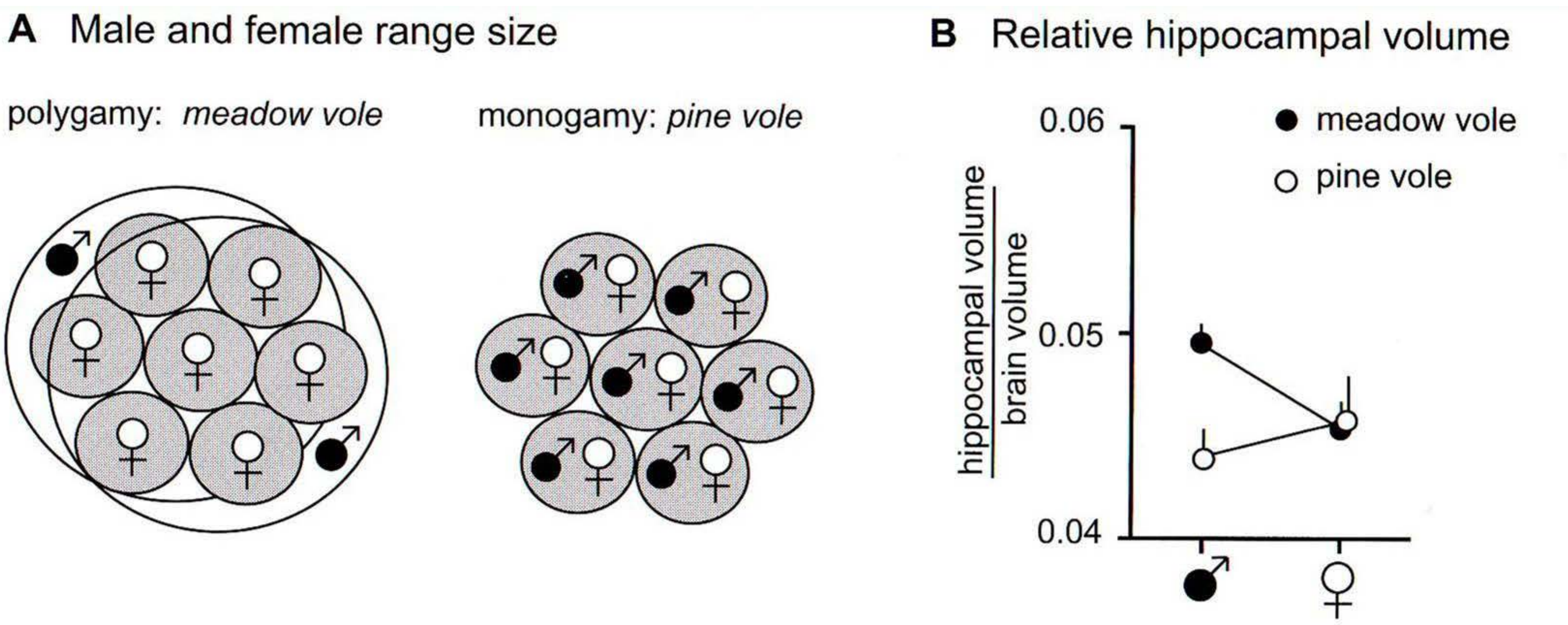


<u>Allocentric navigation</u>: Based on absolute-space coordinates ("north/south")

<u>Egocentric navigation</u>: Based on body's self coordinates ("left/right")

- These deficits of spatial memory occur after lesions in <u>dorsal</u>, not ventral hippocampus
- In rats <u>over-trained</u> for months, animals do show improvements in probe tests after hippocampal lesions, suggesting the memory became (in part) independent of the hippocampus

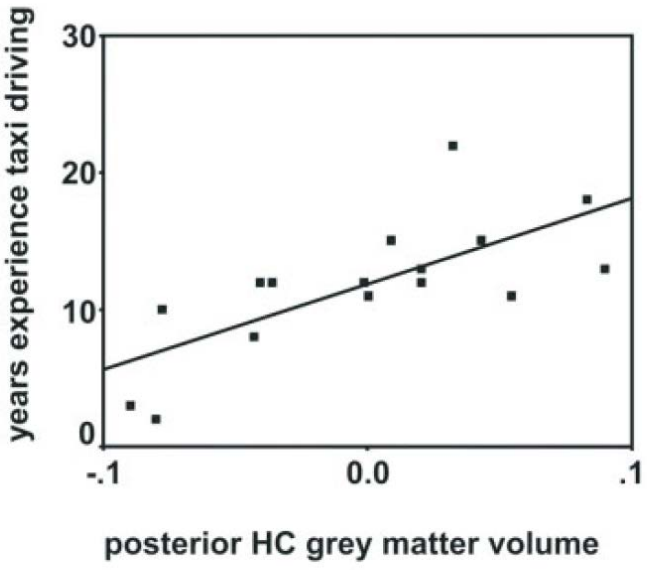
Hippocampal volume correlates with navigational load in rodents



Hippocampal volume correlates with navigational load in humans

Volume of posterior hippocampus in humans (equivalent to dorsal hippocampus in rats):

- Larger in London taxi drivers than in age-matched controls.
- Correlated with time spent as a taxi driver.
- Larger in Taxi drivers than in experience-matched Bus drivers.
- In Bus drivers, no correlation with experience was found.



Maguire et al., *PNAS* (2000)

Maguire et al., *Hippocampus* (2006)

Interpretations:

- The hen and the egg problem: Does posterior hippocampus grow with experience (plasticity), or is a large hippocampus needed in order to do well and “survive” for many years in the demanding profession of a London taxi driver?
- Navigation based on a cognitive-map, allocentric strategy (taxi drivers) requires/causes a larger hippocampus than route-based, egocentric navigation (bus drivers) ?

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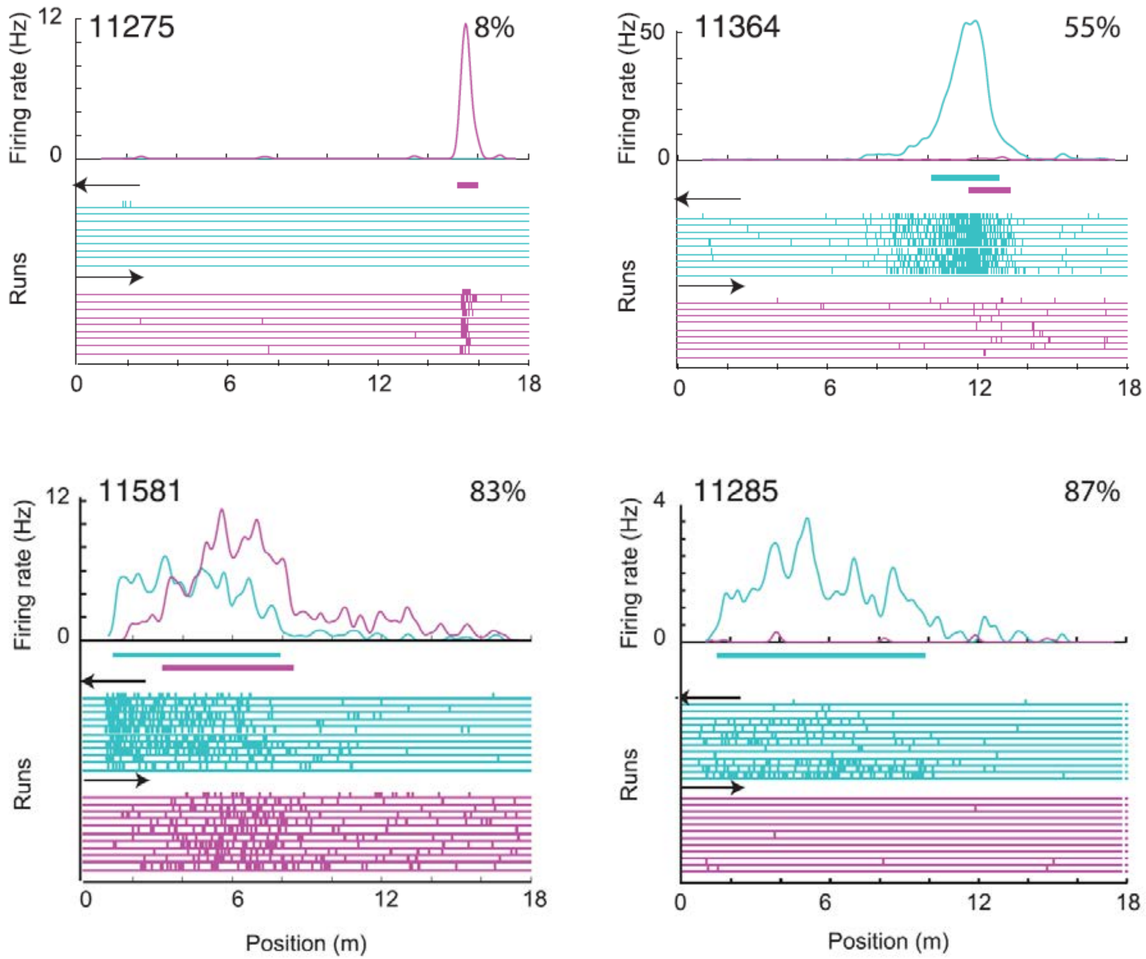
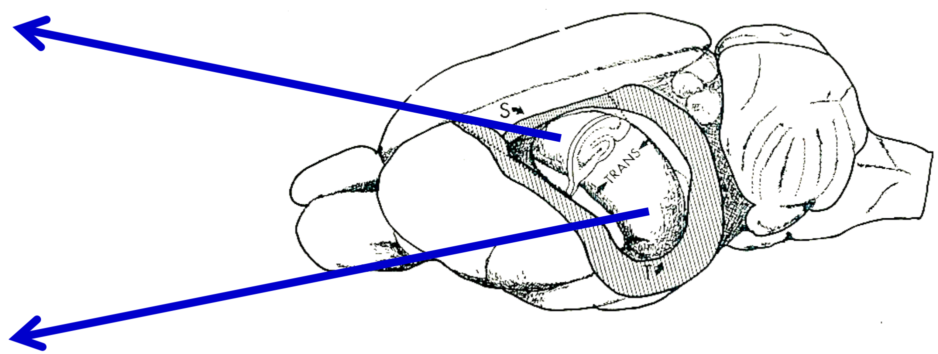
Place fields increase in size along the dorso-ventral (septo-temporal) axis of the hippocampus





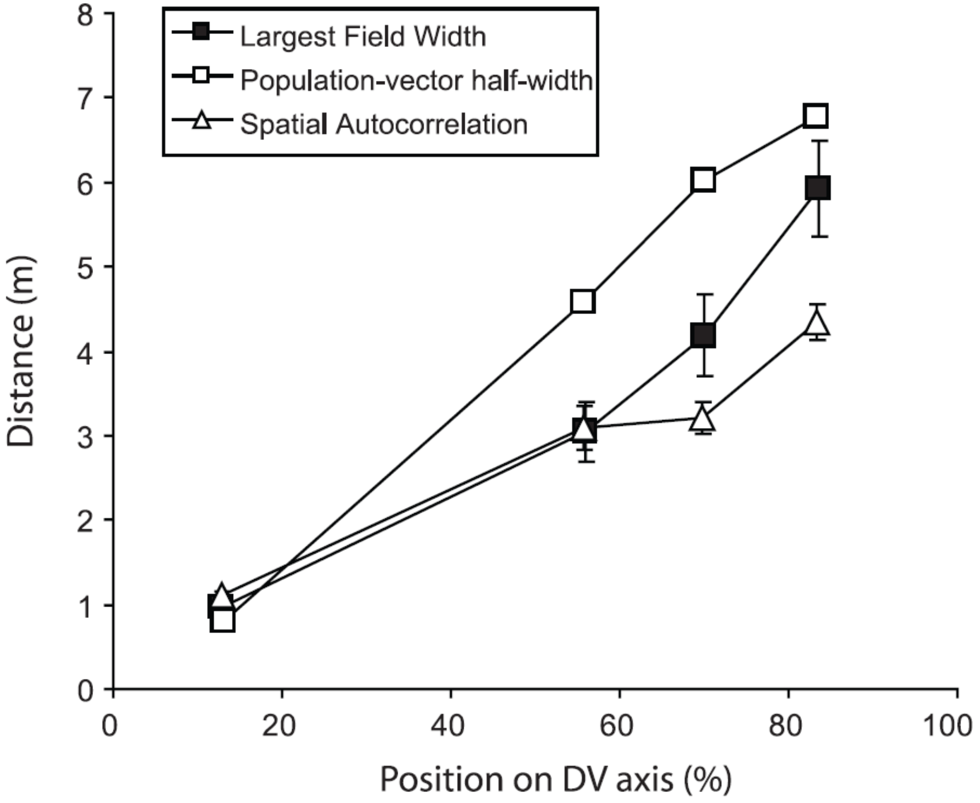
2 cells in dorsal hippocampus

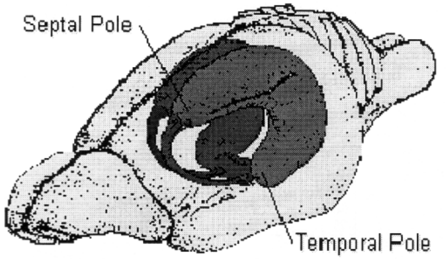
2 cells in ventral hippocampus

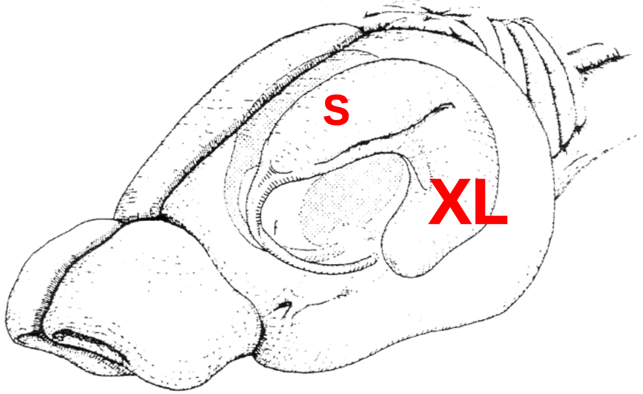
Kjelstrup et al., *Science* (2008)

NOTE the <u>uni-directional firing on this 1-D track</u> (cyan vs. magenta)

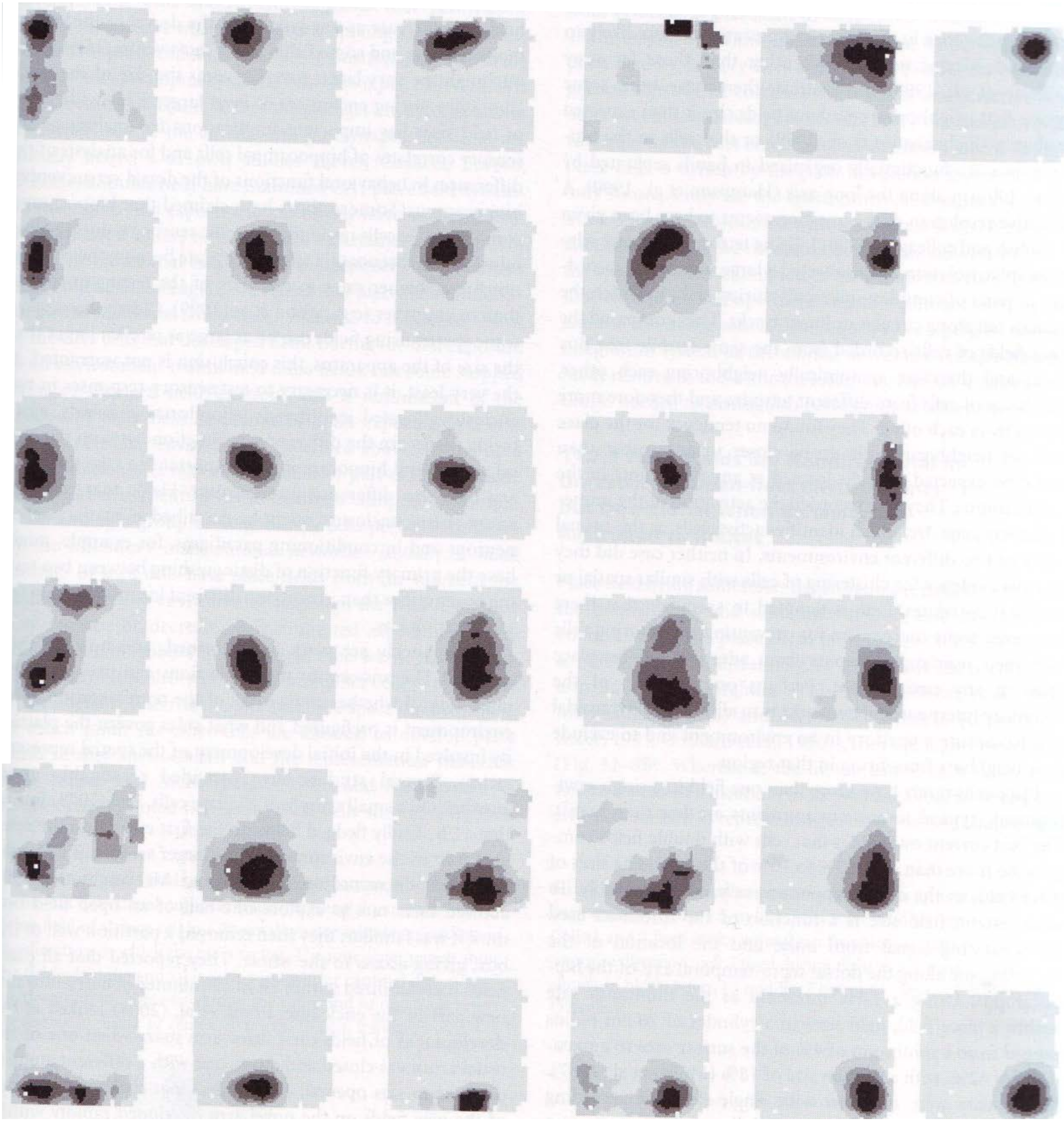
Place fields increase in size along the dorso-ventral (septo-temporal) axis of the hippocampus







The place fields of hippocampal place cells tile the environment



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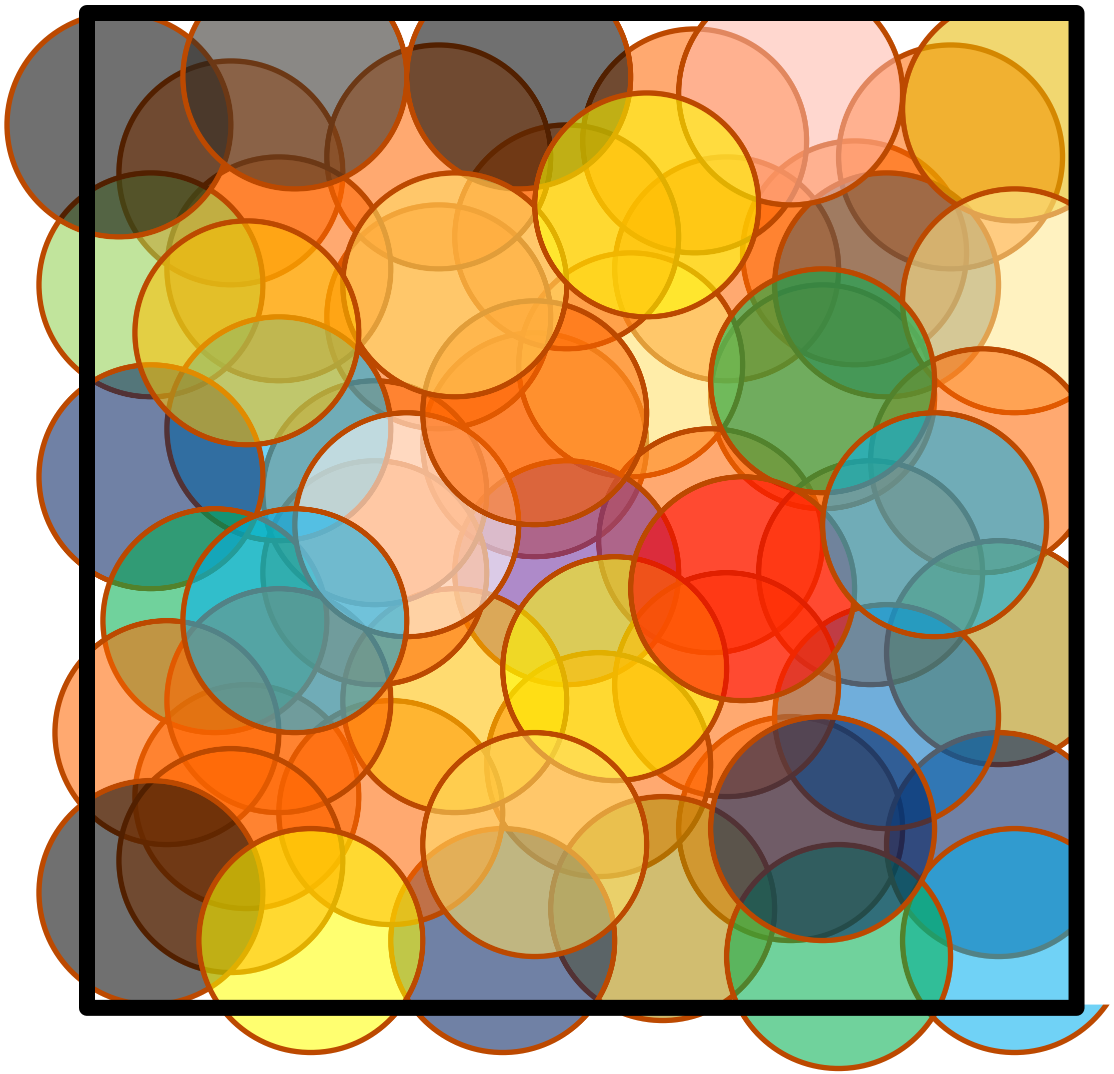
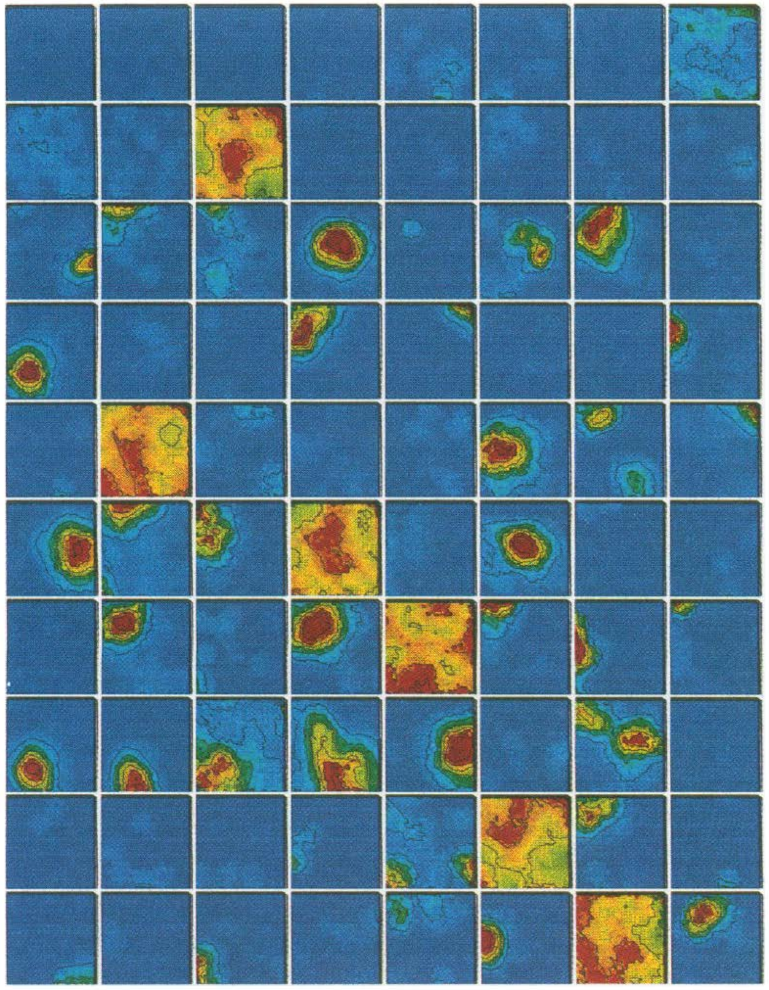
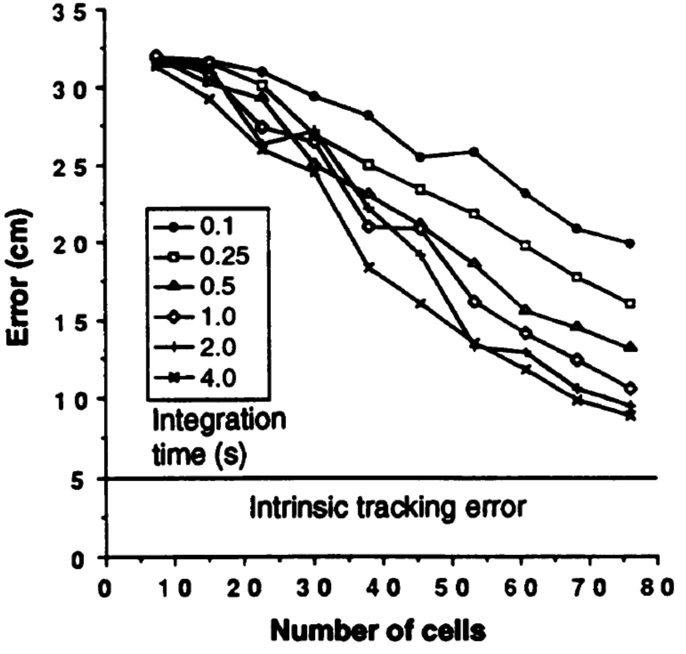


The rat's location can be reconstructed from the activity of an ensemble of simultaneously-recorded place cells

Tetrode recording of 80 neurons simultaneously



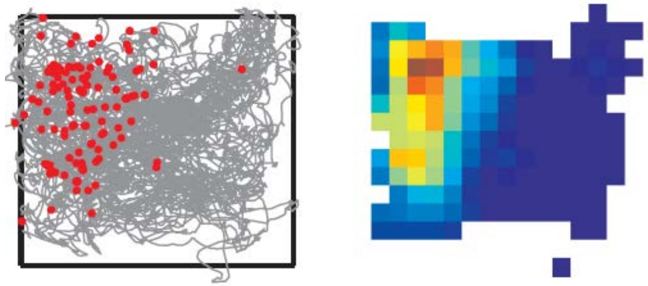


Putative pyramidal neuron (place cell)

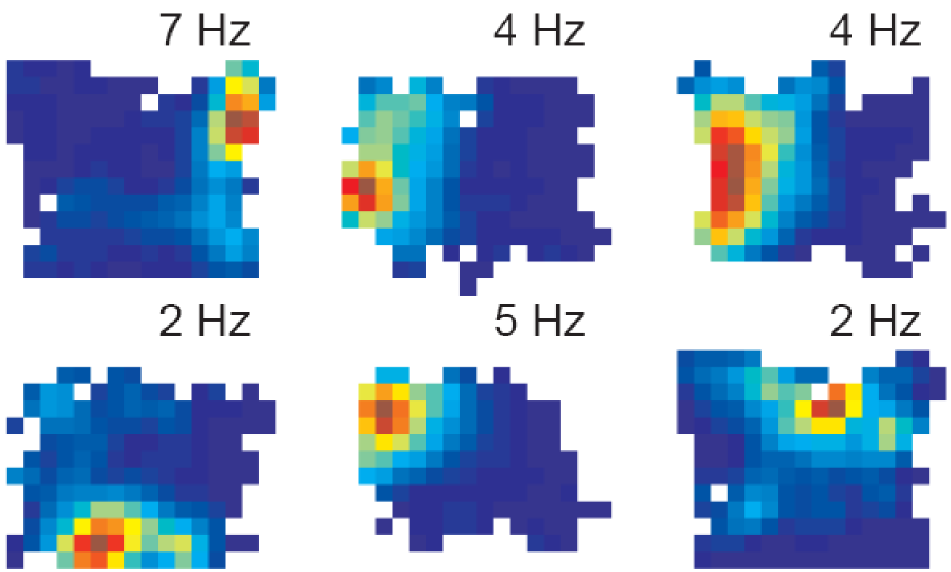
Interneuron (very little spatial modulation)

Wilson and McNaughton, *Science* (1993)

Place cells exits also in other species: Big brown bats



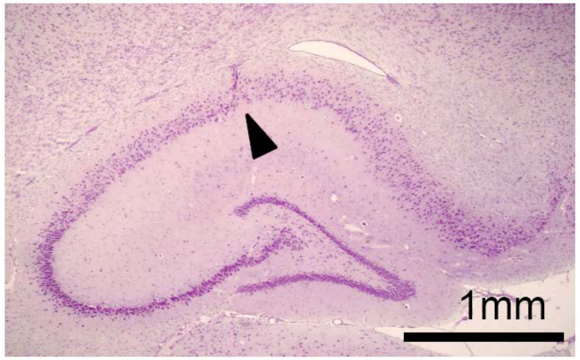
A single cell

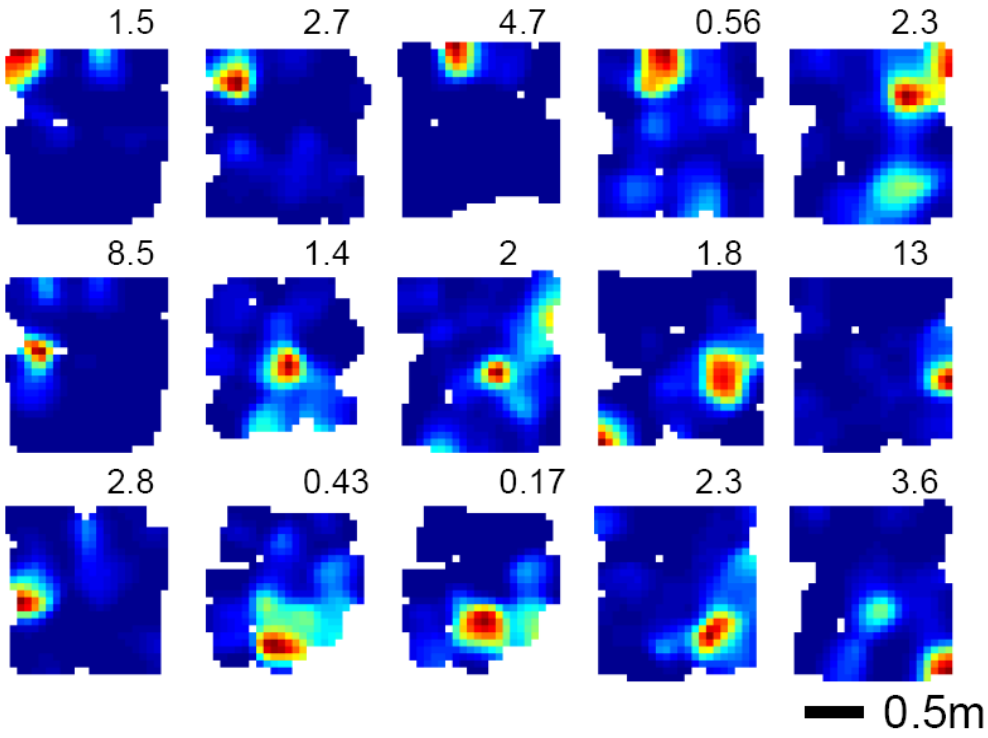


More examples
of place fields
from 6 neurons

Ulanovsky & Moss,
Nature Neurosci. (2007)

And in another bat species: Egyptian fruit bat





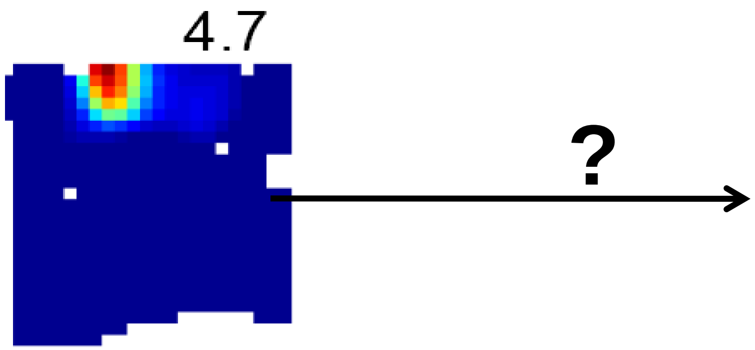
Examples of hippocampal place fields from our current study species, the Egyptian fruit bat.

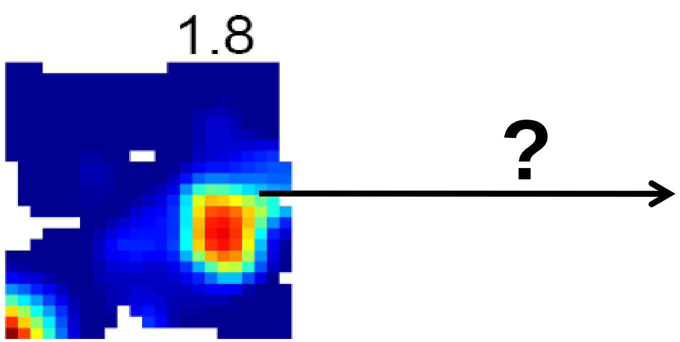
As in rats, these place fields tile the environment, and represent the animal's spatial location.

Yartsev, Witter, Ulanovsky
Nature (2011)

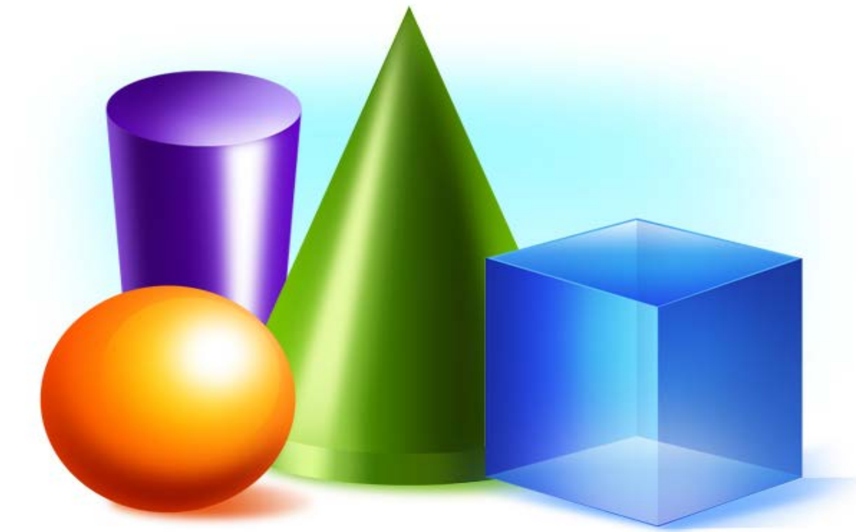
How would 3-D space be represented by place cells?

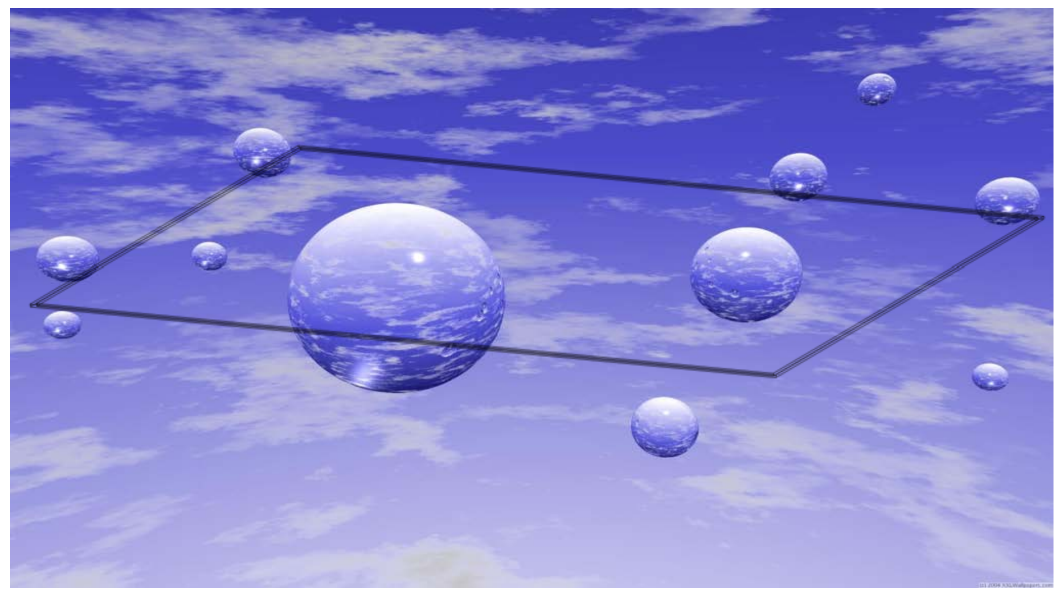
2-D





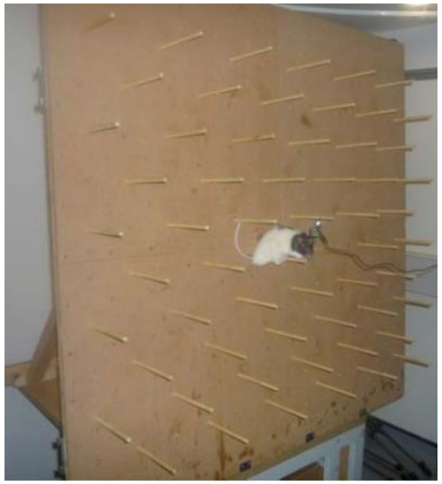
3-D





Previous attempts to address the question of 3-D spatial representation in the mammalian brain

On Planet Earth



Hayman et al, 2011

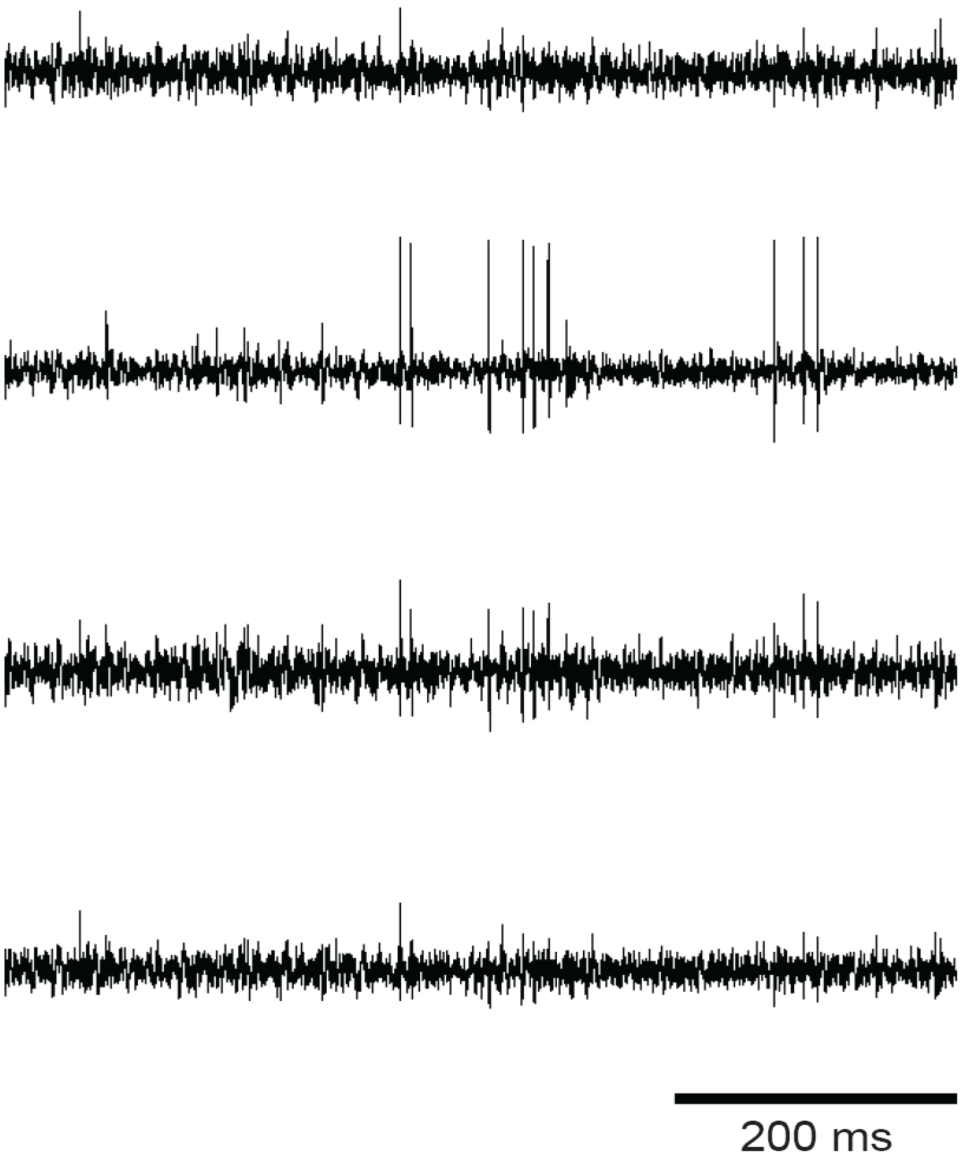
In Outer Space

Knierim et al, 2000

<u>Problem</u>: Animals were moving on <u>2-D</u> planes → could not provide answers regarding volumetric 3-D space.

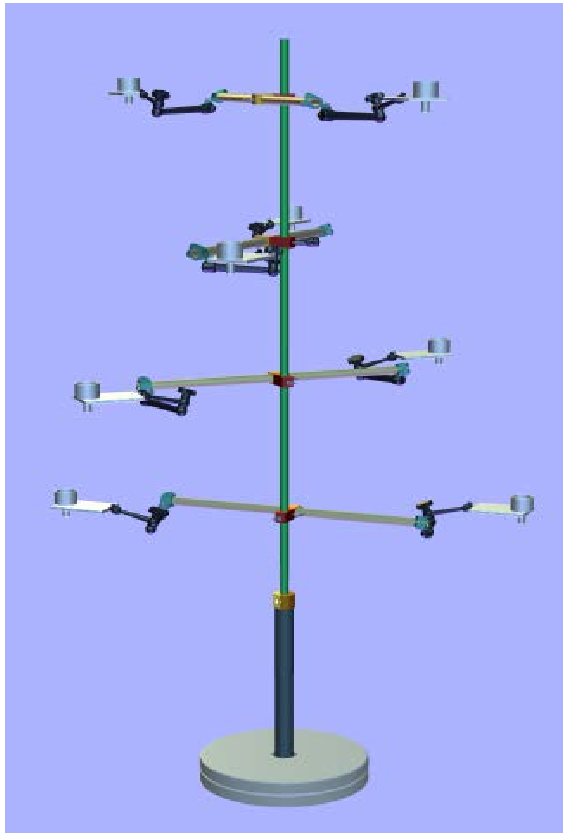
<u>Solution</u>: Use an animal that can move freely in 3-D space.

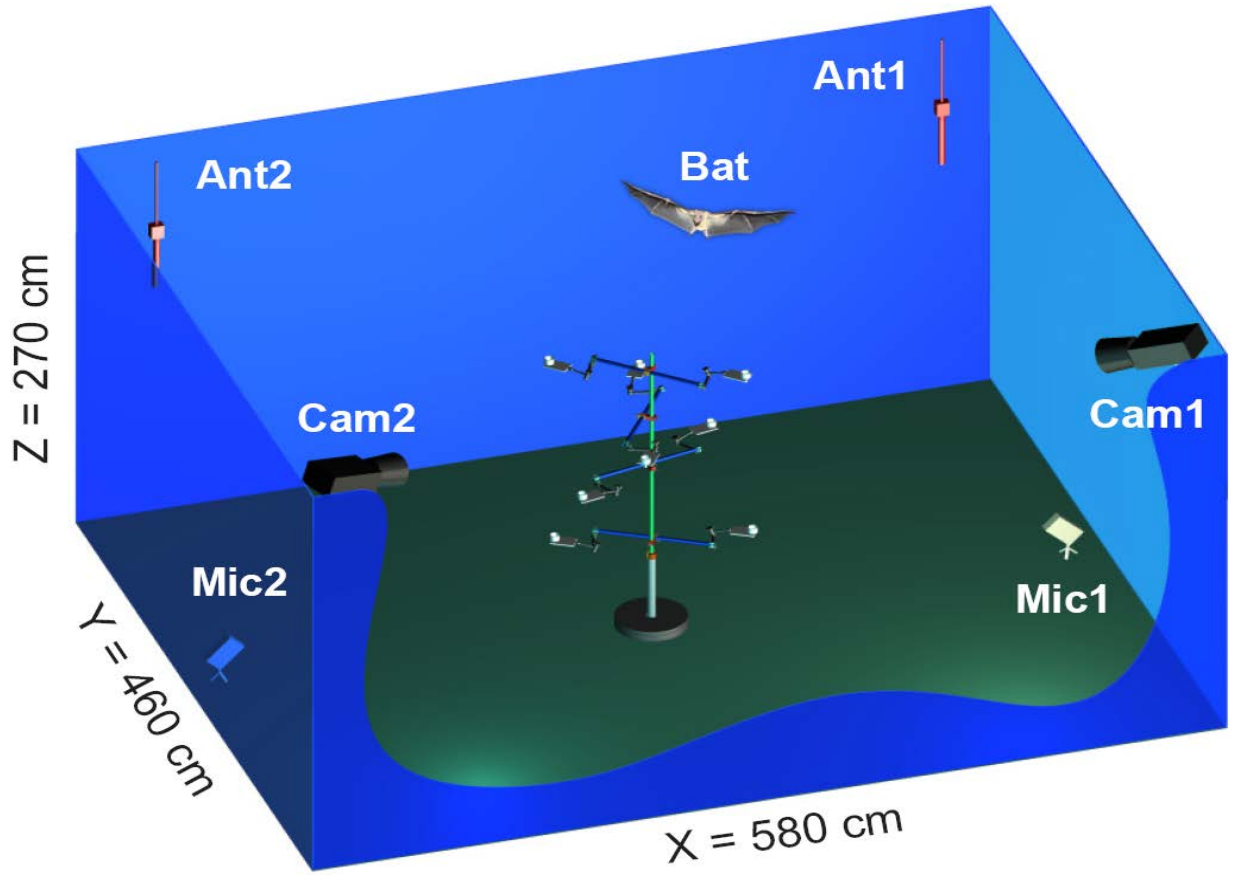
Telemetric recordings from the hippocampus of a flying bat



Yartsev & Ulanovsky
Science (2013)

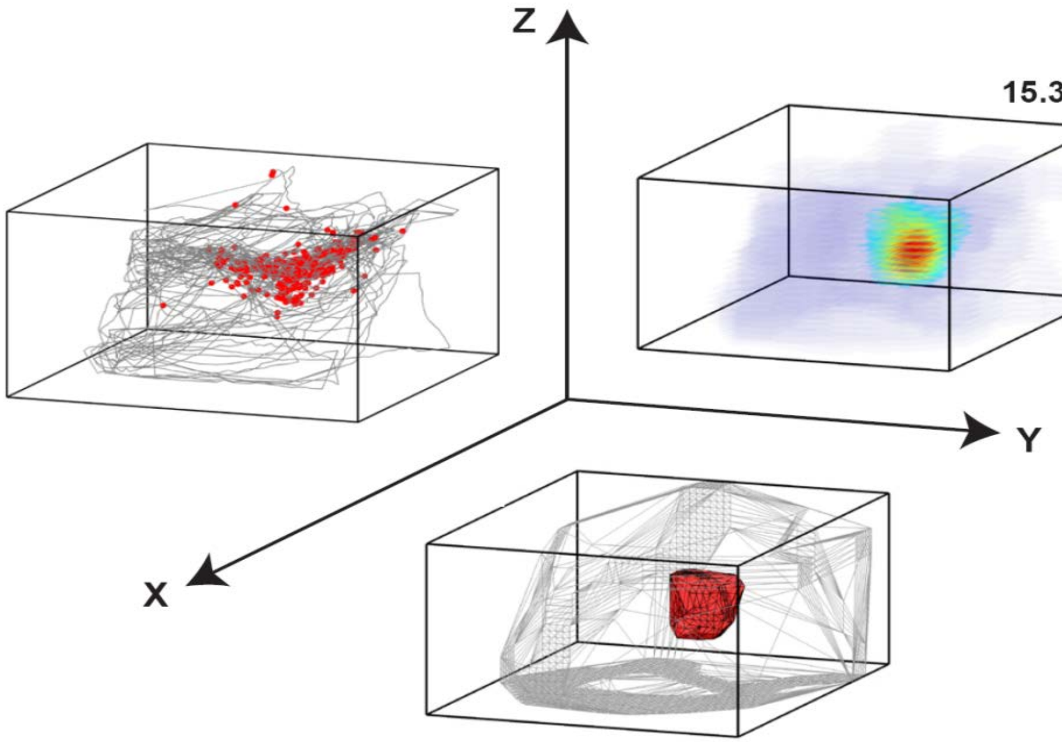
Creating a naturalistic foraging task in the lab





- **2 cameras → 3-D positional reconstruction (~1-cm accuracy)**

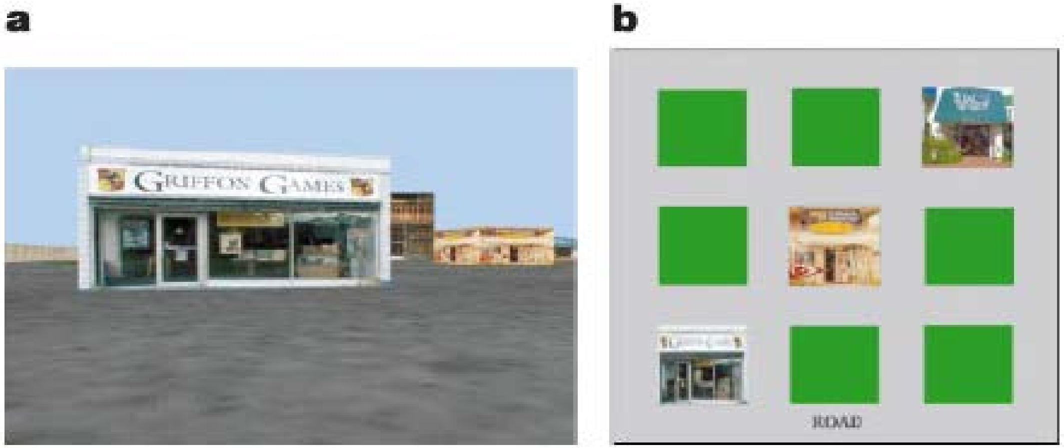
3-D place cells in bats

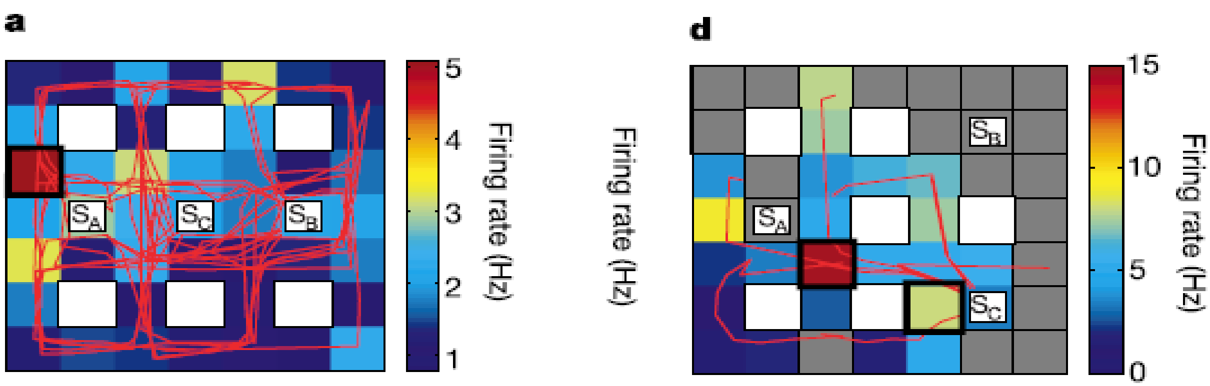


- **3-D place fields are spherical in shape (<u>isotropic</u>): Same resolution in all directions.**
- **3-D place fields tile space <u>uniformly</u>.**

Yartsev & Ulanovsky
Science (2013)

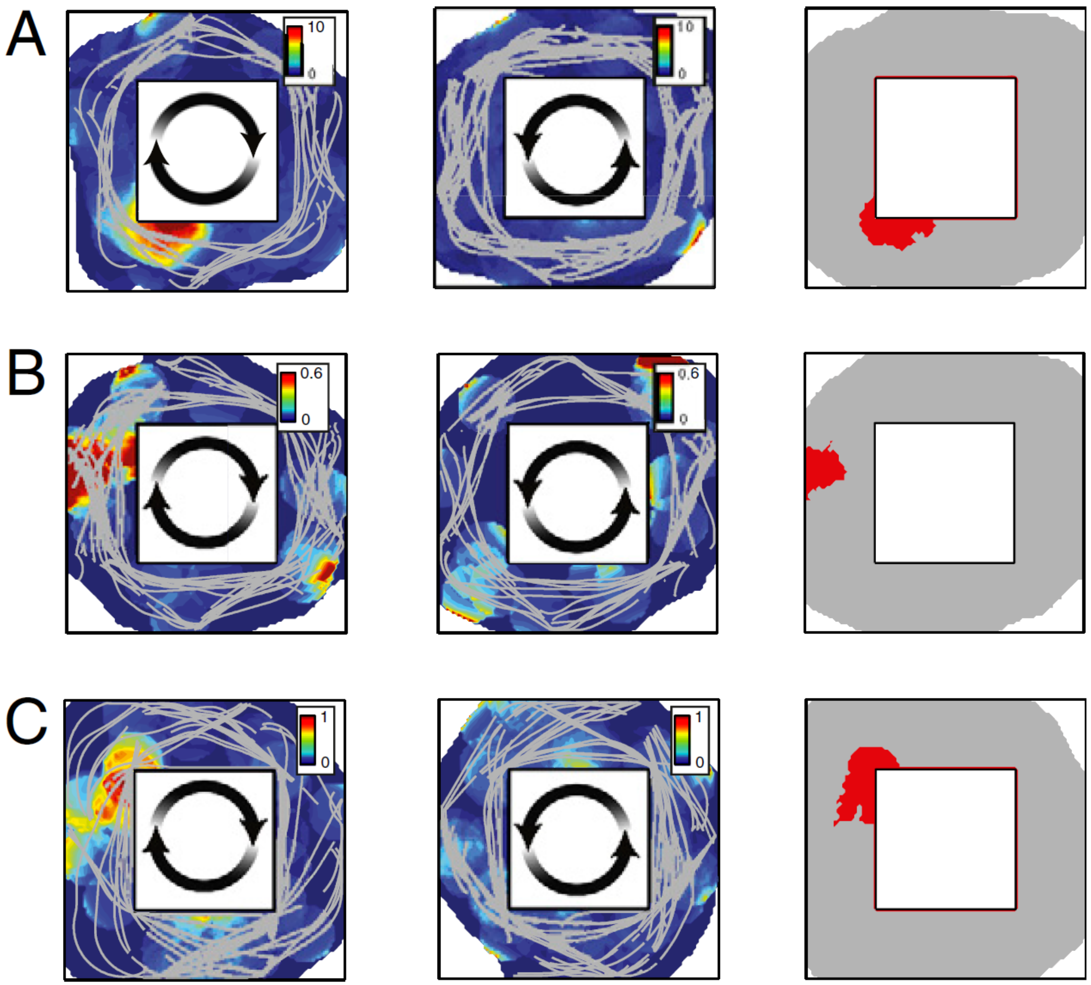
Place cells in humans





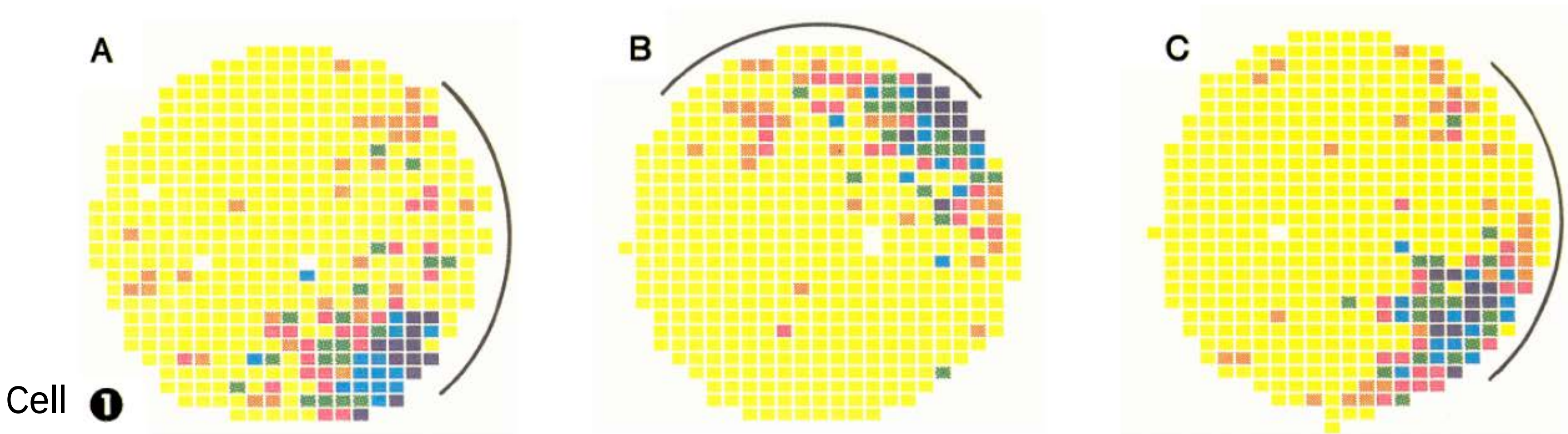
Ekstrom et al, *Nature* (2003)

Place cells in humans



Jacobs et al, *PNAS* (2010)

Place fields rotate with the rotation of prominent external landmarks

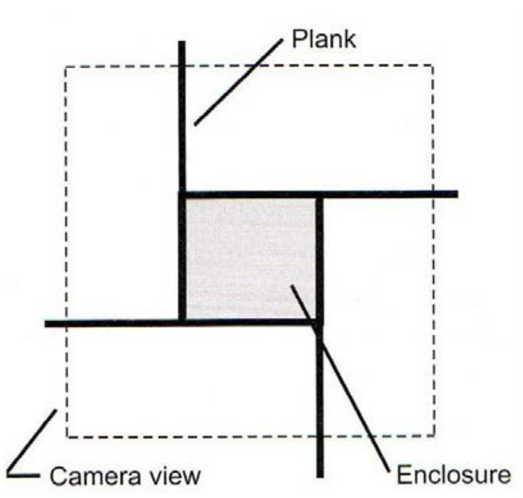


Rotation of cue card

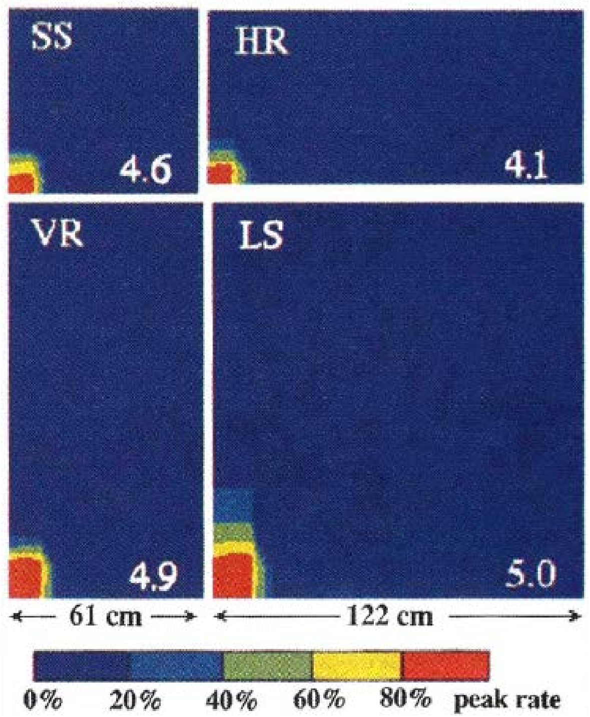
(Muller and Kubie 1987)

Note that this place field is quite <u>stable</u>
(session A vs. session C)

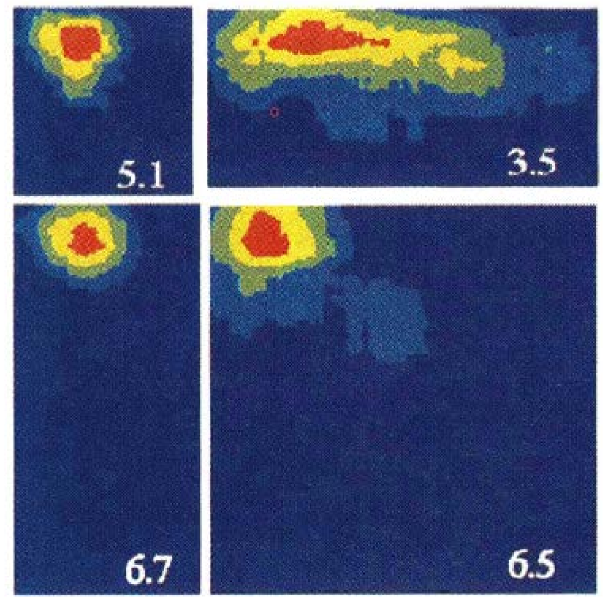
Place fields are affected by manipulations of the environment’s geometry



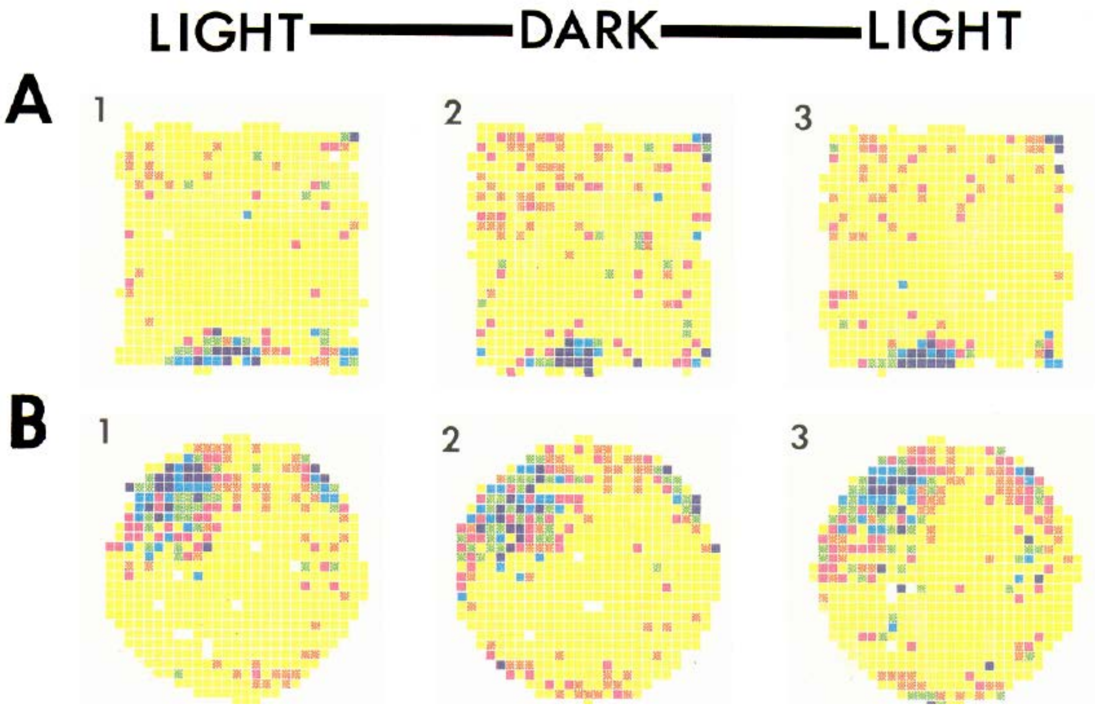
Cell 1



Cell 2



Place fields, however, are not purely visual, and are not even modality-specific – they are multi-modal

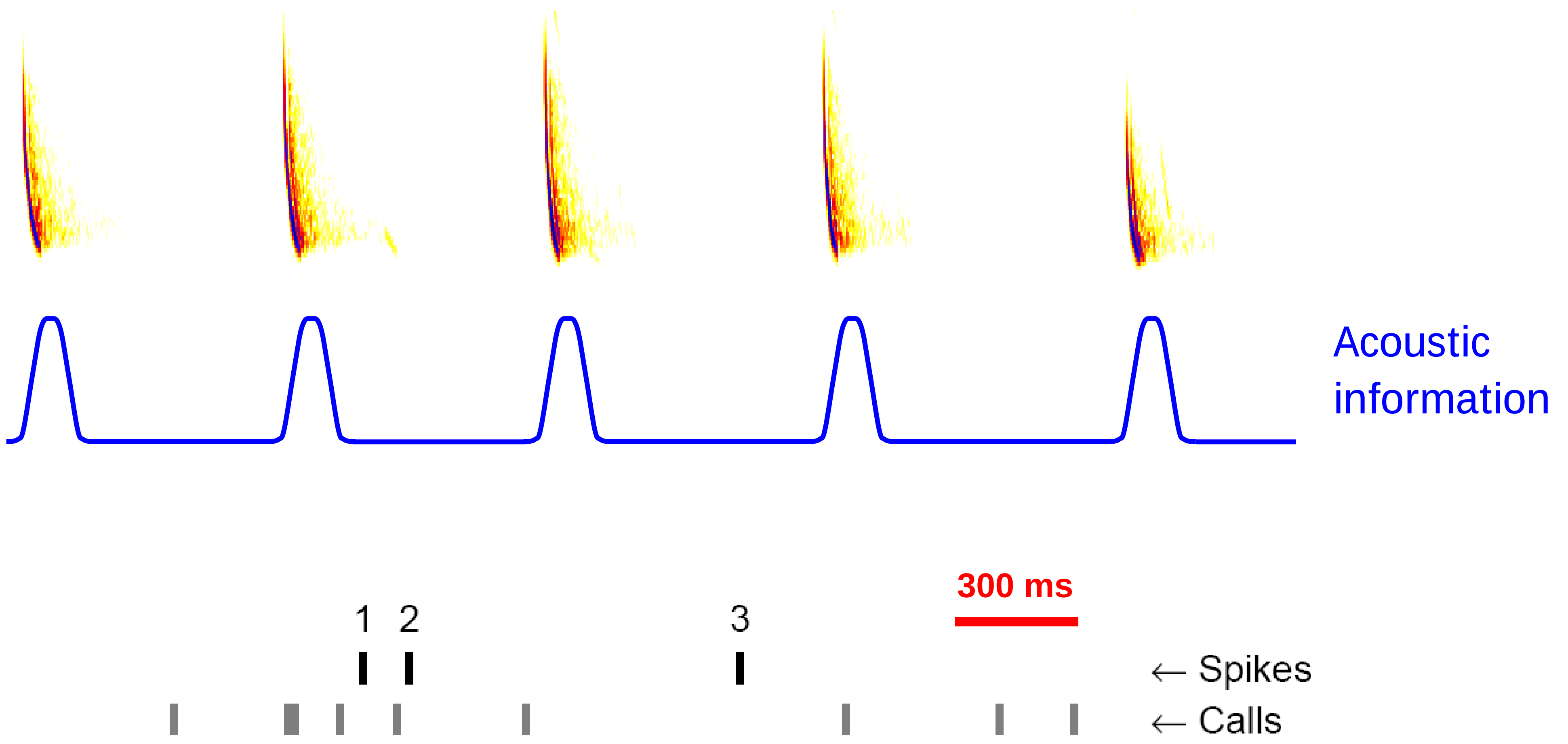


G. J. Quirk, R. U. Muller, J. L. Kubie *(1990)*

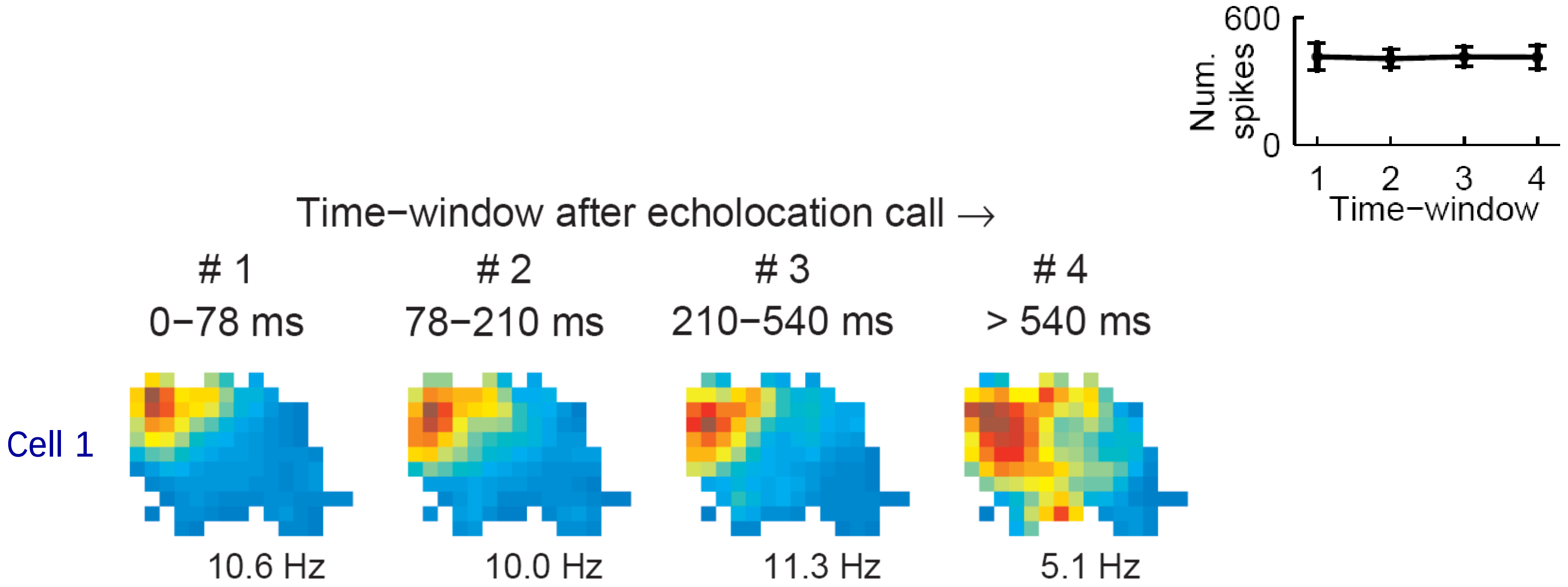
- In this experiment, the place-fields were likely determined mostly by <u>odors</u> on the floor
- In a later, very similar experiment (Save et al. 2000), when lights were turned off *and* odors were thoroughly cleaned, place-cell firing was severely disrupted

Are place fields affected by the timing of sensory inputs?

The case of bat sonar calls

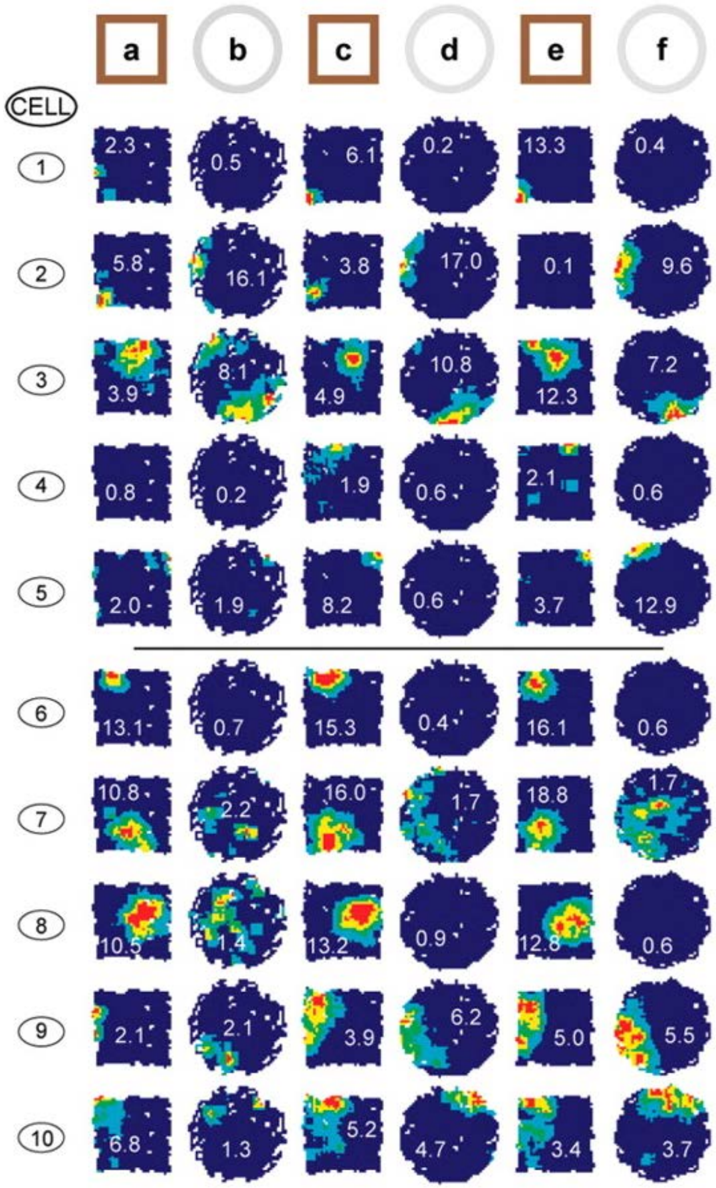


Rapid dynamics of place-fields after each sonar call in bats



Ulanovsky & Moss,
Hippocampus (2011)

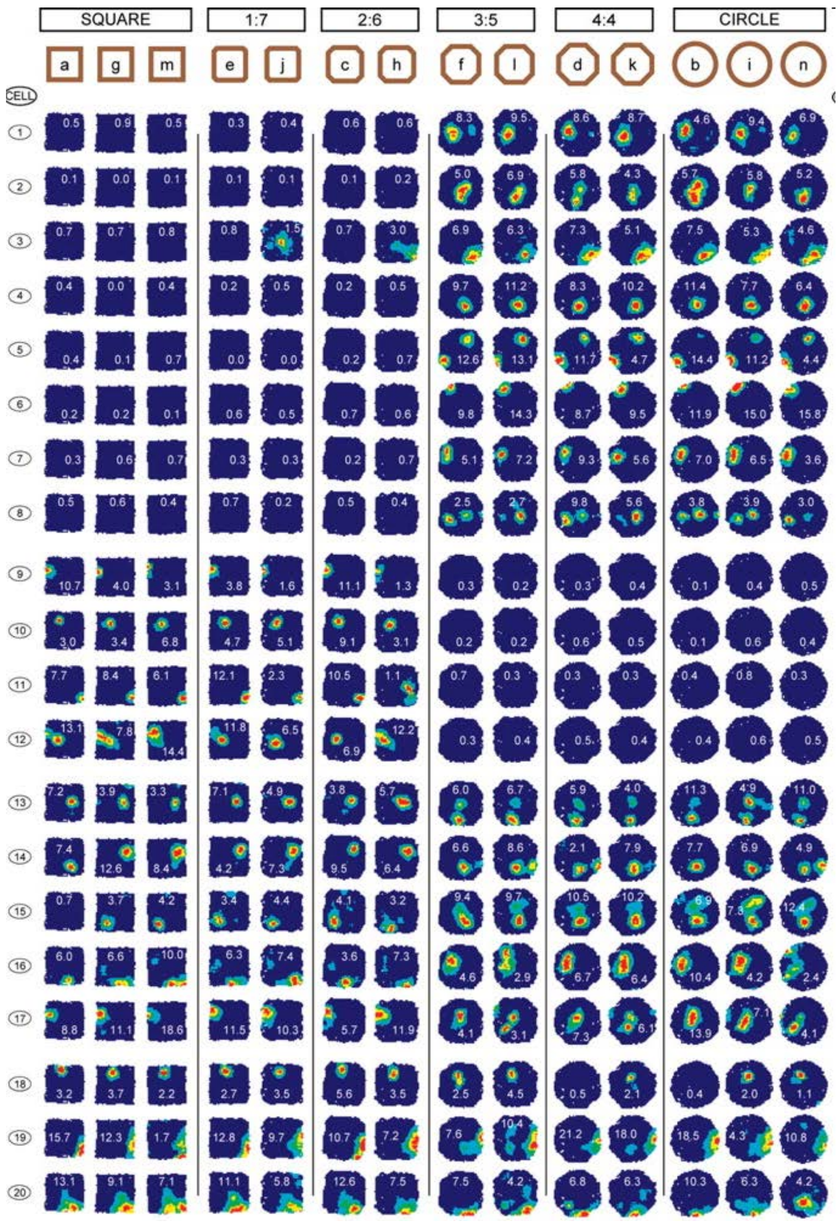
Multiple maps are stored simultaneously in rat hippocampus



<u>“Remapping”</u> between representations of square and circular environments.

Wills et al., *Nature* (2005)

Multiple maps are stored simultaneously in the hippocampus

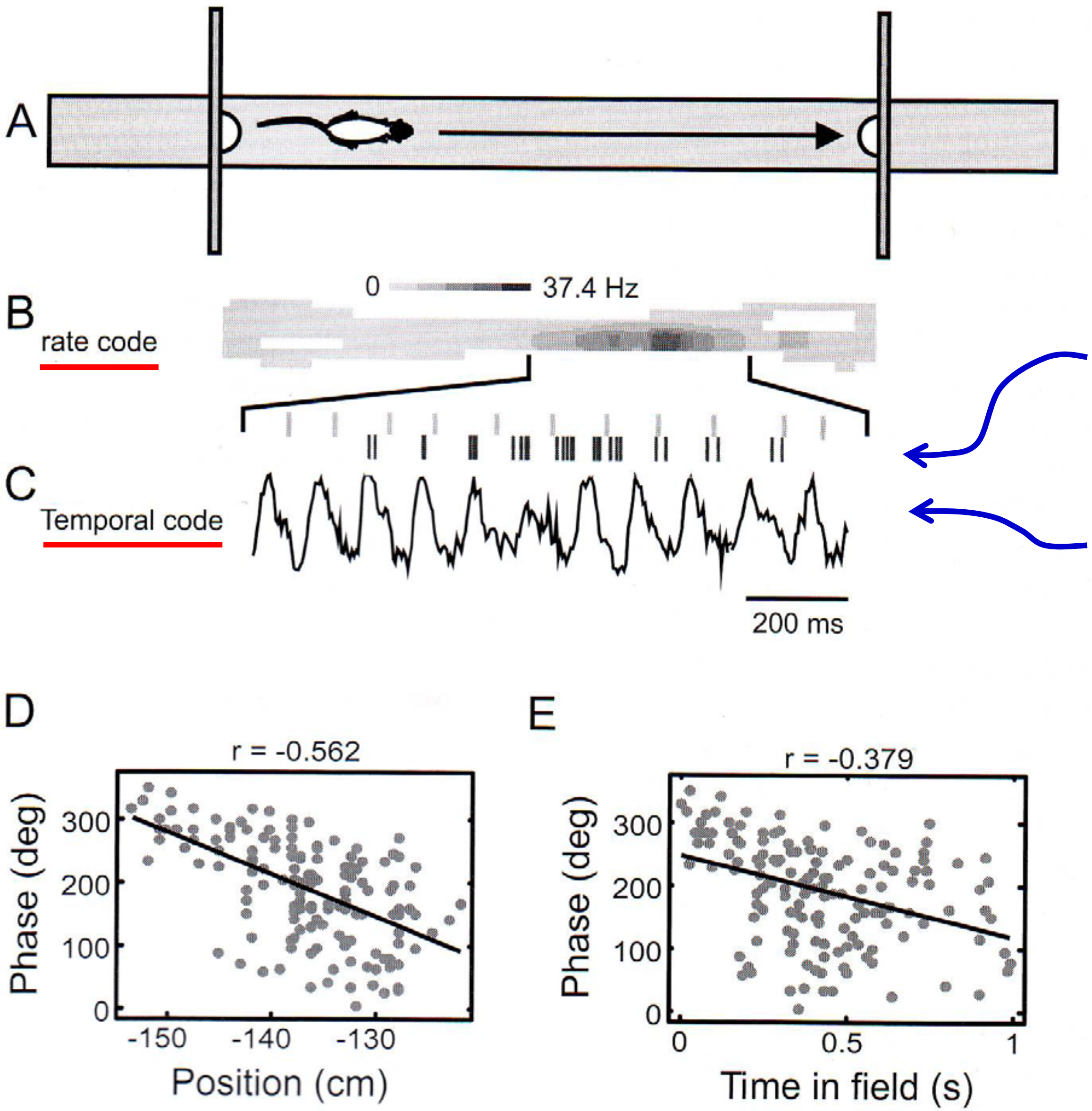


Abrupt **phase transition** between square-like and circle-like representations in intermediate octagonal environments: Evidence for **attractor dynamics** in the hippocampal network.

Attractor neural network models are useful as memory models – and we will come back to memory later on.

Wills et al., *Nature* (2005)

Temporal coding of location: Theta phase precession

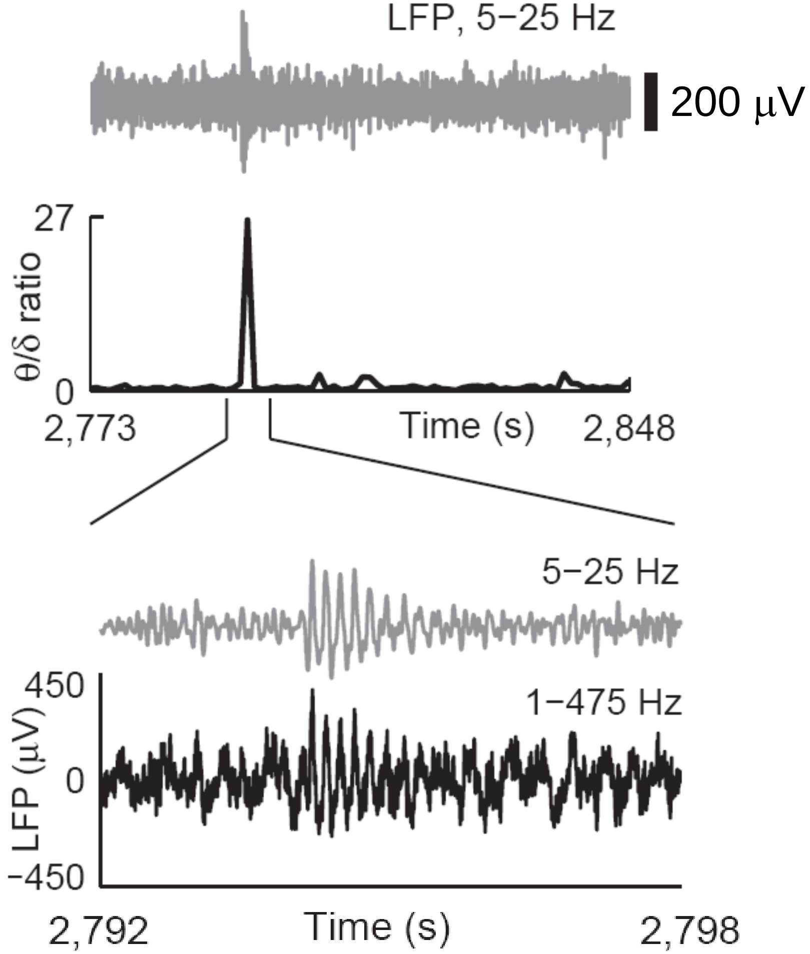


<u>"Theta Phase precession"</u>: Place cells are firing at progressively earlier and earlier phases of the cycle of the **<u>theta oscillation</u>**, as the animal runs through the place field.

Thus, spike phase relative to the theta oscillation provides information about the animal's position (**<u>temporal code</u>**), on top of the information from the place-field (**<u>rate code</u>**).

Theta oscillation in bats is very different, casting doubt on the usefulness of theta-based temporal coding of location

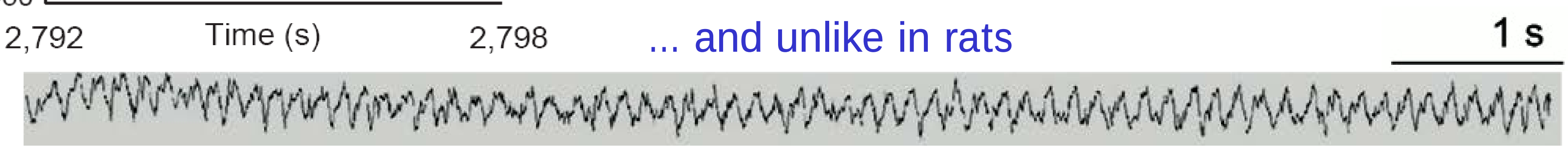
Short theta-bouts in bats



Like in humans...

(Cantero et al. 2003)

... and unlike in rats

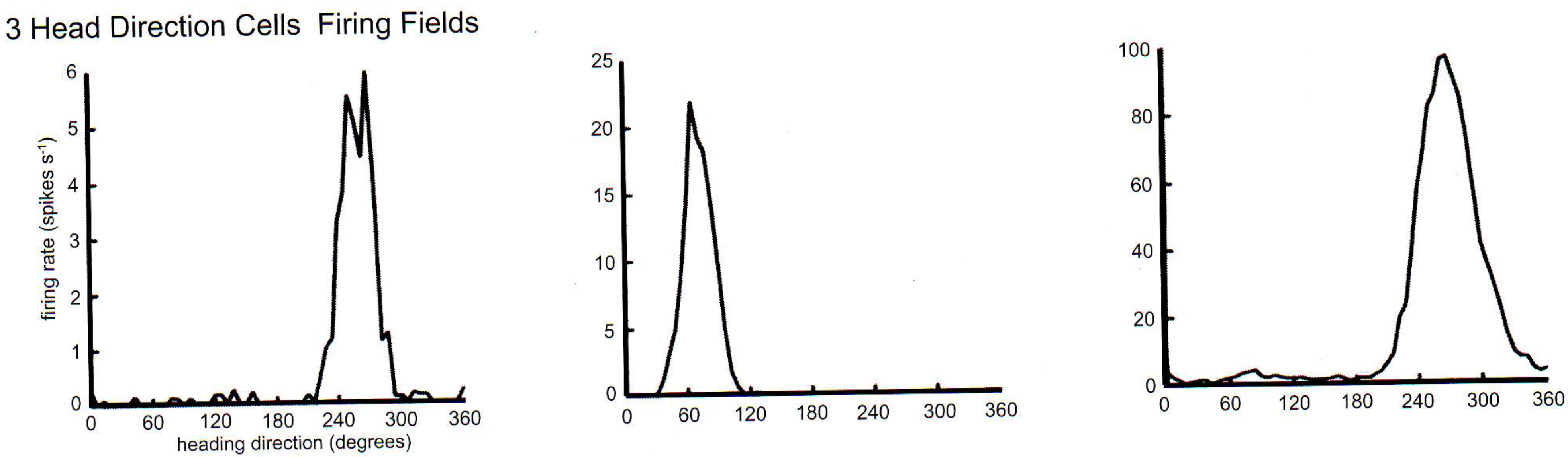


(Hollup et al. 2001)

Outline of today's lecture

- Hippocampus: Introduction and early discoveries
- Spatial maps in the hippocampus and related regions:
    - Place cells
    - **Head direction cells**
    - Grid cells
- *Intermezzo*: Structure-function relations in the hippocampus
- Beyond the cognitive map: Hippocampus and memory
- Open questions

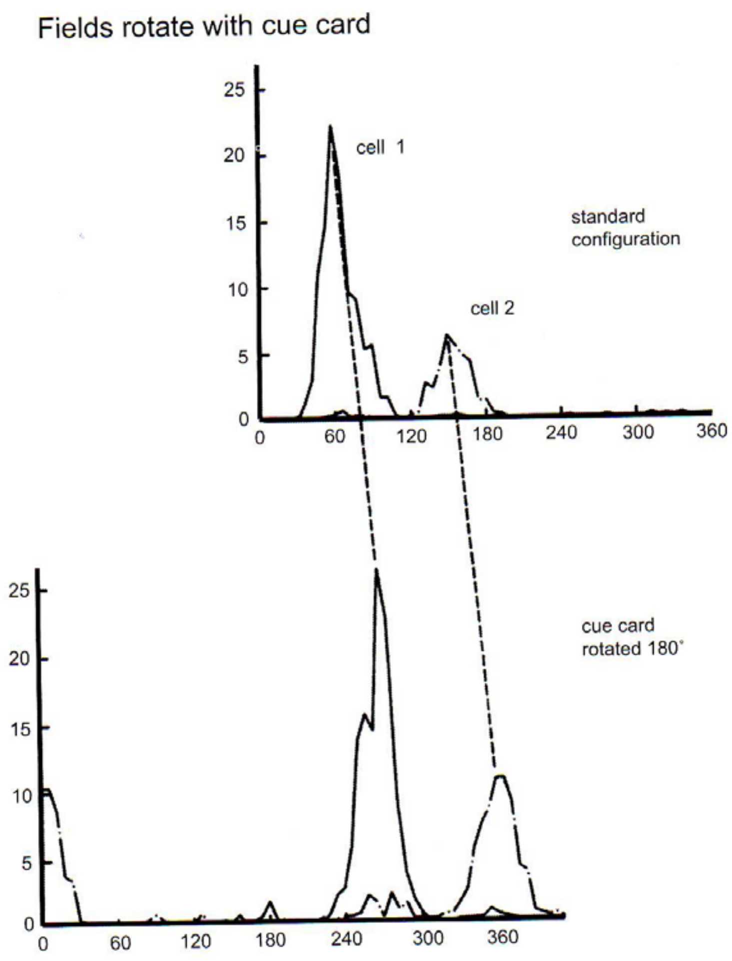
Head direction cells in dorsal presubiculum



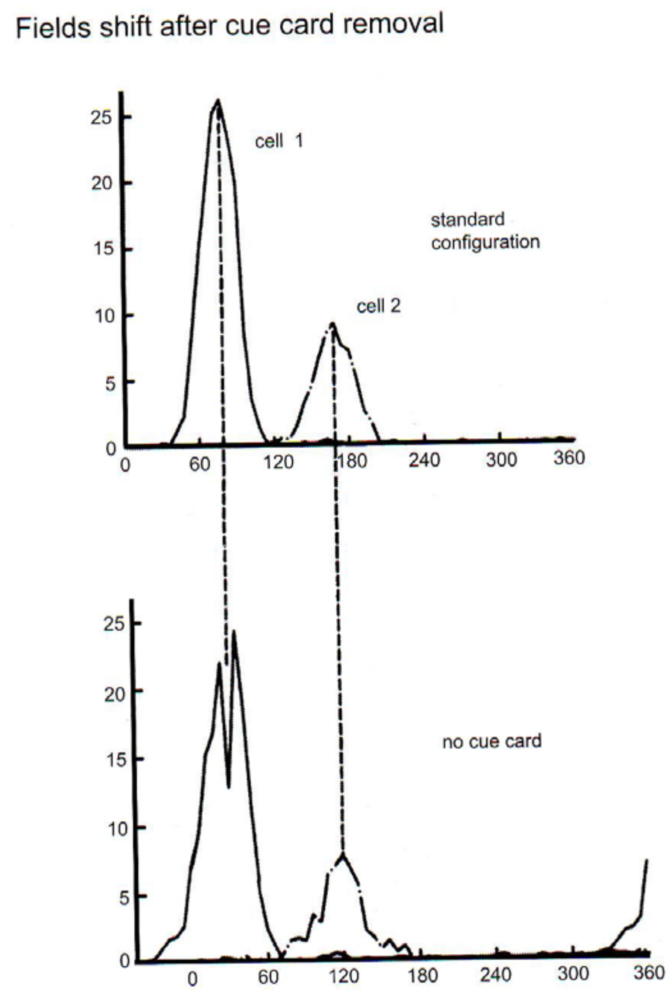
- Head direction cells are found in the dorsal presubiculum, anterior thalamus, medial entorhinal cortex, and in several other brain areas adjacent to the hippocampus.
- These cells are tuned to head direction, but *not* to place – i.e. they fire more or less uniformly with respect to the animal's location.

Head direction cells in dorsal presubiculum

Head direction cells <u>rotate together</u>

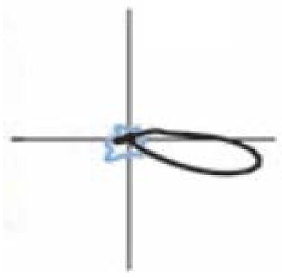


Head direction cells “remap” to a new random direction upon removal of cue card – but they <u>remap together</u>



Is there a representation of 3-D head direction in the mammalian brain = “3-D neural compasses” ?

Head-direction cells
In rats



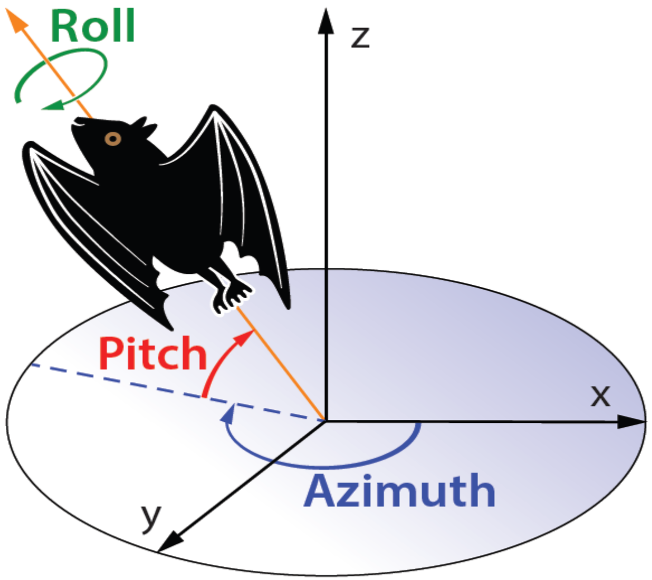
Solstad et al.
Science 2008

Head-direction cells
In bats

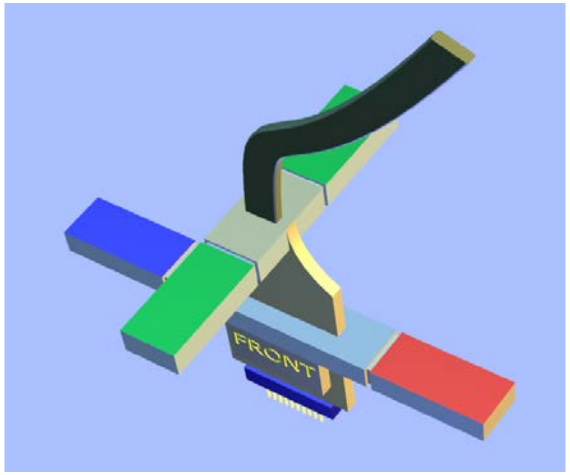
Yarsev, Witter, Ulanovsky
Nature 2011

Tracking the rotation angles (Euler angles) of the bat's head in 3-D

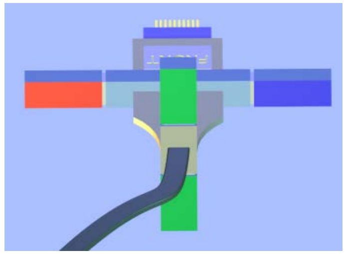
Euler Angles



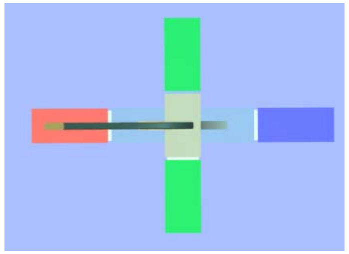
4-LEDs tracking head-stage



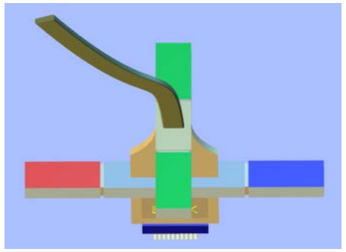
Bat looking up
(positive Pitch)



Bat looking straight
(0 Pitch)

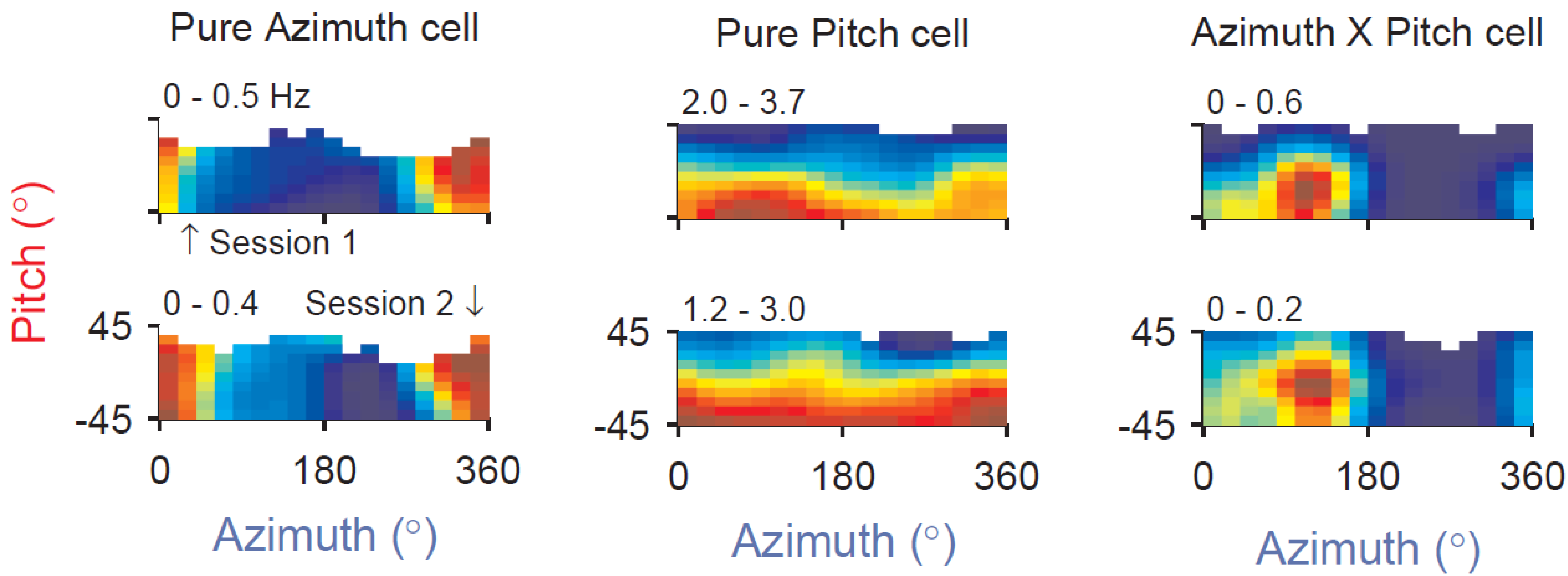


Bat looking down
(negative Pitch)



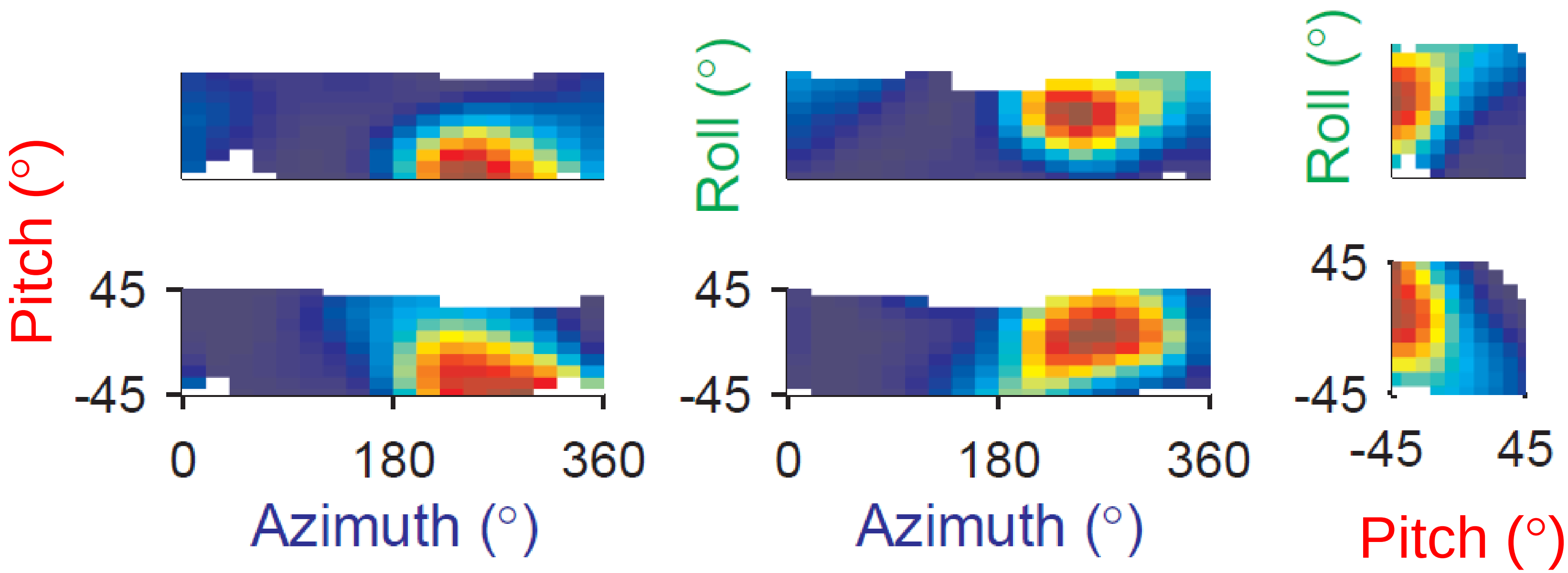
Finkelstein et al.
Nature (2015)

Example cells #1-3:
Azimuth, Pitch, and conjunctive Azimuth x Pitch



Finkelstein et al.
Nature (2015)

Example cell #4:
Triple conjunctive neuron: Azimuth x Pitch x Roll



About <u>35%</u> of Azimuth-tuned cells were also tuned to Pitch or Roll.

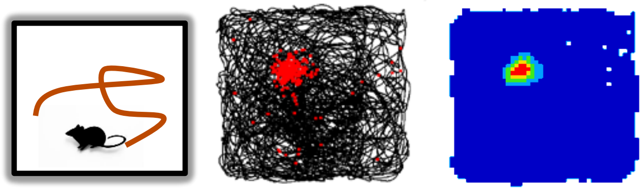
Finkelstein et al.
Nature (2015)

Neural basis of map-and-compass navigation ?

1. *Map* → *Place cells*

Hippocampus

CA3_11546_210606_t4c1.avi



Movie courtesy of Dori Derdikman, 2010

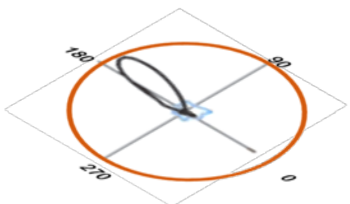
2. *Compass*

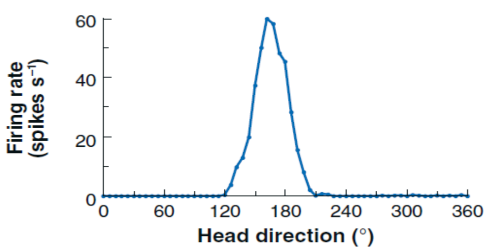
↓

Head-direction cells

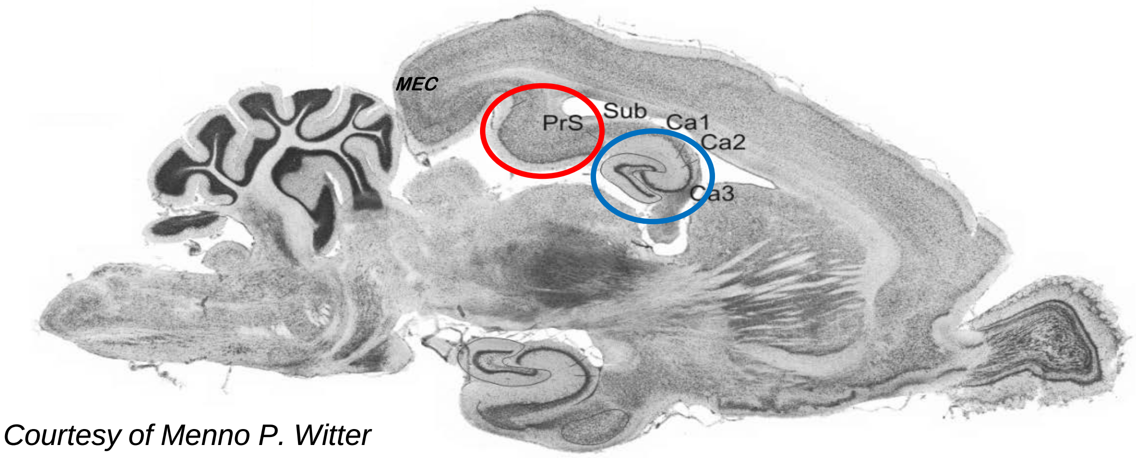
Presubiculum (PrS)

MBvideoHD_smaller.wmv





Ranck & Taube
JNS 1990



Courtesy of Menno P. Witter

Movie courtesy of Tor Kirkesola, 2010

Outline of today's lecture

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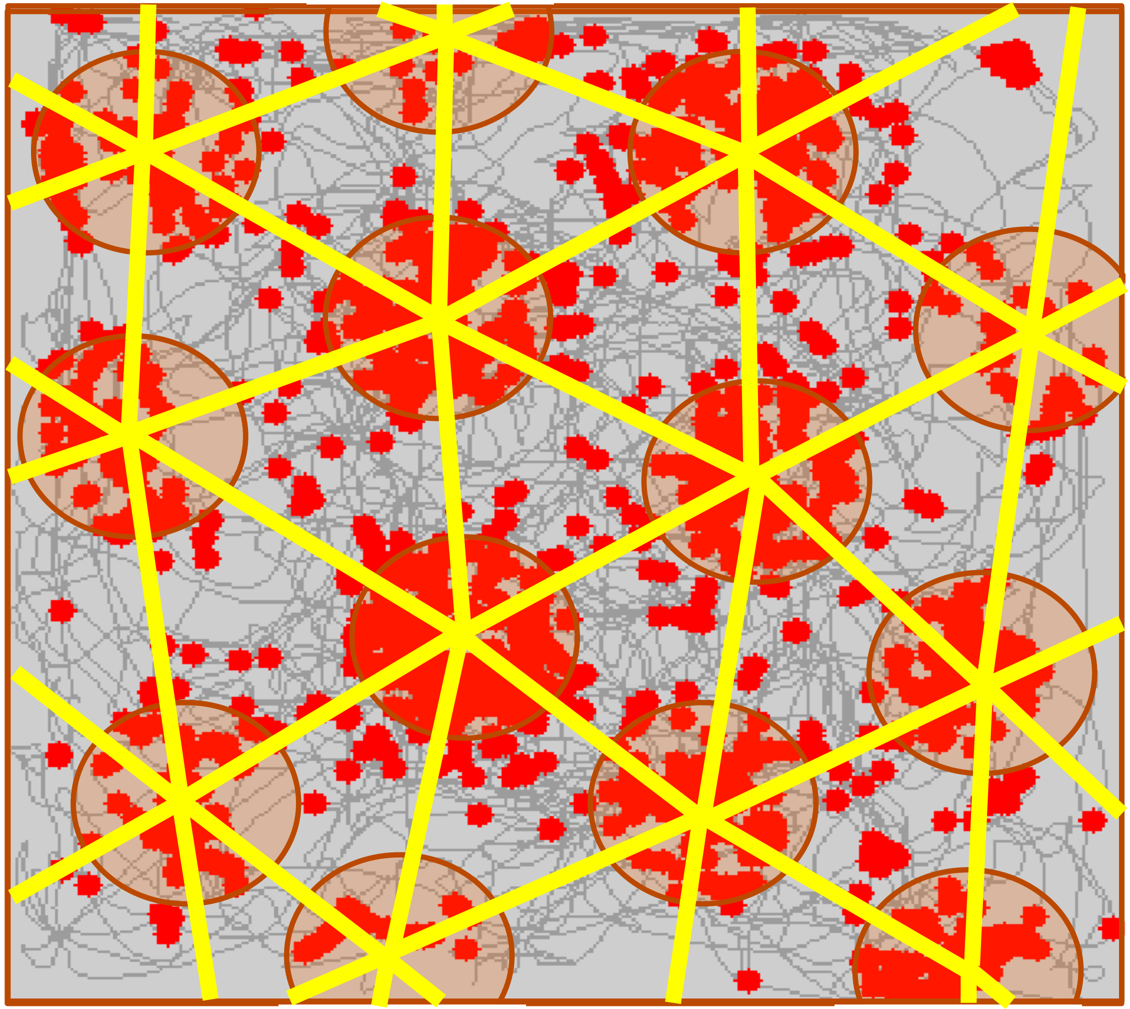
- **Open questions**

Grid cells

May-Britt Moser

Edvard Moser



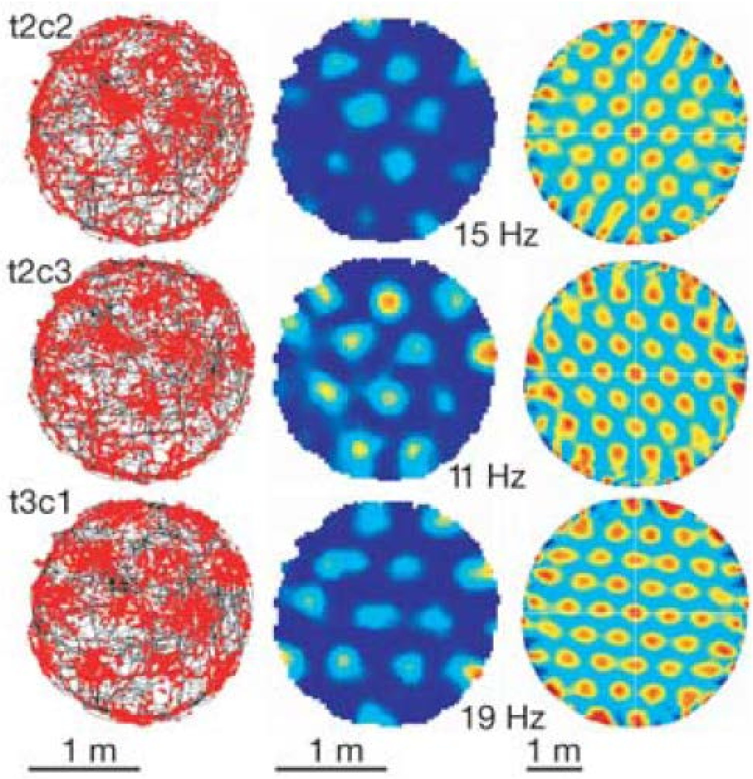
Marianne Fyhn

Torkel Hafting

Hafting T, Fyhn M, Molden S, Moser MB, Moser EI (2005) Nature 436:801-806

Grid cells in medial entorhinal cortex (MEC)

Three grid-cells recorded
simultaneously on the same tetrode



Cell 1

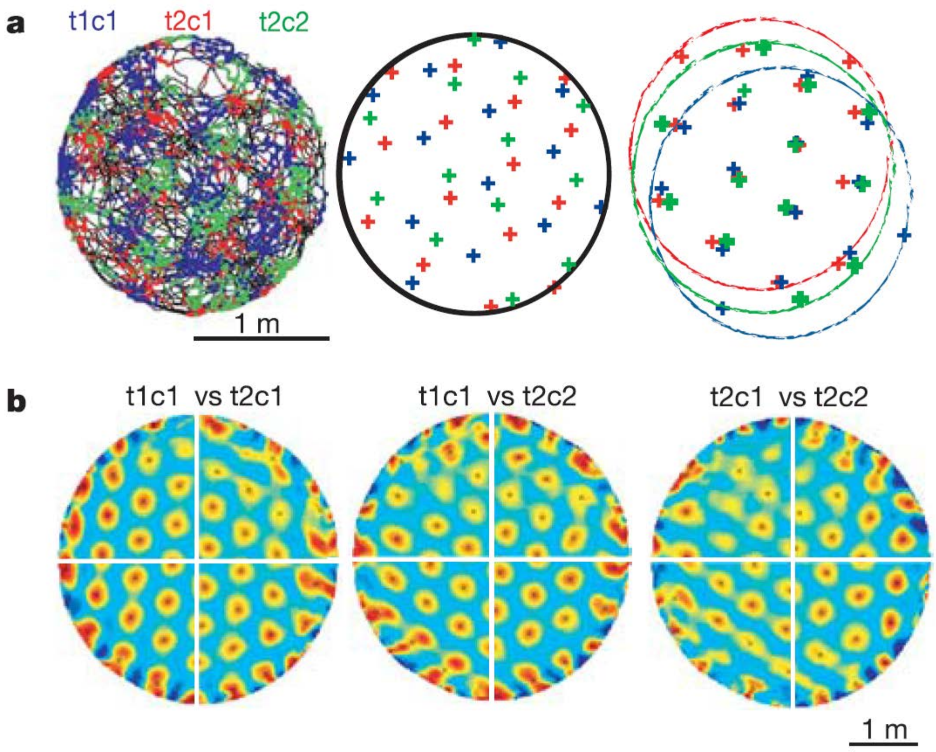
Cell 2

Cell 3

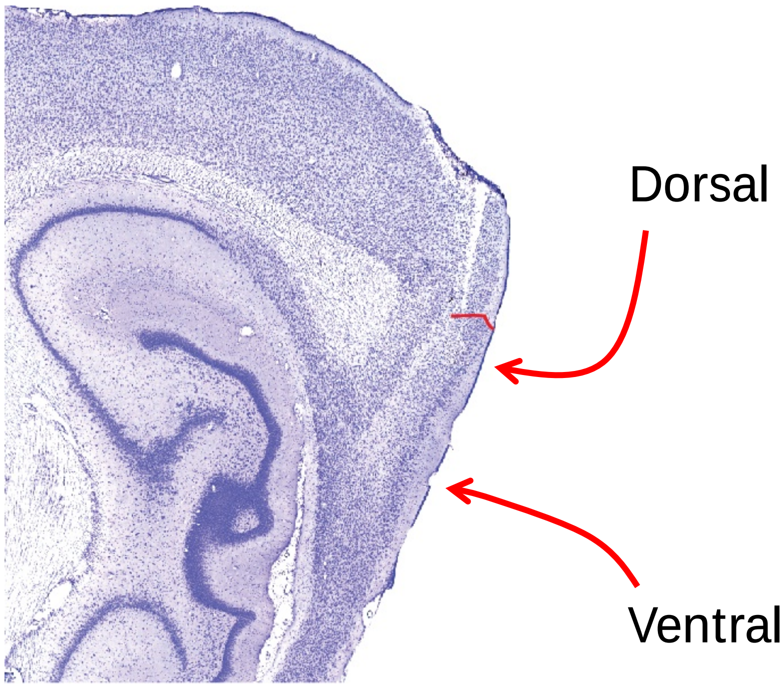
- Columnar structure in entorhinal cortex

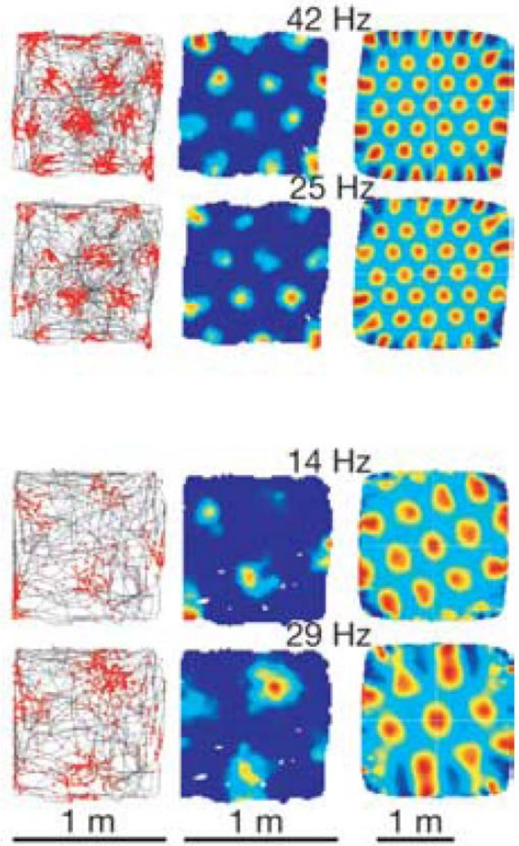
  Grids of simultaneously-recorded grid cells look quite similar

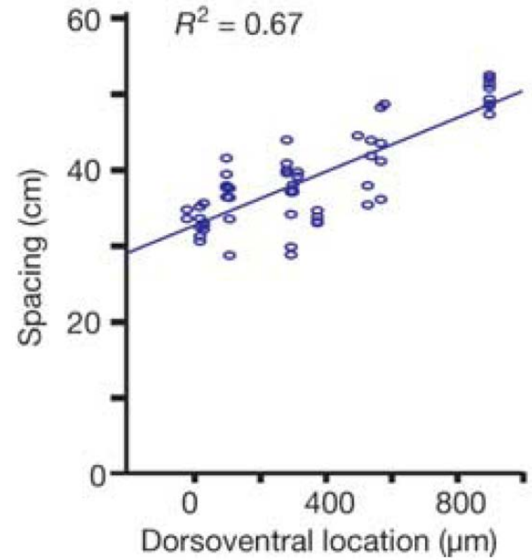
Nearby grid cells have the same grid spacing and orientation, but random grid phase



Grid spacing increases in size along the dorso-ventral axis of the entorhinal cortex

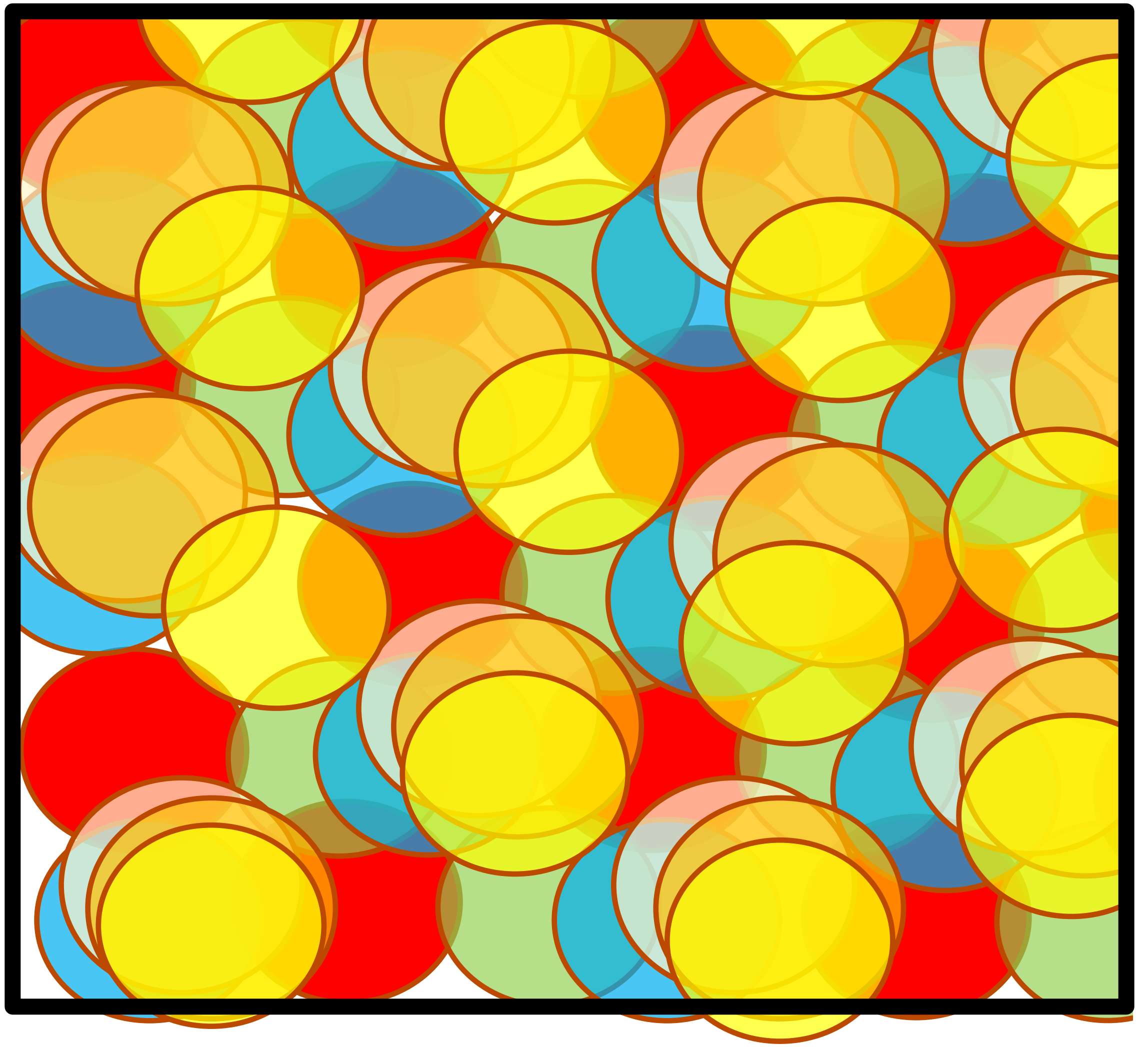




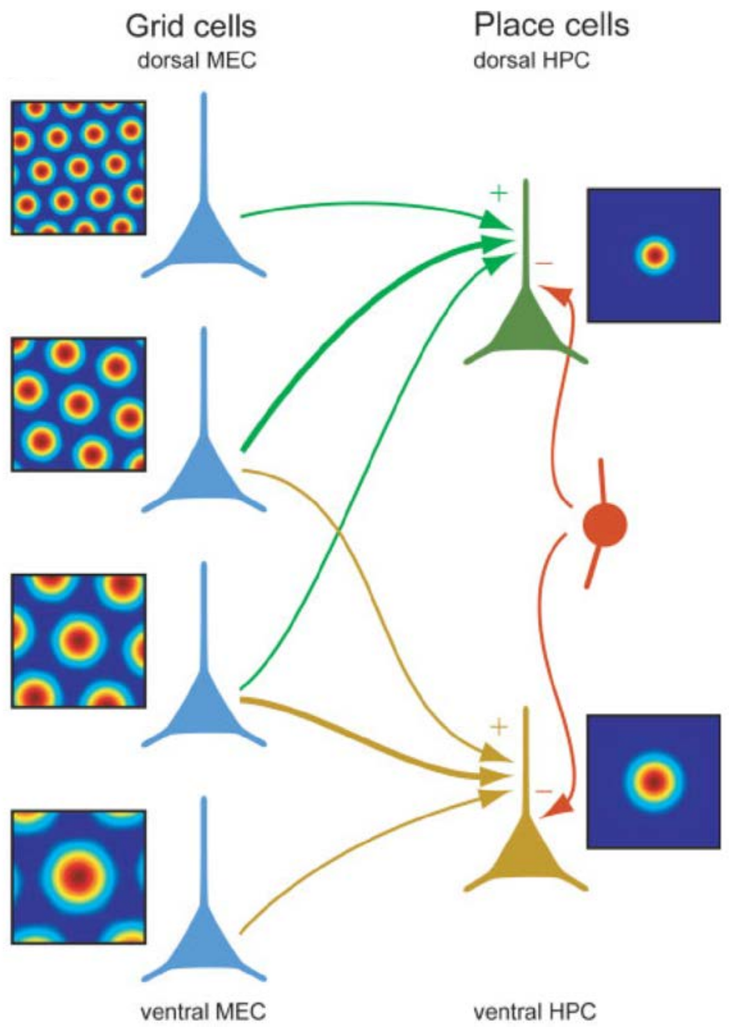


Data from multiple animals
pooled together

Multiple grid cells can map the environment



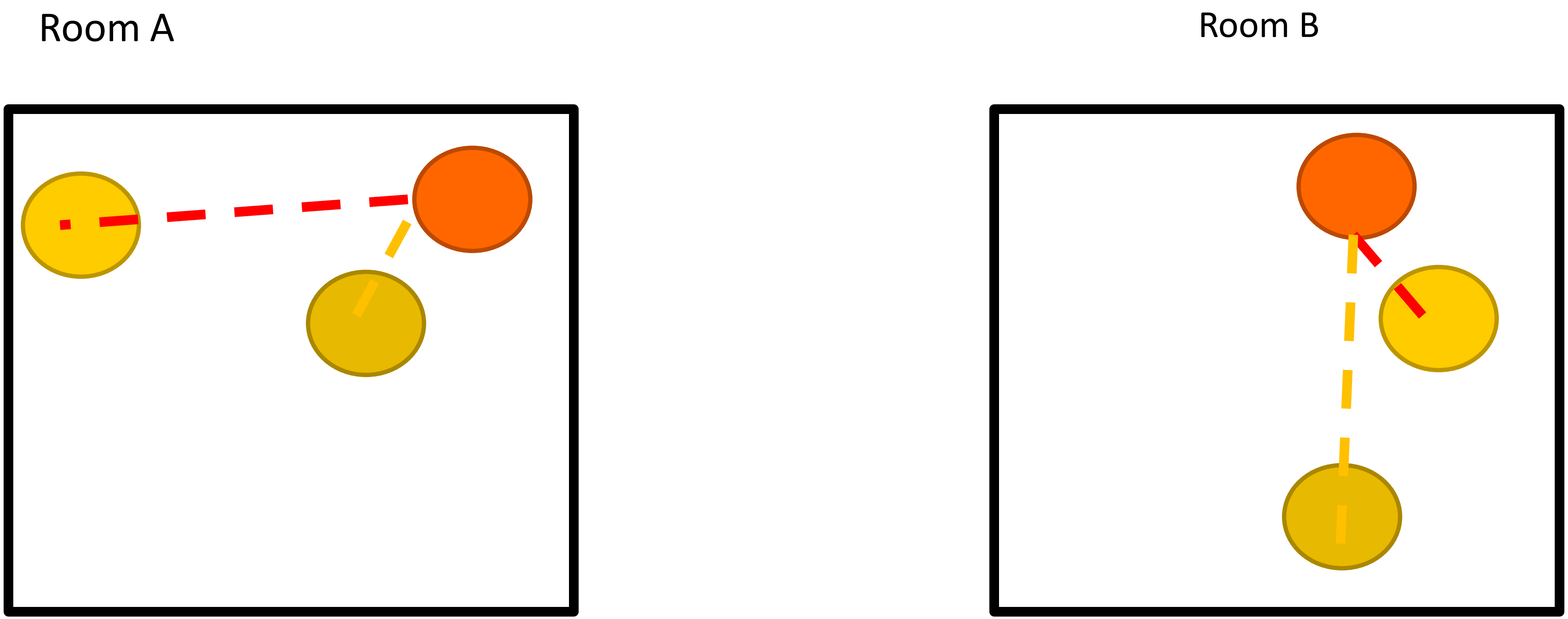
Entorhinal grids might be combined to produce hippocampal place fields (or vice versa): Hexagonal Fourier-like decomposition



Model

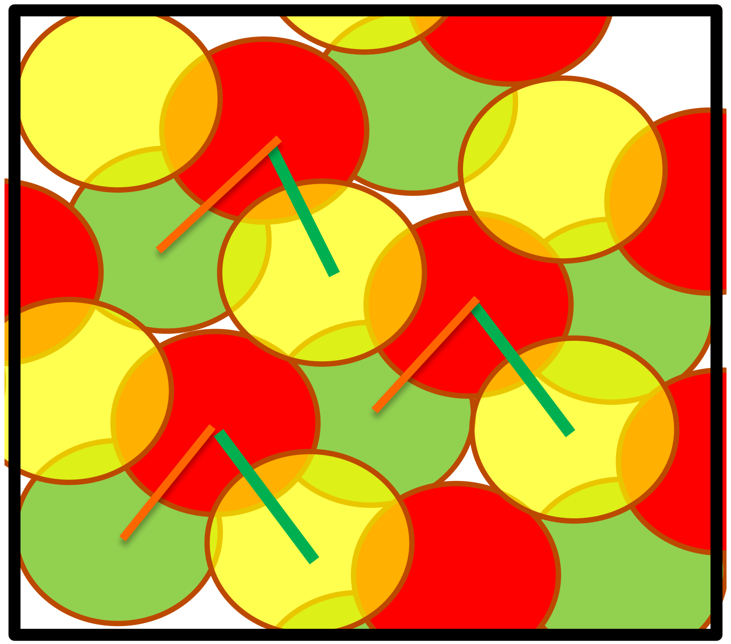
by Solstad et al. (2006)

During global remapping, place cells do not preserve distances

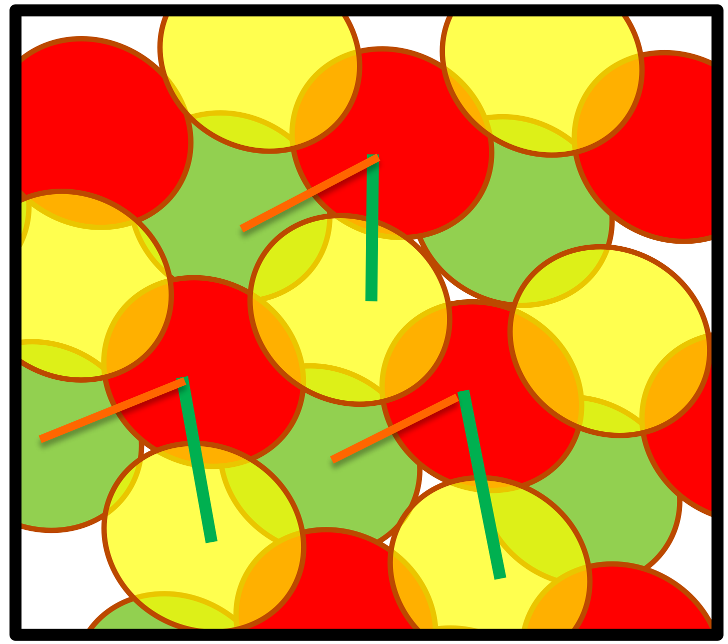


Grid cells of similar scale do preserve a distance metric

Room A

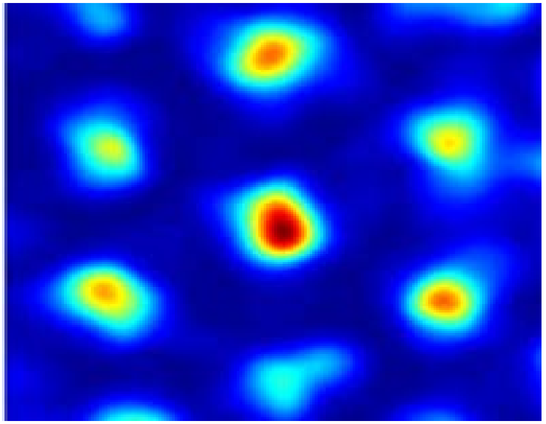


Room B



- During remapping, the grid cells exhibit a coherent shift & rotation (<u>all of them shift & rotate *together*</u> – like remapping in head-direction cells).

The Mystery: How are the grids formed?



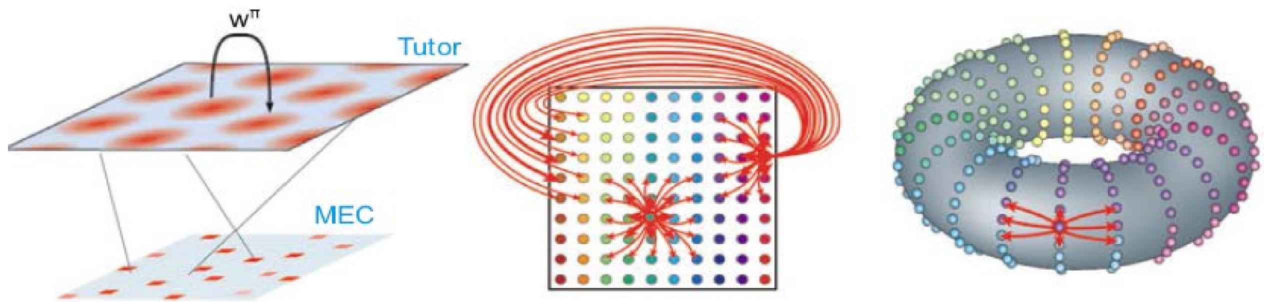
Rat grid cell

Two major models of grid-cell formation:

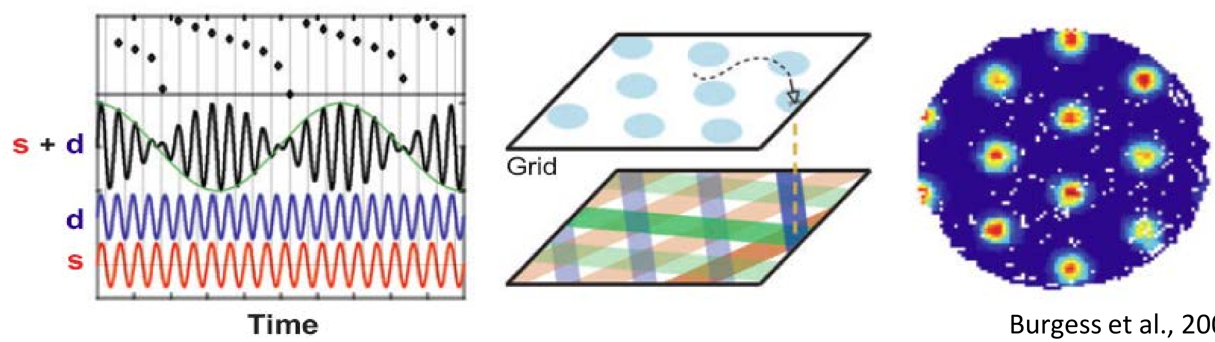
1. Network interactions

2. Path integration using continuous theta oscillation

('from oscillations in time to oscillations in space')



McNaughton et al, 2006



Burgess et al., 2008

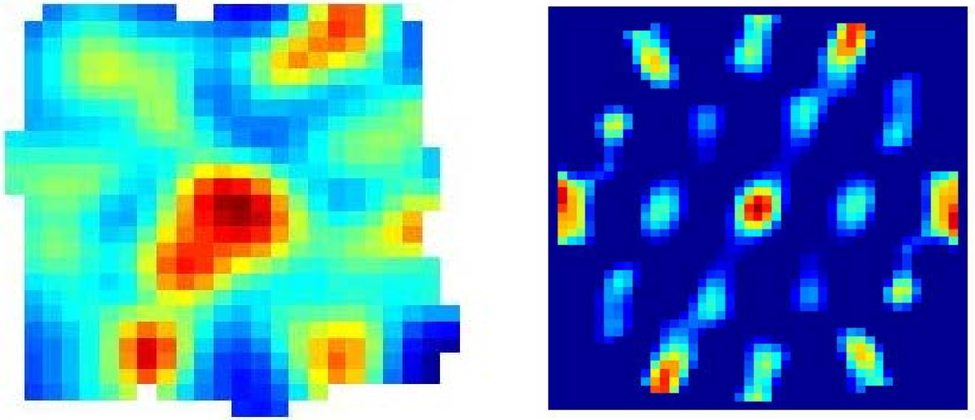
Rationale of bat experiments:

→ In rodents, grid cells and theta oscillation are not dissociable

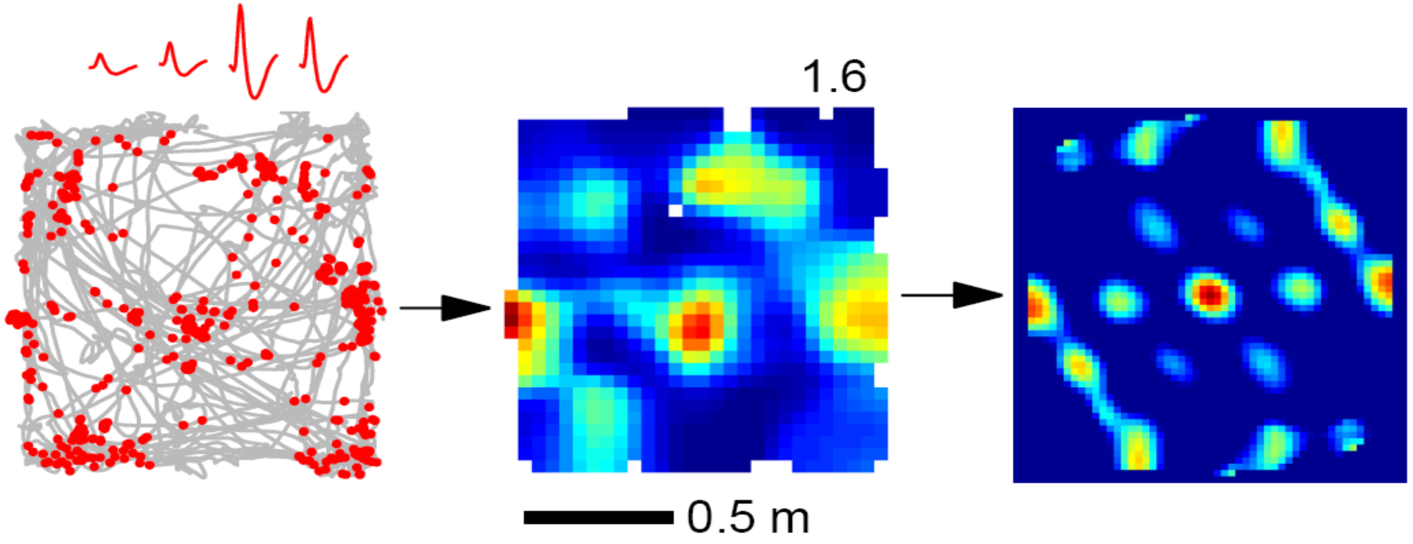
→ If we find in the bat grid cells without theta oscillation, this will contradict the second class of models

Grid cells in bats

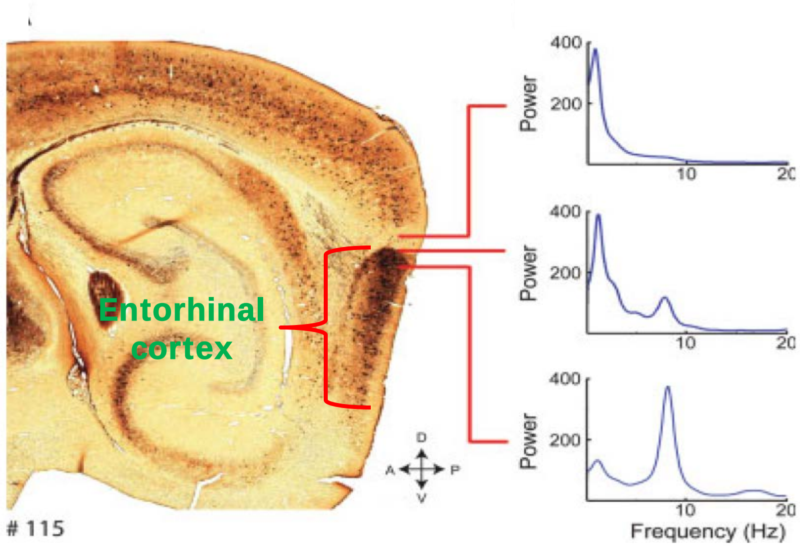
One of the first grid cells that we recorded in bat entorhinal cortex

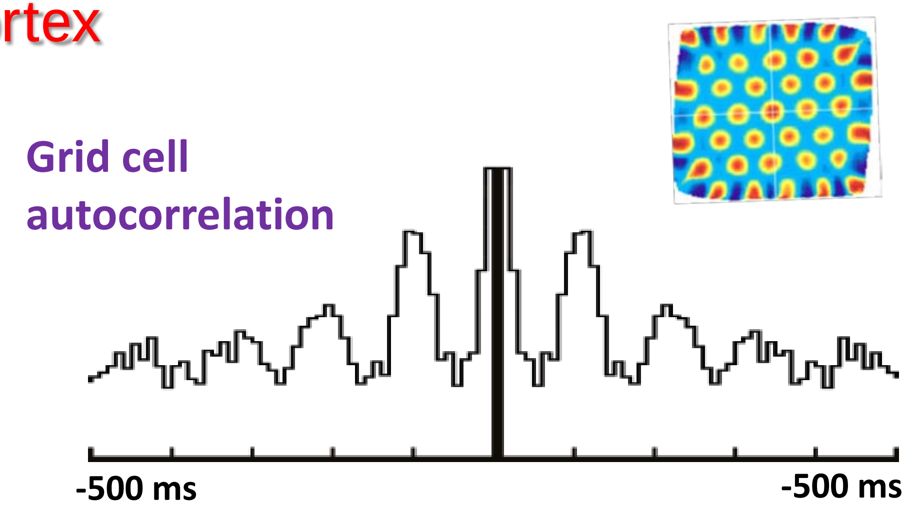


Another example

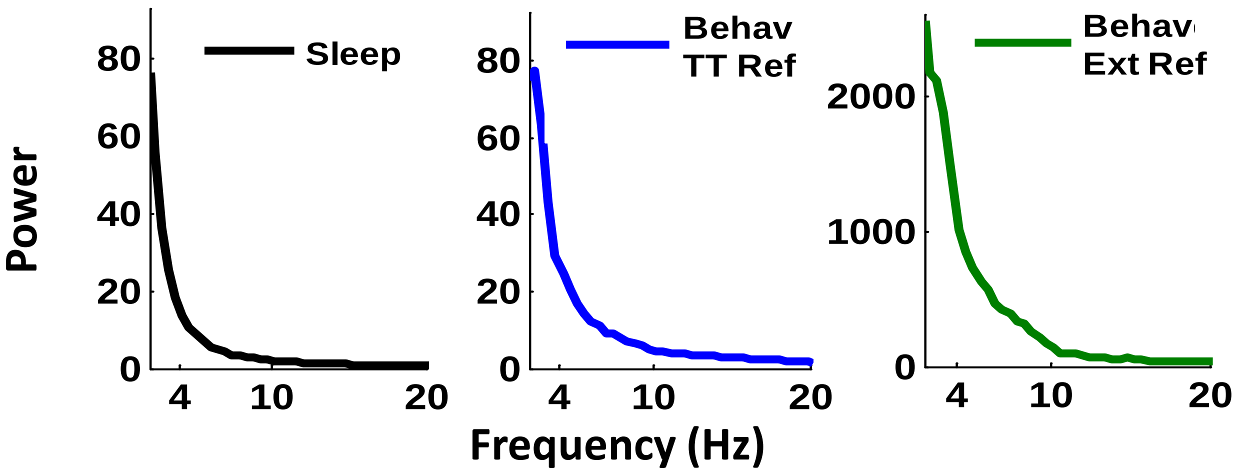


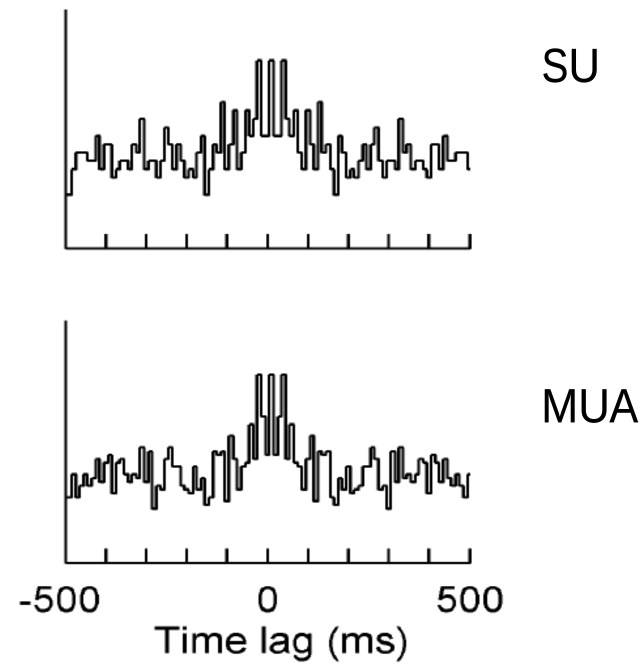
Theta oscillation in the rodent entorhinal cortex



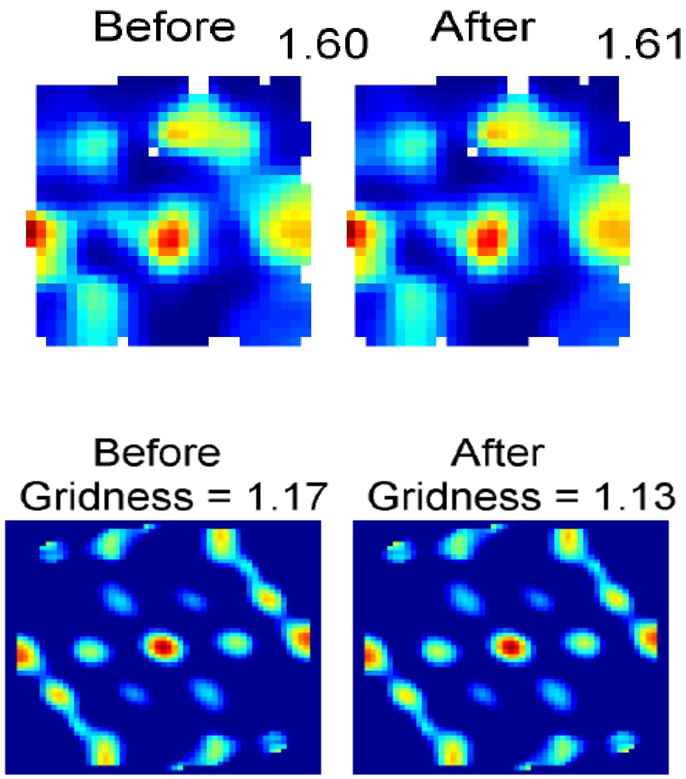


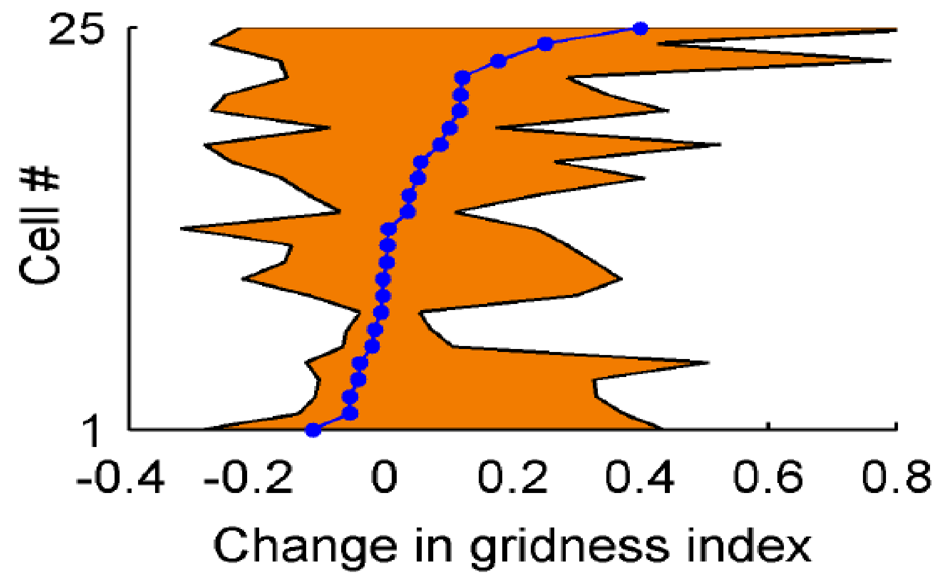
Theta in the bat entorhinal cortex…





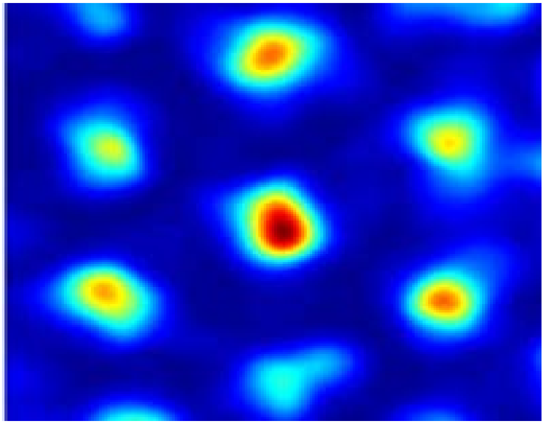
Theta bouts are not required for creating the grids





Yartsev, Witter, Ulanovsky
Nature (2011)

But how are the grids formed?



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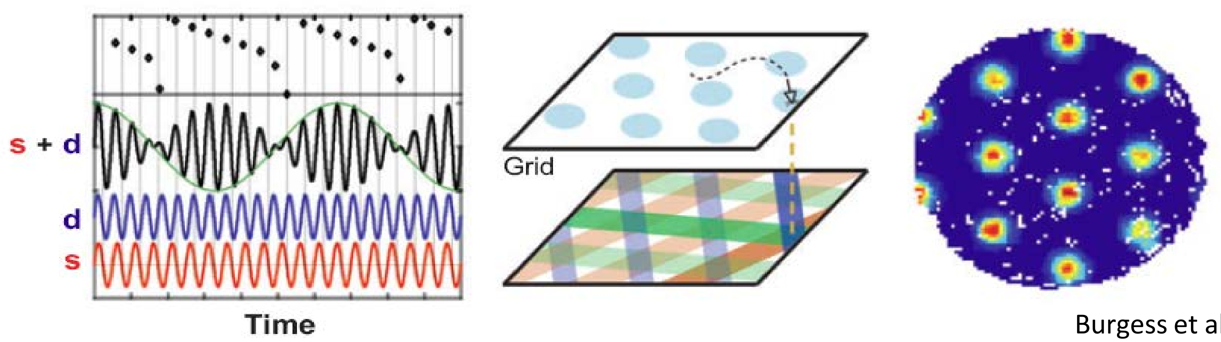
McNaughton et al, 2006

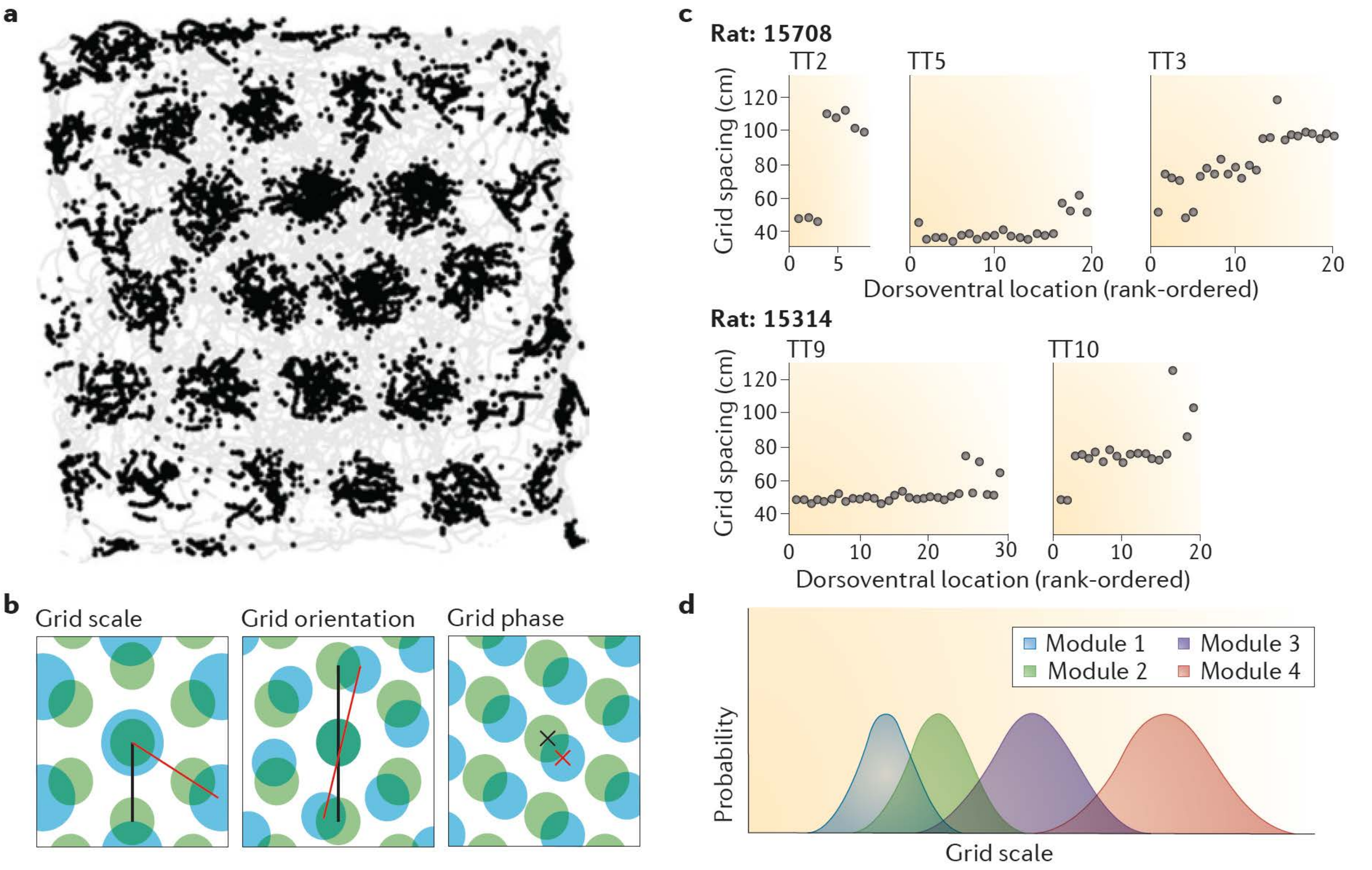


Burgess et al., 2008

Conclusion:

Theta oscillations are *not* required for the grids → Argues against the "oscillatory interference models" of grid cells

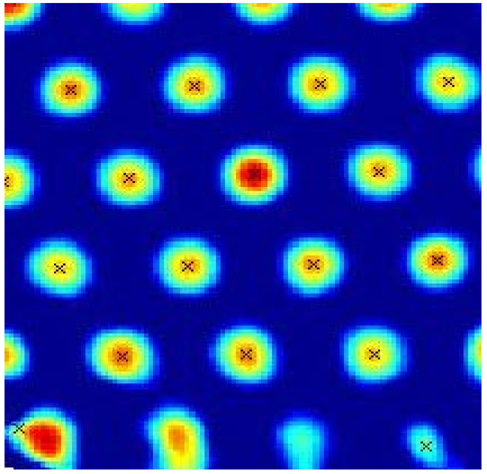
Support for the attractor network model of grid cells comes from the recent finding that grid cells are organized in *discrete* 'modules'



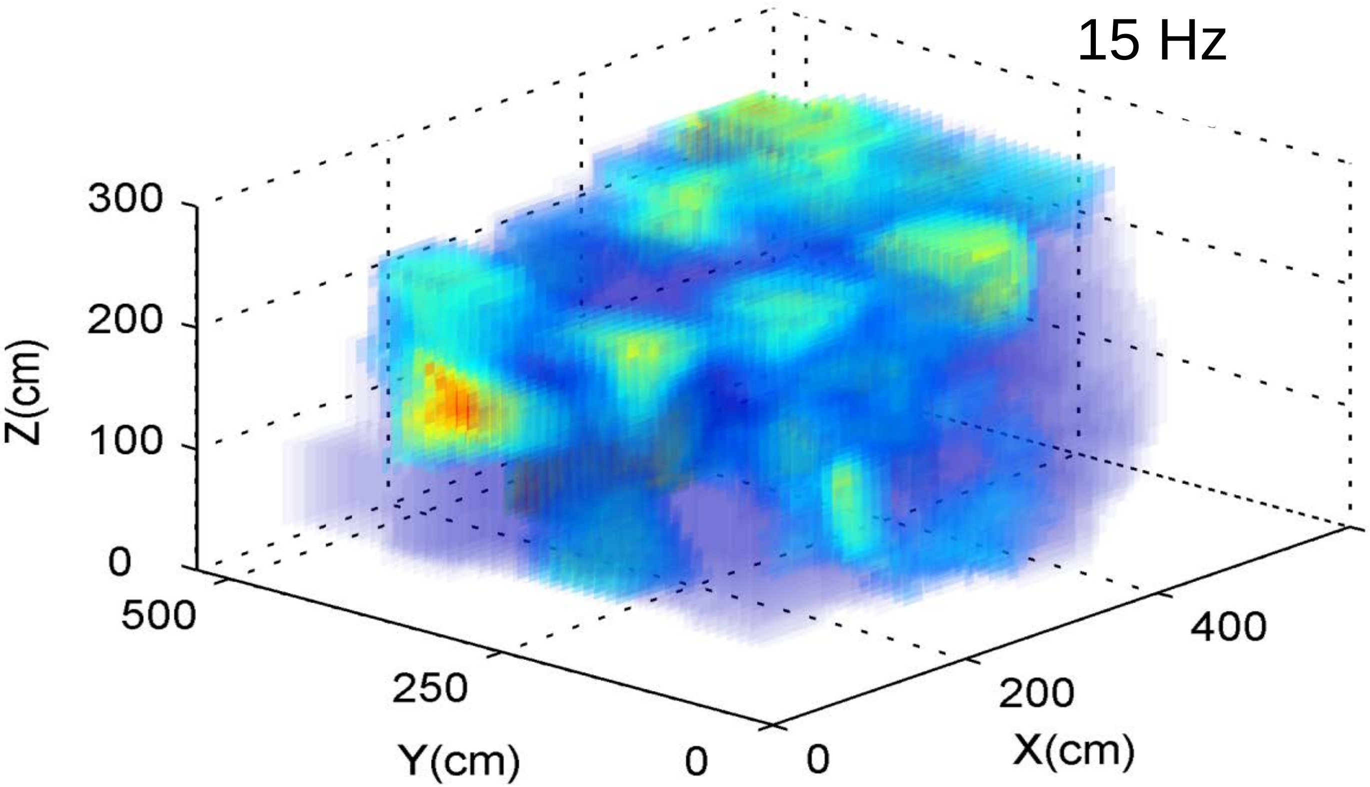
Stensola et al., *Nature* (2012)

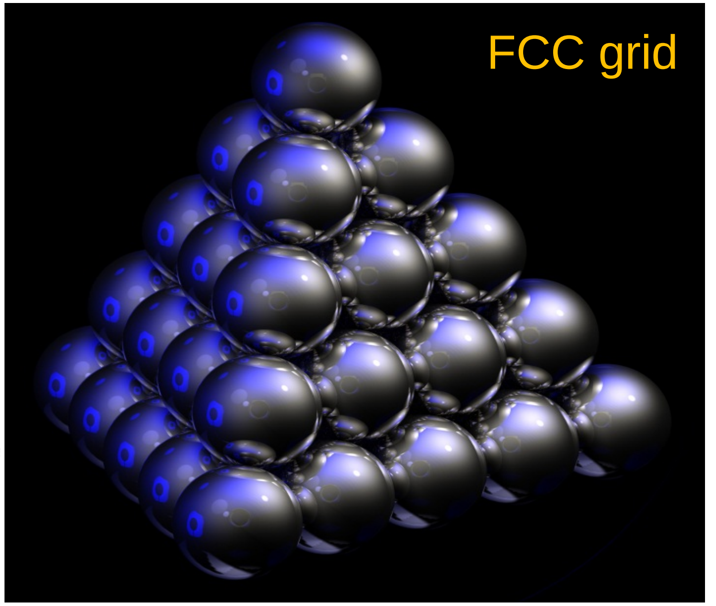
Moser et al., *Nat. Rev. Neurosci.* (2014)

Hexagonal grid shapes as optimal packing?



3-D grid cells in bats as 3-D optimal packing?

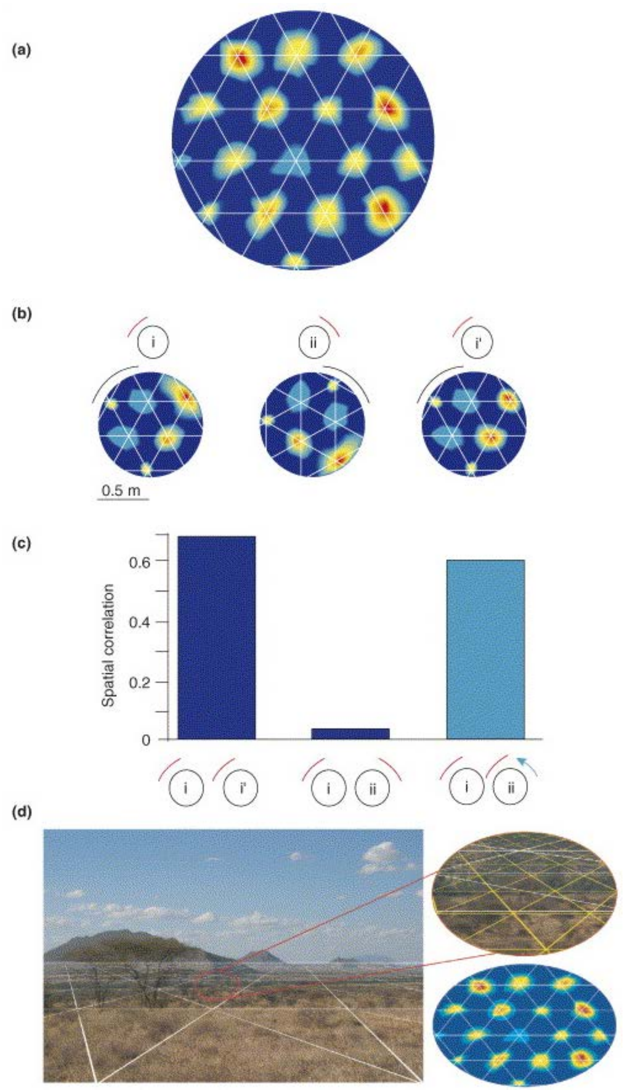




BUT we also observe a variety of other 3-D shapes

Gily Ginosar

Hypothesized role of grid cells in large-scale navigation



Option 1:

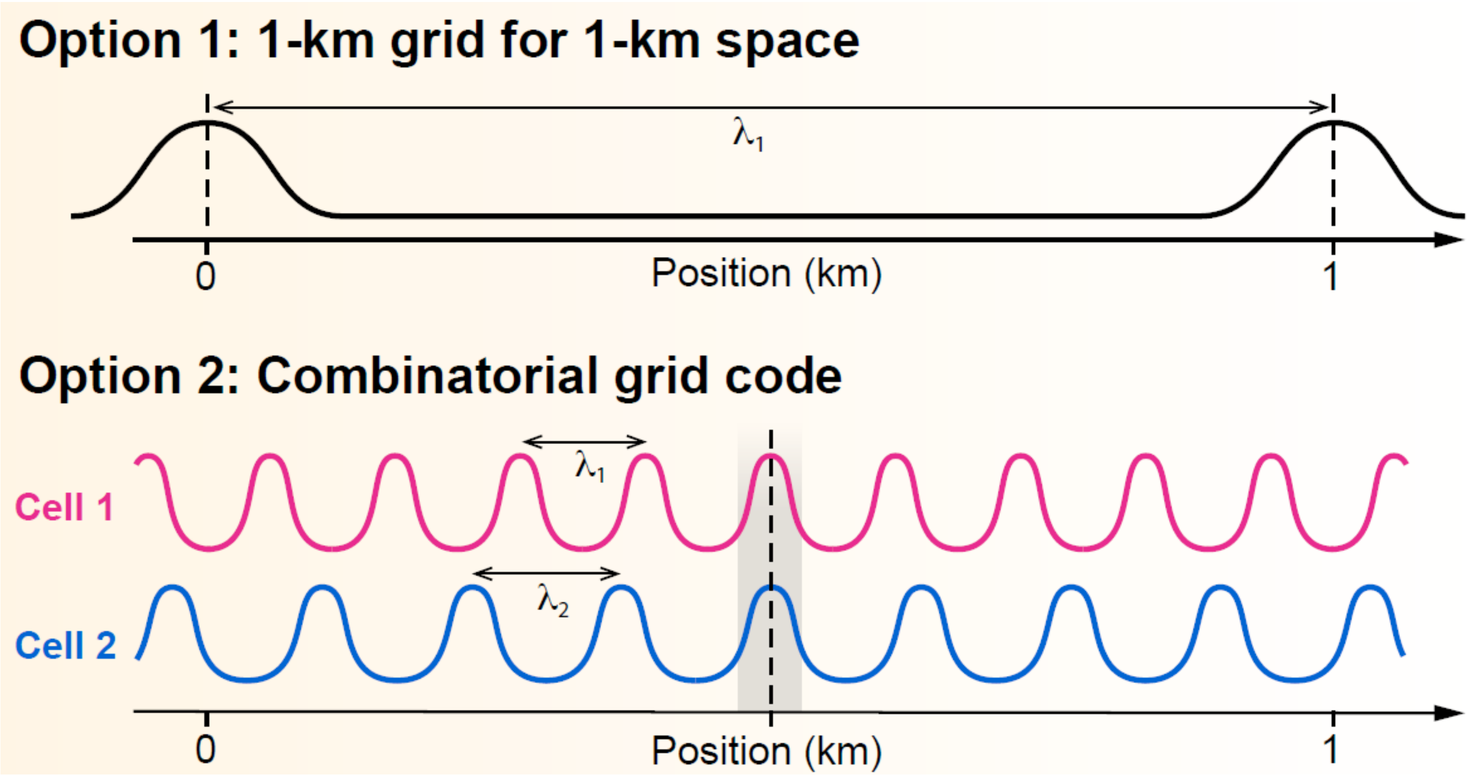
Very large grids for representing very large spaces

How a researcher of bird navigation imagined grid cells might be useful for long-distance navigation (Frost & Mouritsen, *Curr. Opin. Neurobiol.* 2006)

BUT: No such huge grids were found yet (and it is difficult to look for them). The same goes for place cells.

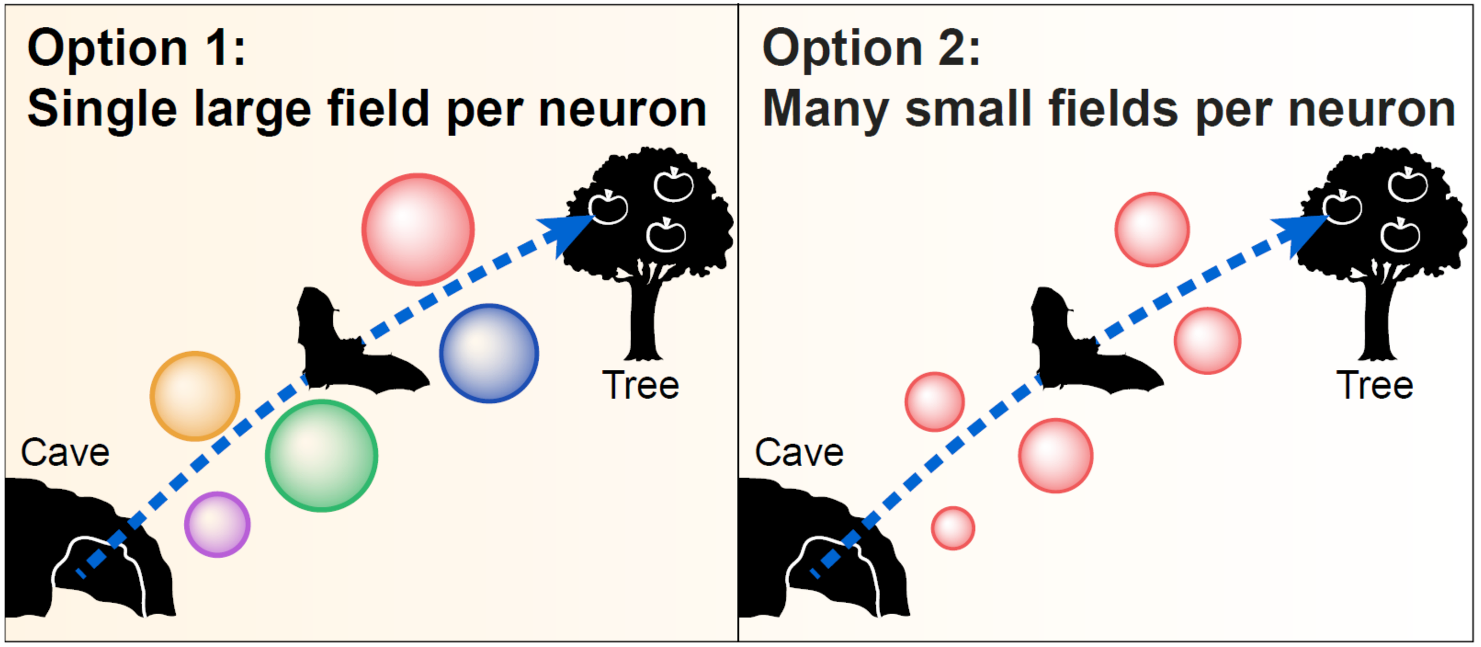
Hypothesized role of grid cells in large-scale navigation

<u>Option 2:</u> **Perhaps you do *not* need large grids for representing very large spaces, but instead kilometer-sized environments are represented *combinatorially* by populations of small grids (*Ila Fiete et al.*)**



Geva-Sagiv, Las, Yovel & Ulanovsky,
Nature Rev. Neurosci. (2015)

Similar questions can be asked about the role of place cells in large-scale navigation – which is another major open question



Geva-Sagiv, Las, Yovel & Ulanovsky,
Nature Rev. Neurosci. (2015)

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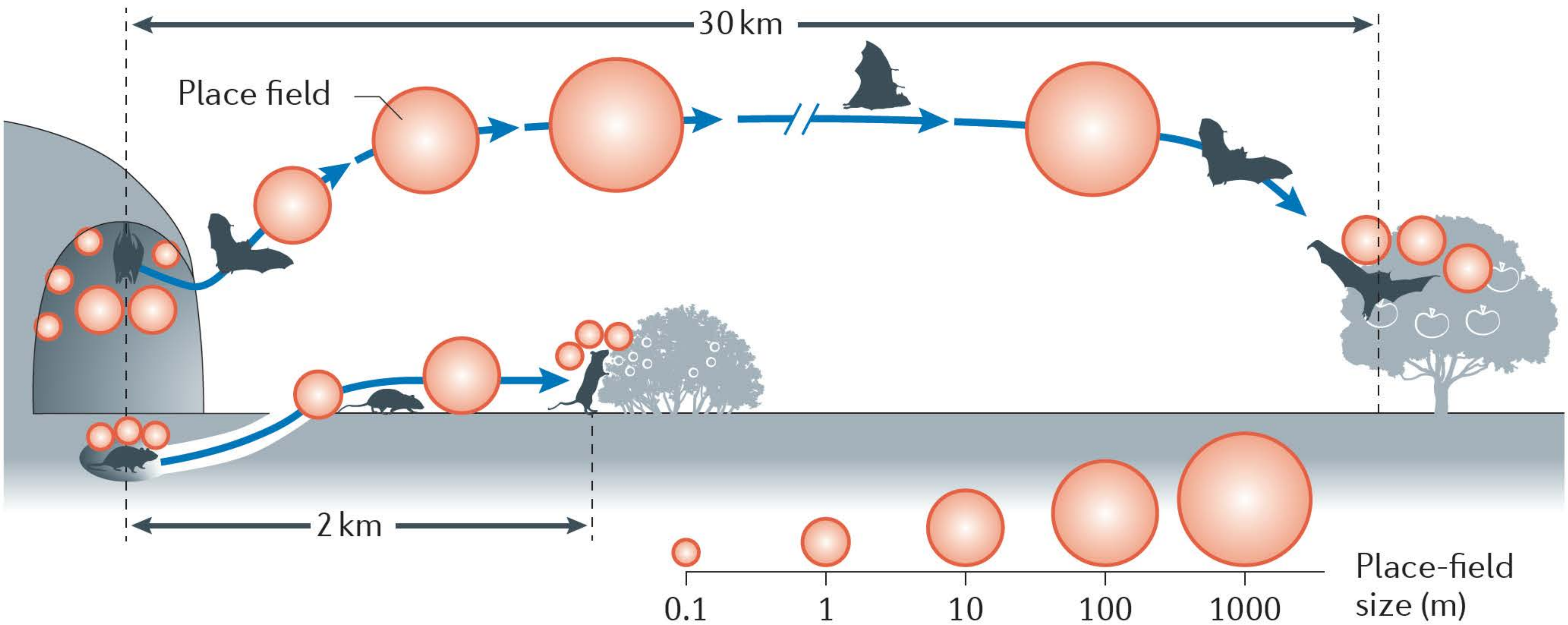


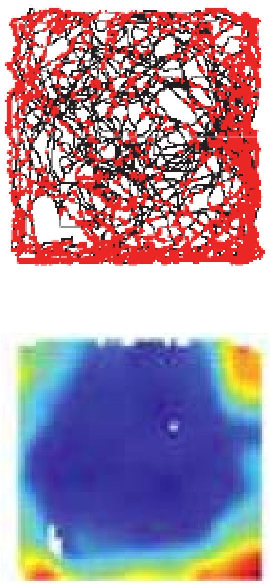
Geva-Sagiv, Las, Yovel & Ulanovsky,
Nature Rev. Neurosci. (2015)

SUMMARY: Spatial cell types in the hippocampus and entorhinal cortex: The basic elements of the "brain navigation circuit"

Medial entorhinal cortex

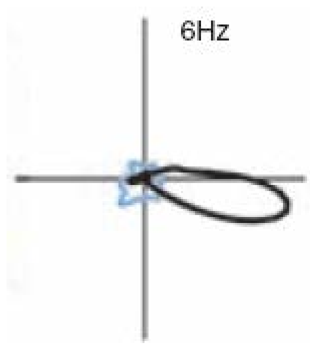
Hippocampus

Border Cells



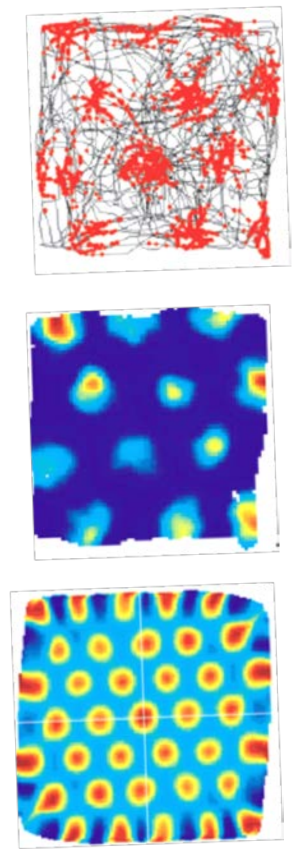
Mosers, O'Keefe, Knierim
2008

Head-direction cells



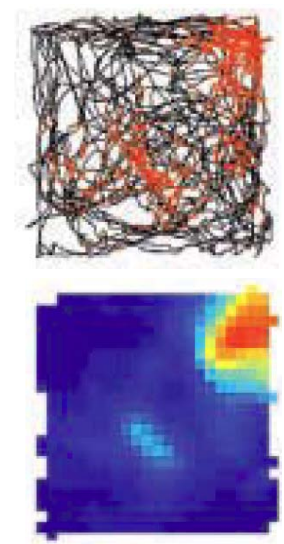
Ranck, Taube – 1980's

Grid cells



Mosers – 2005

Place cells



O'Keefe – 1971

SUMMARY: Spatial cell types in the hippocampus and entorhinal cortex: The basic elements of the “brain navigation circuit”

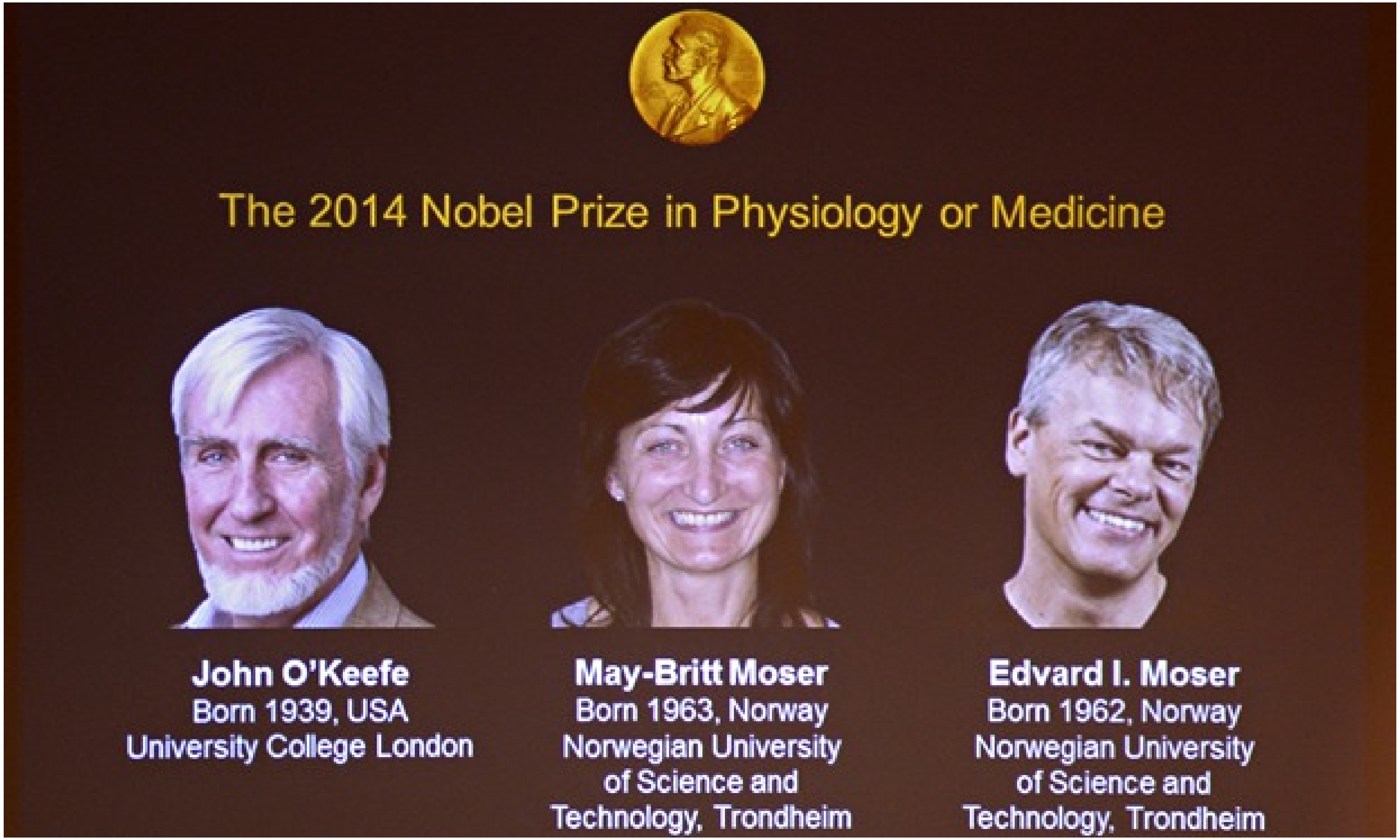
SUMMARY:

- **Place cell** → Position (where am I)
- **Grid cells** → Position or Distance (“ruler”)
- **Border cells** → Borders of the environment

Map

- **Head-direction cells** → Direction

Compass


The 2014 Nobel Prize in Physiology or Medicine
John O'Keefe
Born 1939, USA
University College London
May-Britt Moser
Born 1963, Norway
Norwegian University
of Science and
Technology, Trondheim
Edvard I. Moser
Born 1962, Norway
Norwegian University
of Science and
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- **Spatial maps in the hippocampus and related regions:**
  - **Place cells**
  - **Head direction cells**
  - **Grid cells**
- ***Intermezzo*: Structure-function relations in the hippocampus**
- **Beyond the cognitive map: Hippocampus and memory**
- **Open questions**

The importance of neuroanatomy I :
How grid cells were discovered

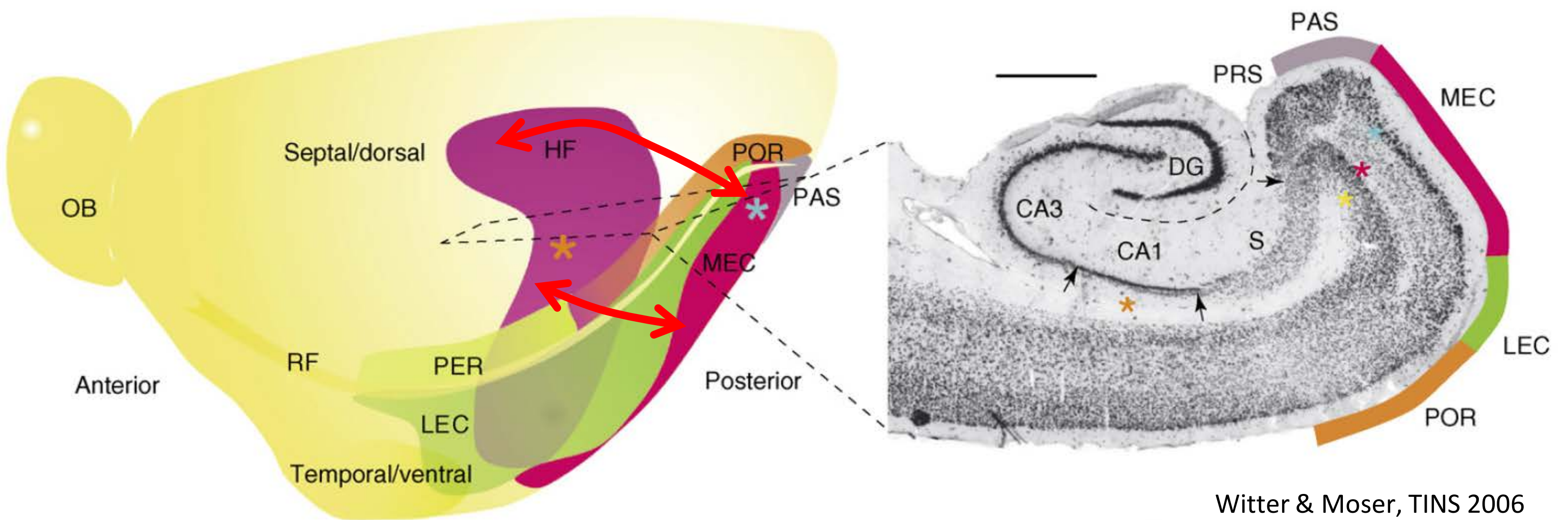
A detective story, or – the rationale that led Menno Witter (neuroanatomist) and the Mosers (electrophysiologists) to look for tight spatial responses in dorsal MEC – which led to the discovery of grid cells in 2004/5:

1) Ventral regions of medial entorhinal cortex (MEC) were studied electro-physiolgically before (Frank et al. 2000), but spatial responses were diffuse. Dorsal regions of MEC were not studied electrophysiologically before the Mosers.

2) The tightest place-fields are found in cells of dorsal hippocampus, whereas place-fields in ventral hippocampus are larger / more diffuse.

The importance of neuroanatomy I :
How grid cells were discovered

3) Anatomical connections between MEC and hippocampus are arranged topographically: Dorsal hippo. ↔ Dorsal MEC , Ventral hippo. ↔ Ventral MEC

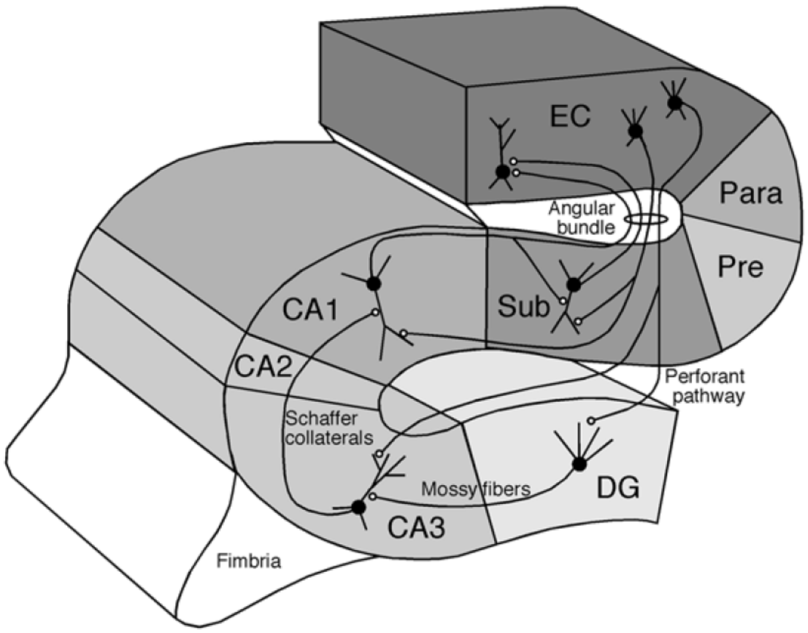


Witter & Moser, TINS 2006

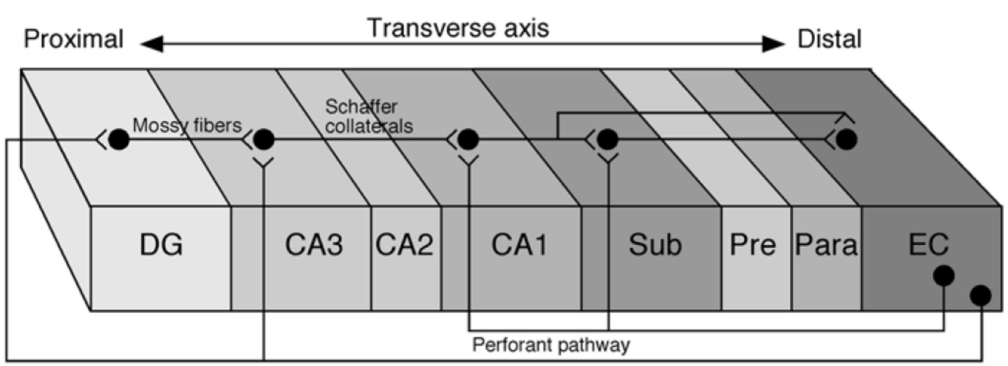
→ Menno Witter proposed to the Mosers to record at the dorsal end of MEC – the area of MEC which connects to that hippocampal area (dorsal hippo.) where tight place fields were observed in the past. And thus, grid-cells were discovered.

The importance of neuroanatomy II :

Place cells along the proximo-distal axis of CA1

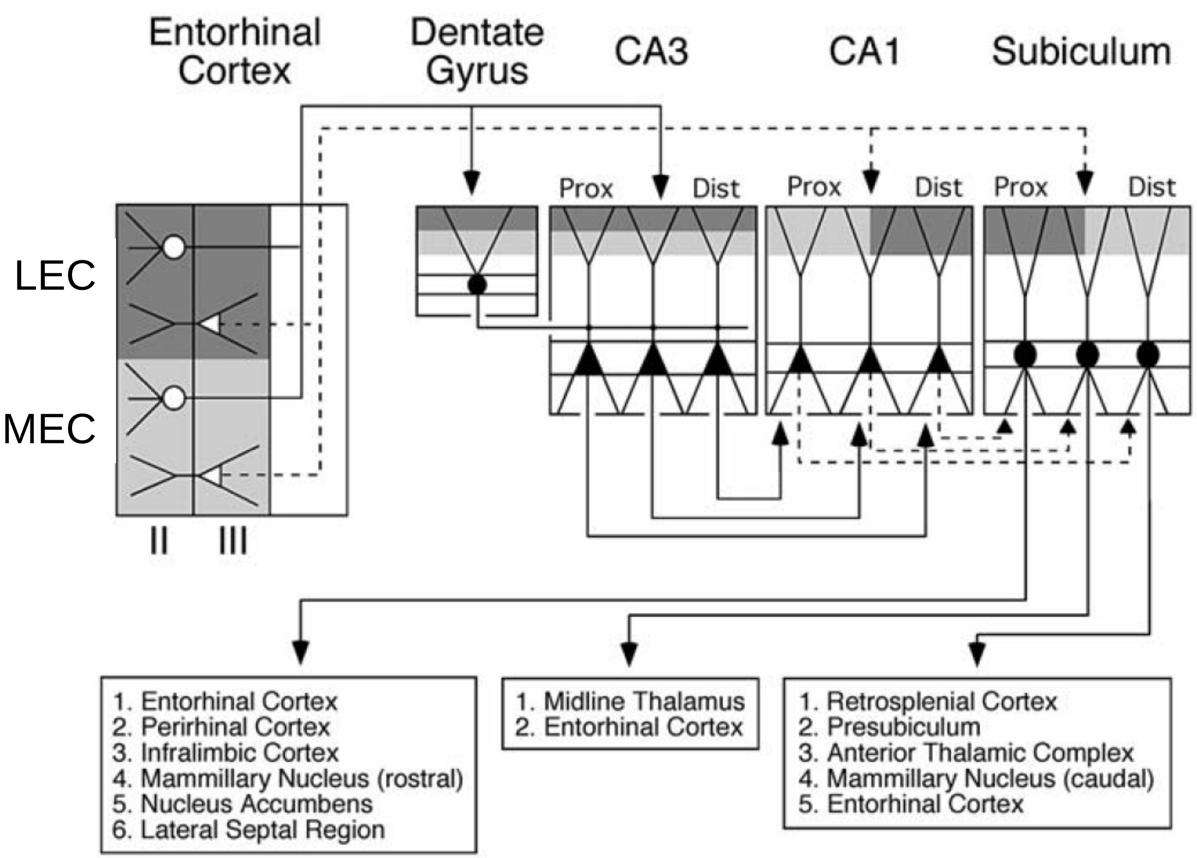


- The proximo-distal (transverse) axis of CA1:
  proximal = close to dentate gyrus
  distal = far from dentate gyrus



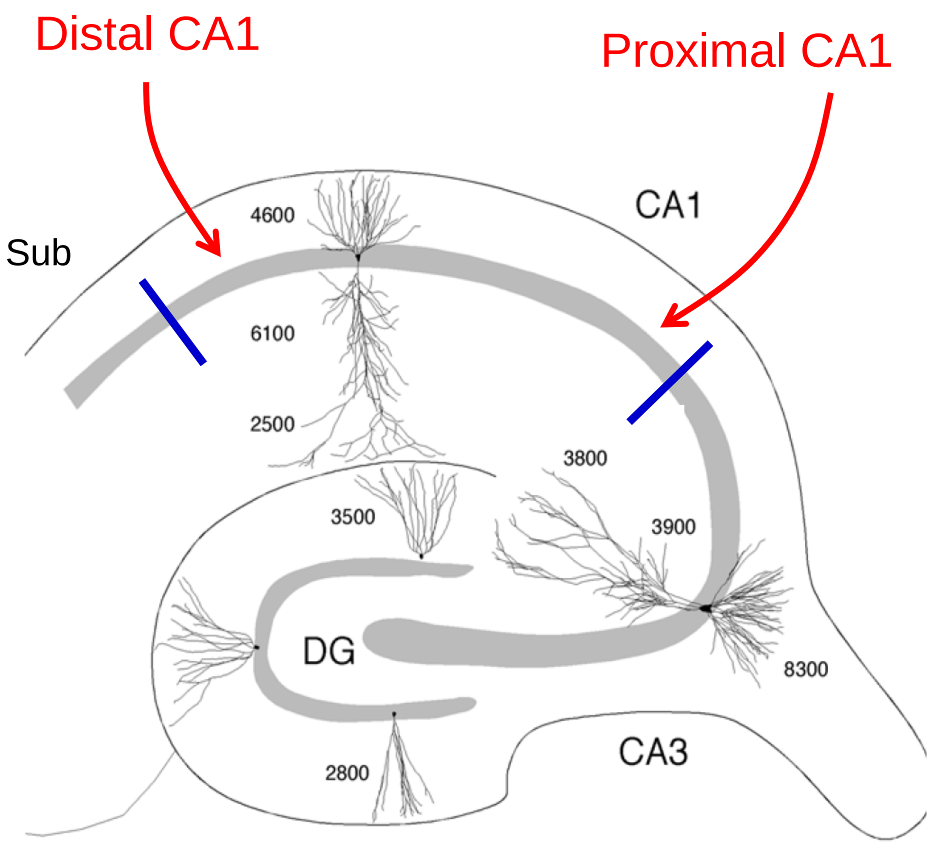
The importance of neuroanatomy II :

Place cells along the proximo-distal axis of CA1

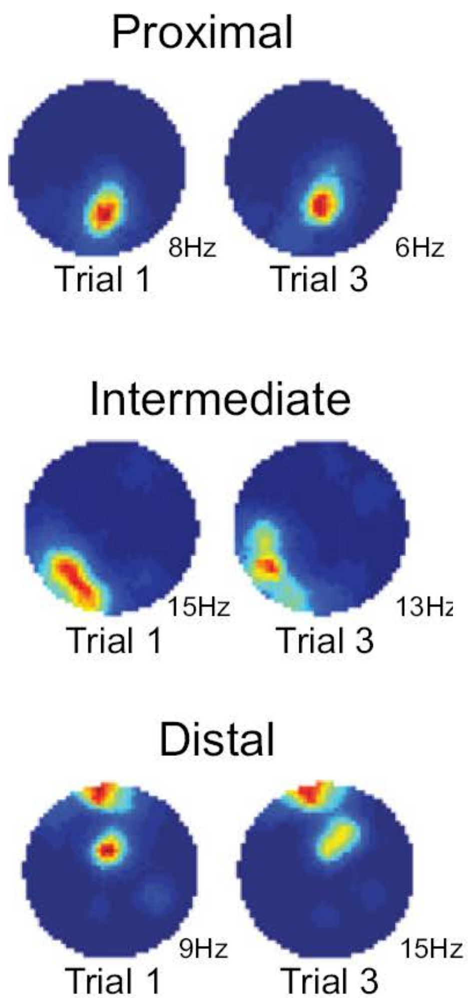


- Specific connectivity patterns along the proximo-distal axis, with mirror-image connectivity between CA3→CA1, and then between CA1→Subiculum.
- Entorhinal→CA1 connectivity: MEC (grid cells) projects to proximal CA1, whereas LEC (lateral entorhinal cortex=diffuse spatial responses) projects to distal CA1
- Prediction?
- Prediction: Place cells with small place fields would be found in proximal CA1, and less nice place fields in distal CA1

The importance of neuroanatomy II :
Place cells along the proximo-distal axis of CA1



Henriksen et al., *Neuron* (2010)



- As predicted, place fields of place-cells in proximal CA1 were “nicer” (single-peaked) compared to place fields in distal CA1 (multi-peaked).

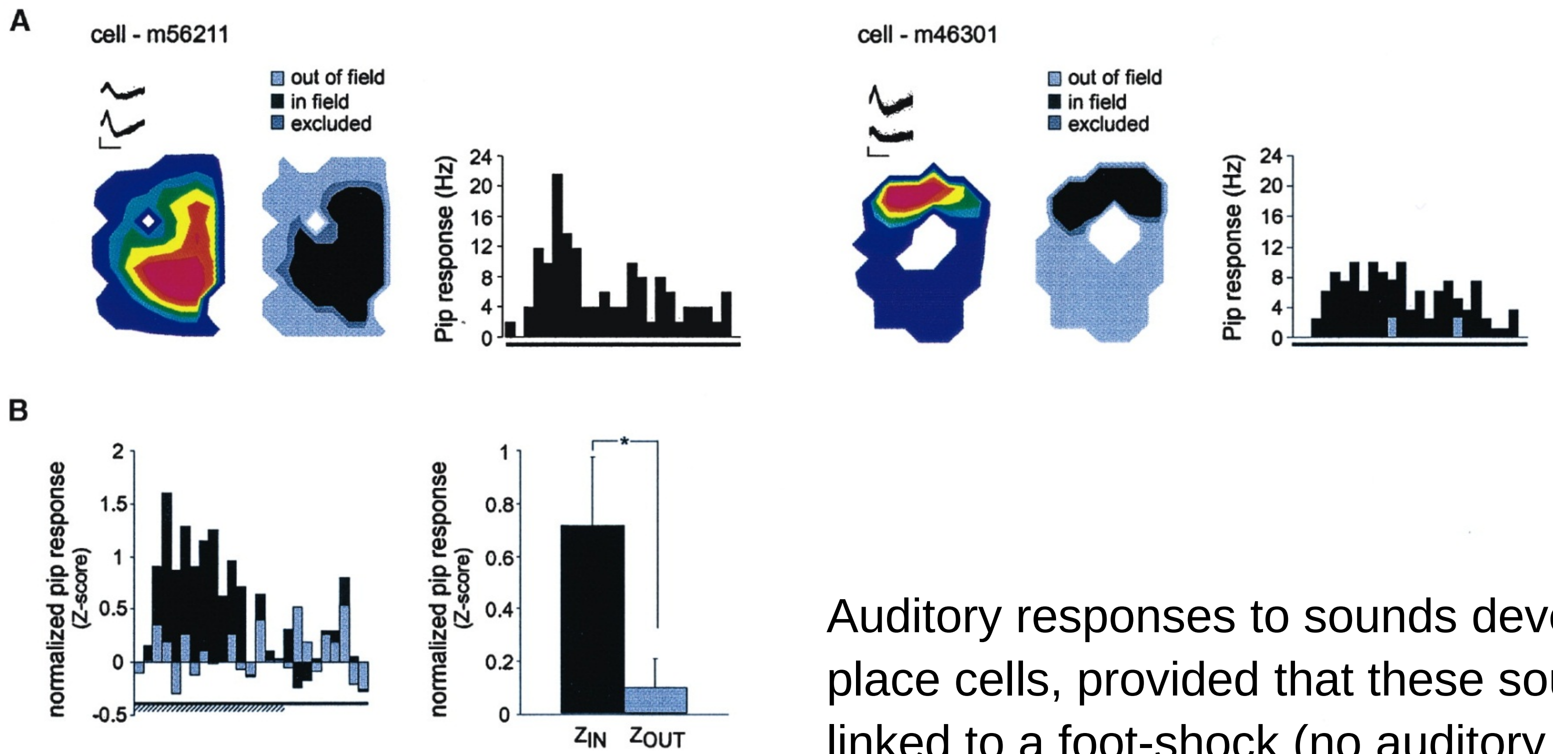
- **Take home message:** Know the anatomy of your favorite brain areas – because:

  Structure ↔ Function

Outline of today's lecture

- **Hippocampus: Introduction and early discoveries**
- **Spatial maps in the hippocampus and related regions:**
  - **Place cells**
  - **Head direction cells**
  - **Grid cells**
- ***Intermezzo*: Structure-function relations in the hippocampus**
- **Beyond the cognitive map: Hippocampus and memory**
- **Open questions**

Coding of place is not everything: Gating of auditory responses by hippocampal place cells



Moita et al., *Neuron* (2003)

Auditory responses to sounds developed in hippocampal place cells, provided that these sounds were temporally-linked to a foot-shock (no auditory responses if the sounds and foot-shocks were presented randomly at the same rate but un-correlated to each other).
Auditory responses occurred only when the animal was inside the place field of the neuron.

Receptive Fields – some properties

(reminder from lecture #1 about receptive fields of sensory neurons)

- The receptive field is NOT the key computational property of the neuron; instead, the receptive field can be thought as a "permissive property":

if

Stimulus is within the receptive field of the neuron

then

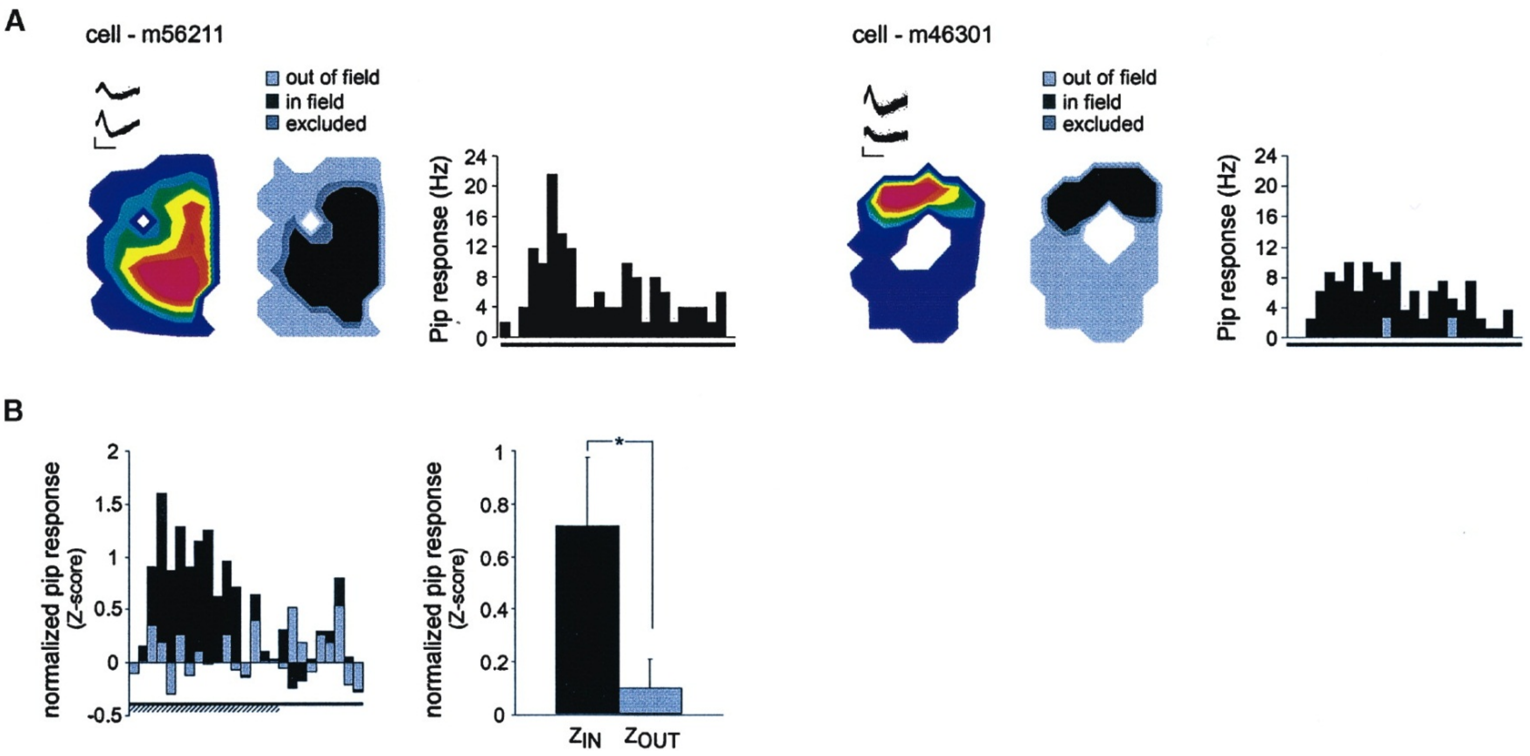
Do whatever (complex) computation the neuron is supposed to do

else

Do nothing

end

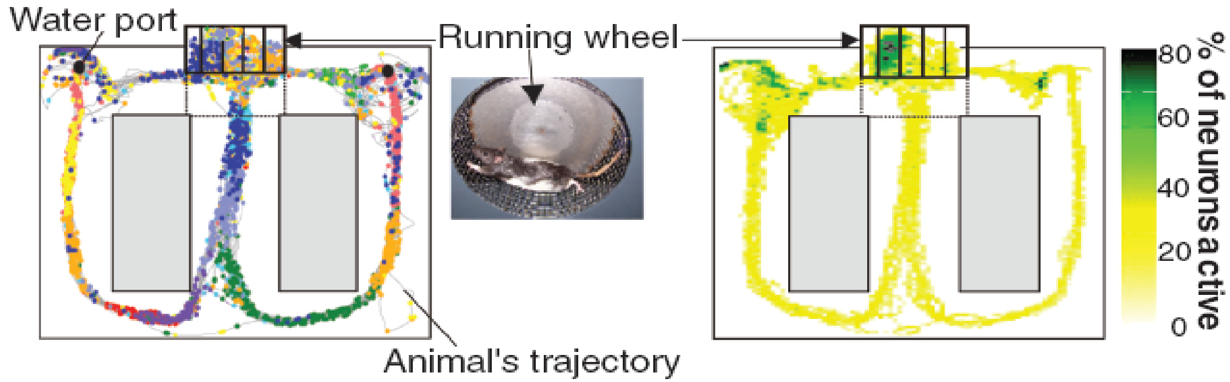
Coding of place is not everything: Gating of auditory responses by hippocampal place cells



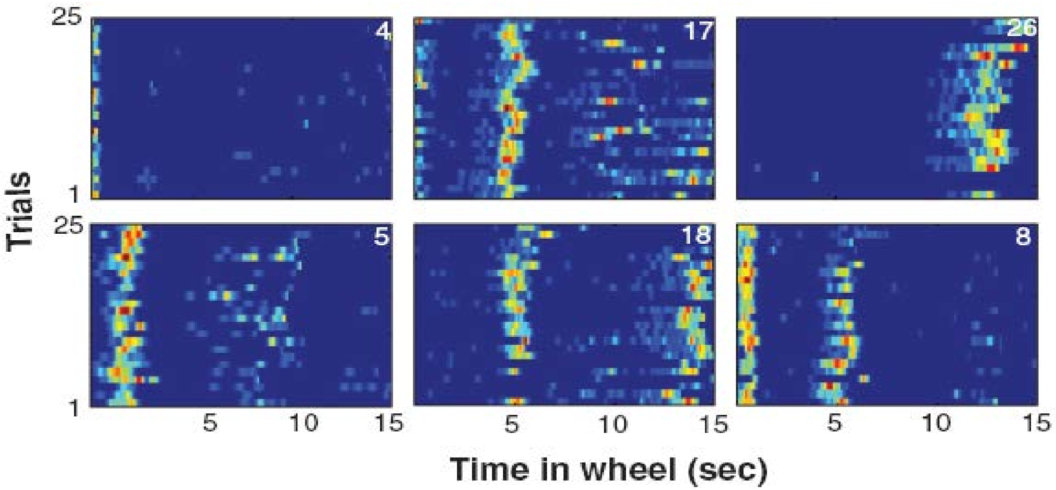
Moita et al., *Neuron* (2003)

Perhaps space is a "permissive property" in place cells, just as it is in the receptive fields of sensory neurons

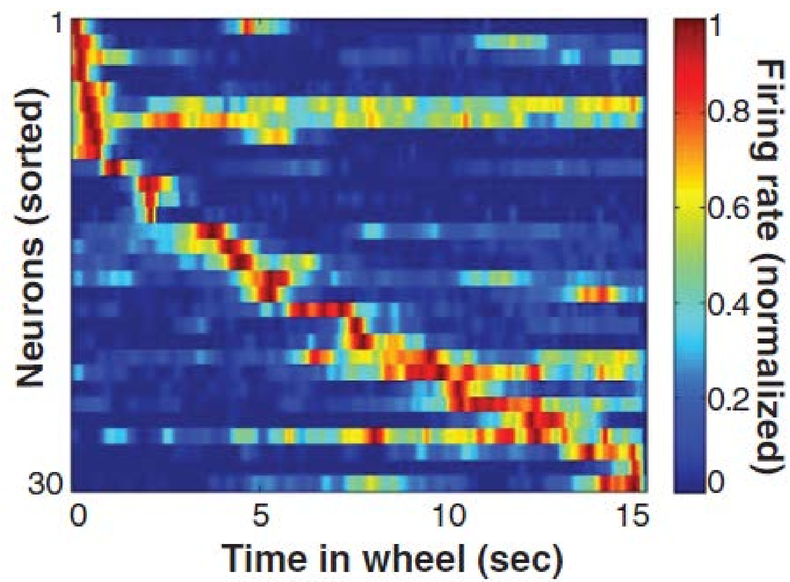
Time cells



Six neurons over multiple trials



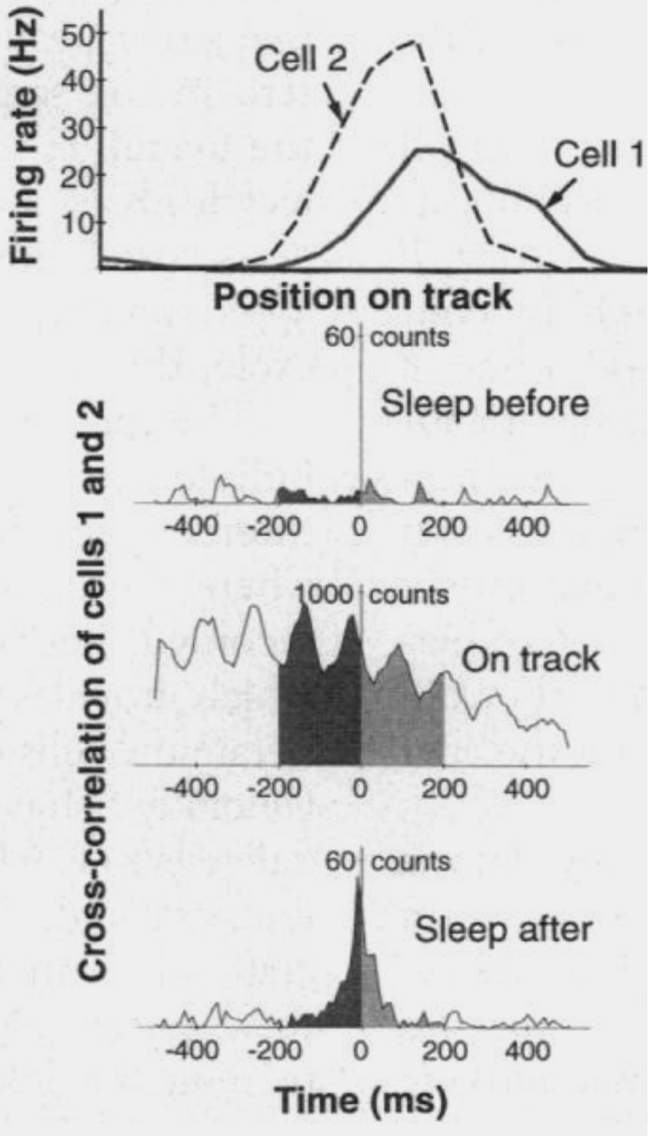
Simultaneously-recorded ensemble of 30 neurons



Caveat: NOT the same ensembles of neurons were activated during actual running (place cells) and during wheel-running (time cells)

Pastalkova et al. , *Science* (2008)

Place cells and memory consolidation during sleep

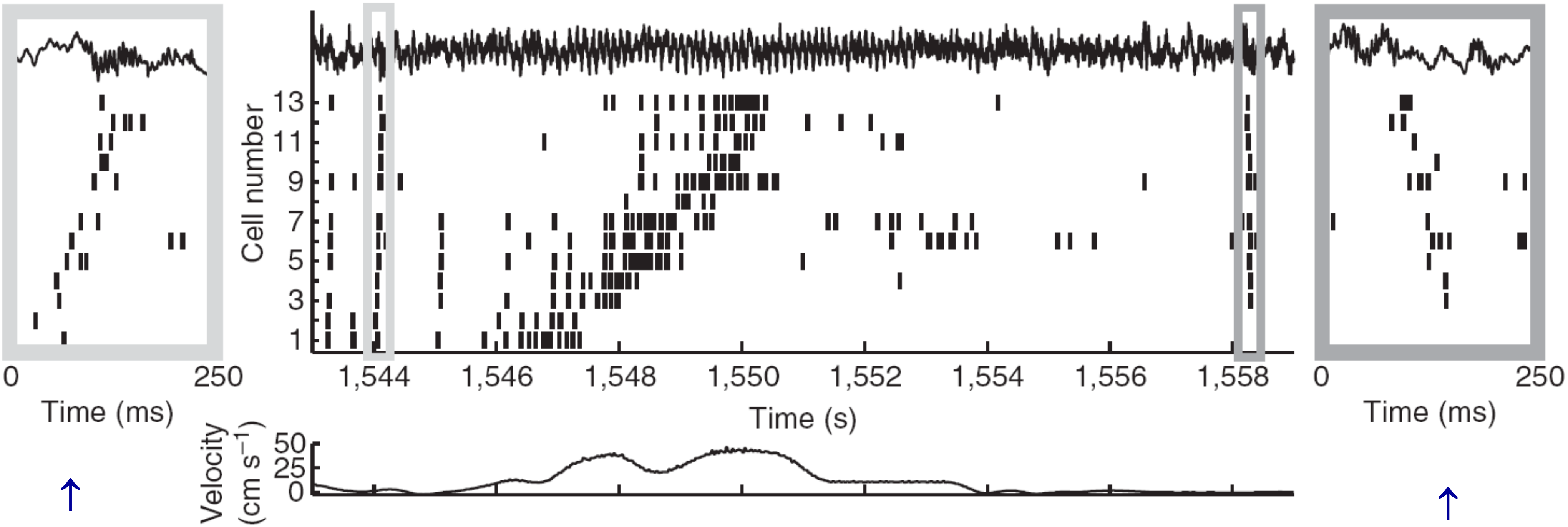


Increased correlations during post-behavior sleep periods, for pairs of cells that were activated together on the linear track.

→ Expected from basic synaptic-plasticity mechanisms (“fire together – wire together”)

Skaggs and McNaughton, *Science* (1996)

Replay and preplay of sequential activity of hippocampal cells, during pauses in behavior: A substrate for memory consolidation?



↑ Preplay event (*usually* forward)

↑ Replay event (*usually* backward)

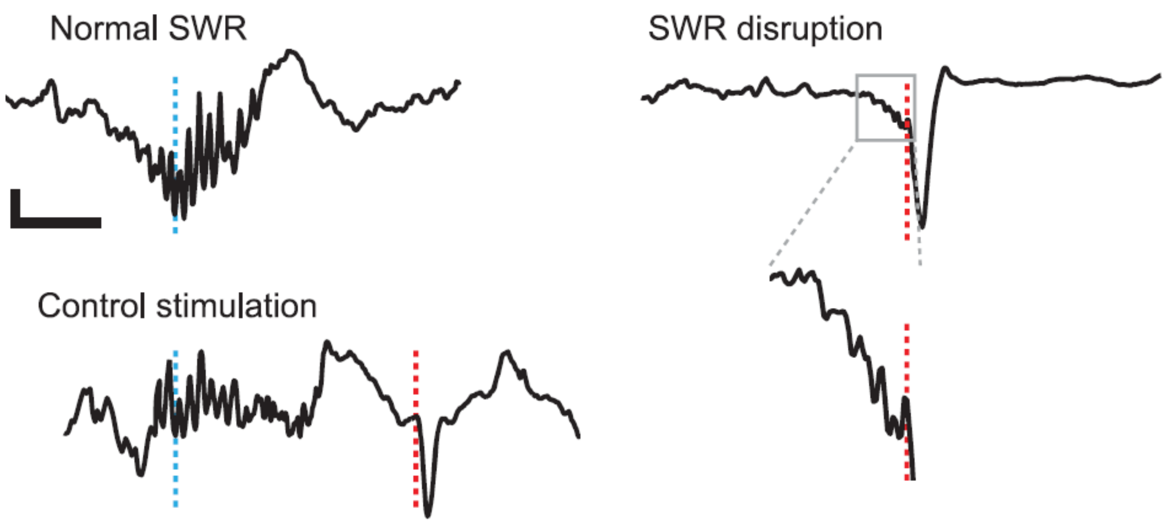
- Cells ordered according to their order of activation during *running*.

Diba and Buzsáki, *Nature Neurosci.* (2007)

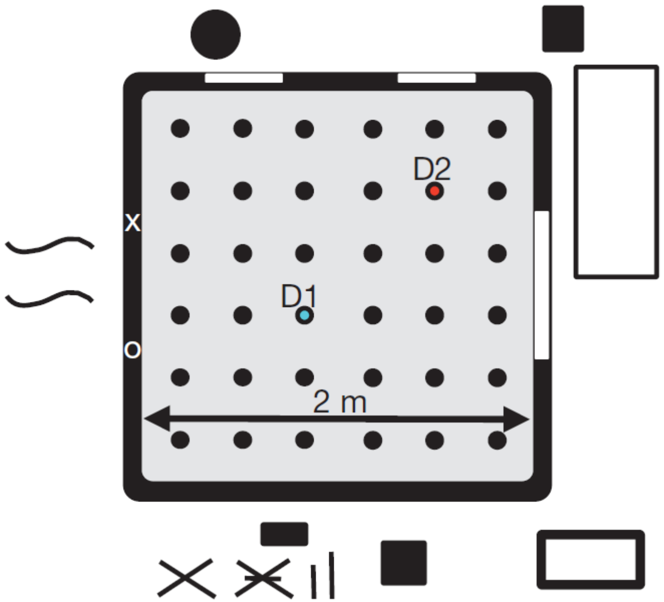
Replay and preplay of sequential activity of hippocampal cells, during pauses in behavior: A substrate for memory consolidation?

- Because a common belief is that memories become ultimately hippocampal-independent, in a "systems consolidation" process – then such replay of events experienced during the day could mark the "writing" of the information from hippocampus to neocortex, on the way of these memories to become hippocampus-independent.

- Preventing hippocampal ripples (and accompanying replay events) impaired performance of rats on a spatial working memory task (Jadhav et al., *Science* 2012).



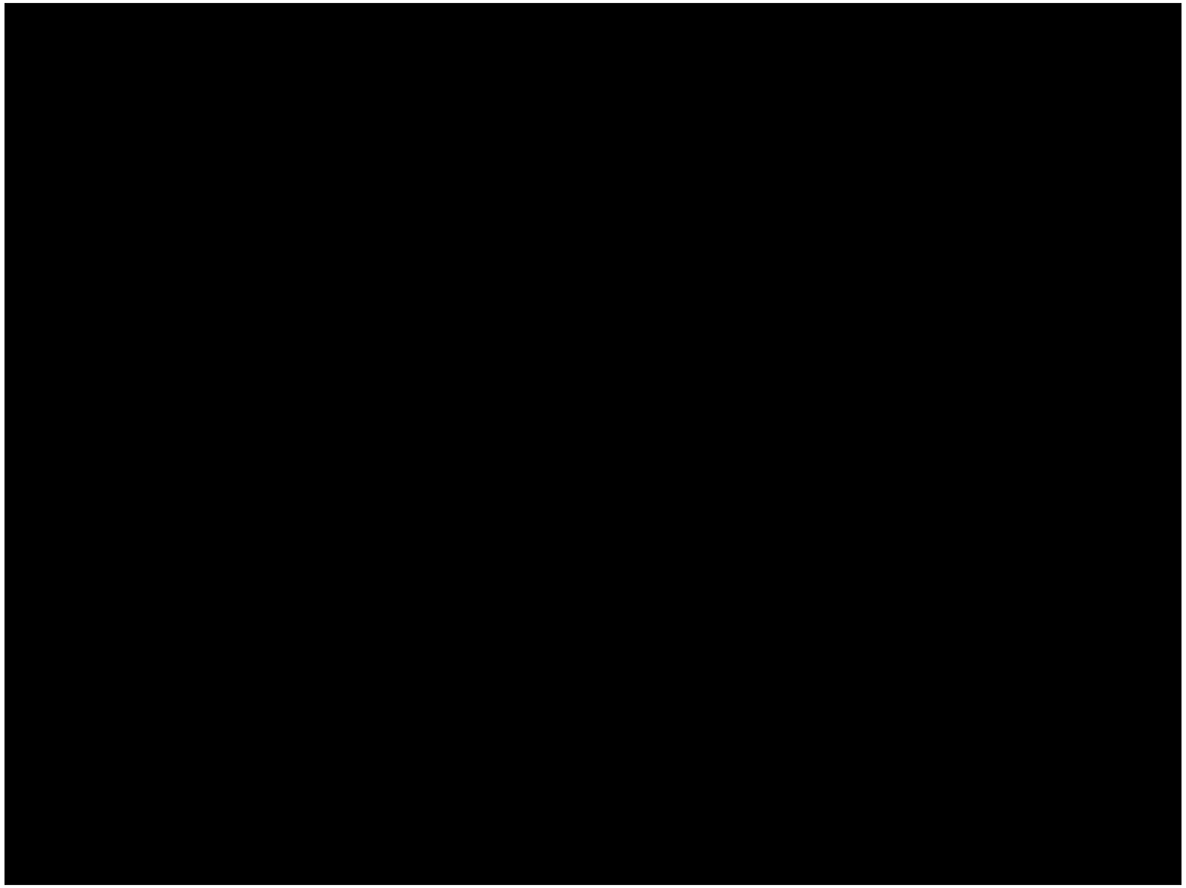
Hippocampal preplay: Future planning



D1: *Home* on Day 1

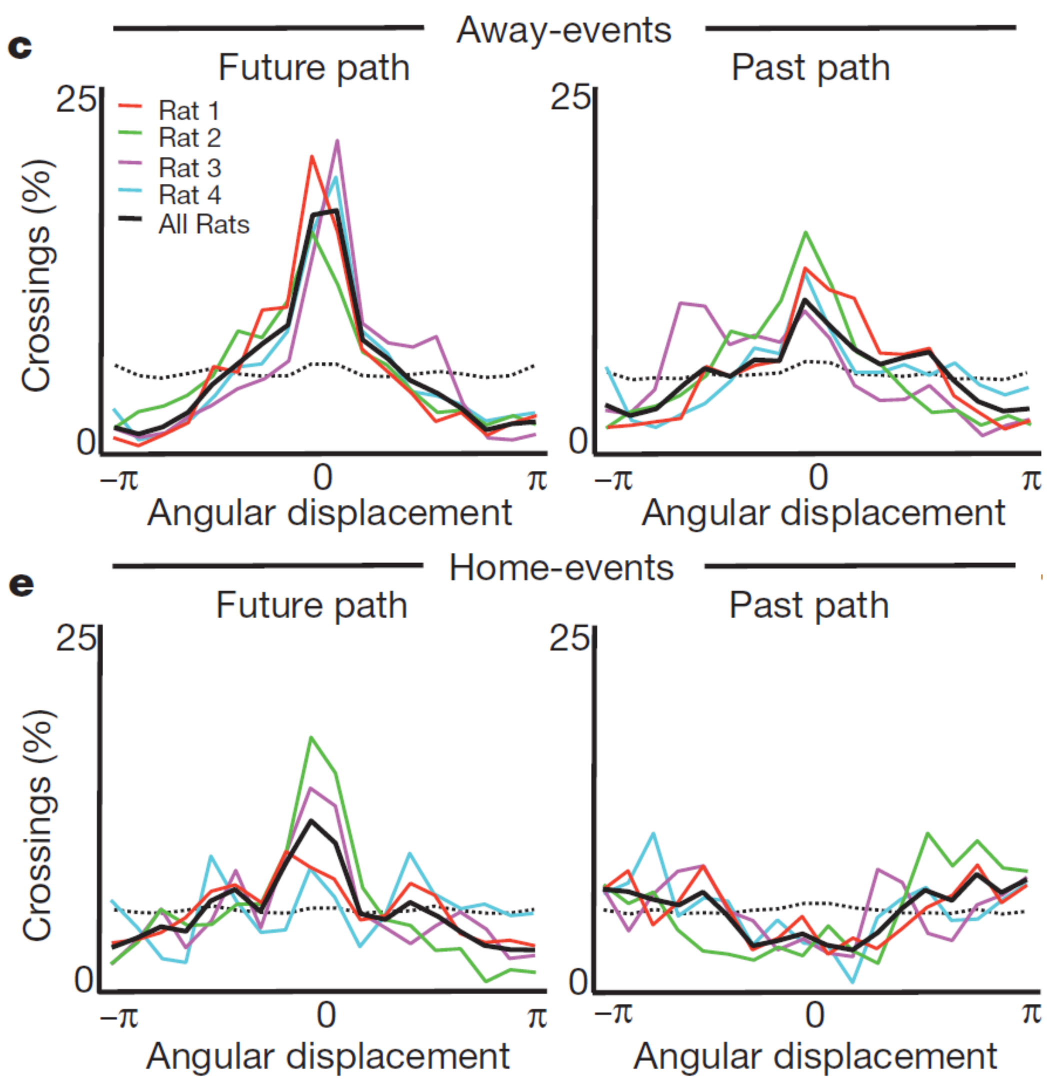
D2: *Home* on Day 2

MOVIE: Trajectory decoding & Preplays towards *Home* and from *Home* to the next goal



Pfeiffer and Foster, *Nature* (2013)

Hippocampal preplay: Future planning

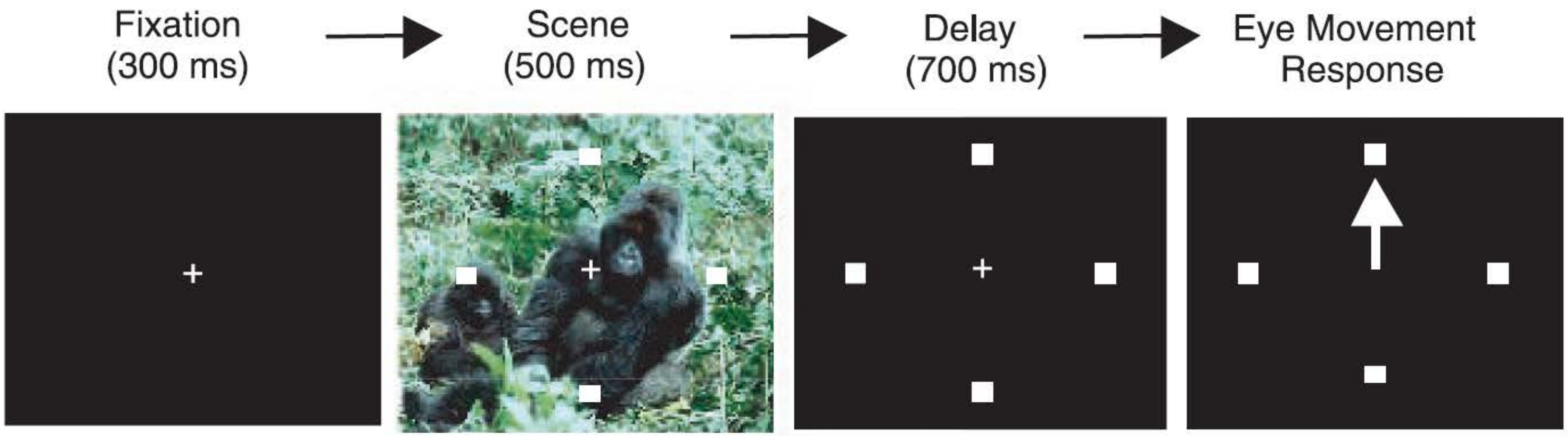


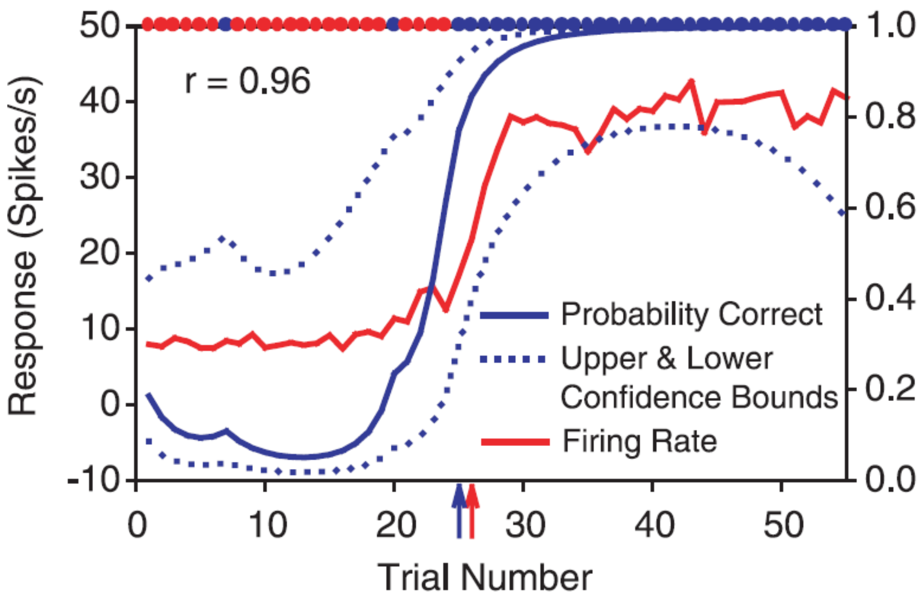
Preplay events that occurred when the rat was away from *Home*

Preplay events that occurred when the rat was at the *Home*

Pfeiffer and Foster, *Nature* (2013)

Hippocampal neural activity in monkeys: Beyond place cells

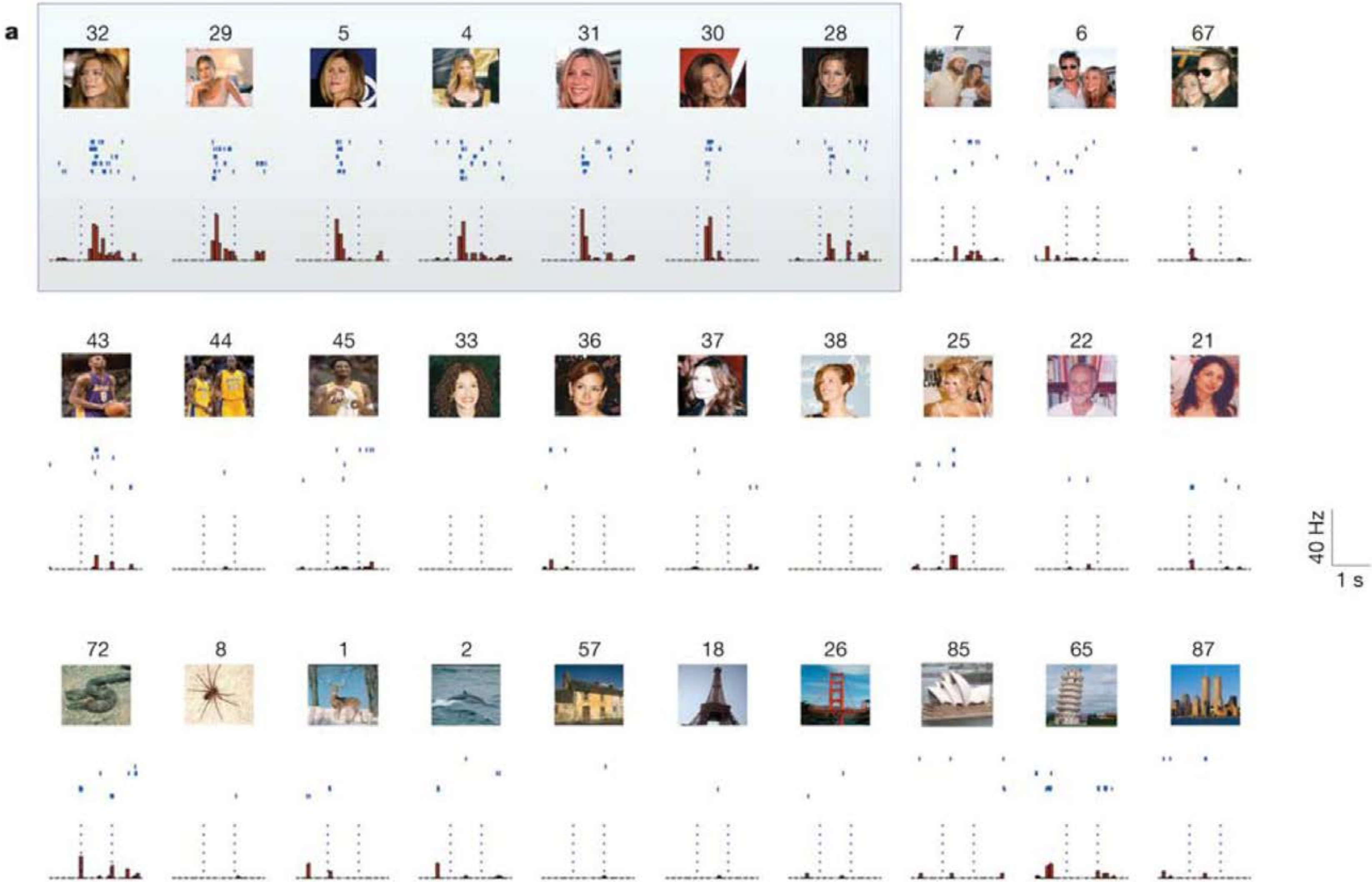




Example of a “changing cell” in monkey hippocampus, which increased its responses simultaneously with the behavioral “Aha moment” during learning of a new association.

Wirth et al., *Science* (2003)

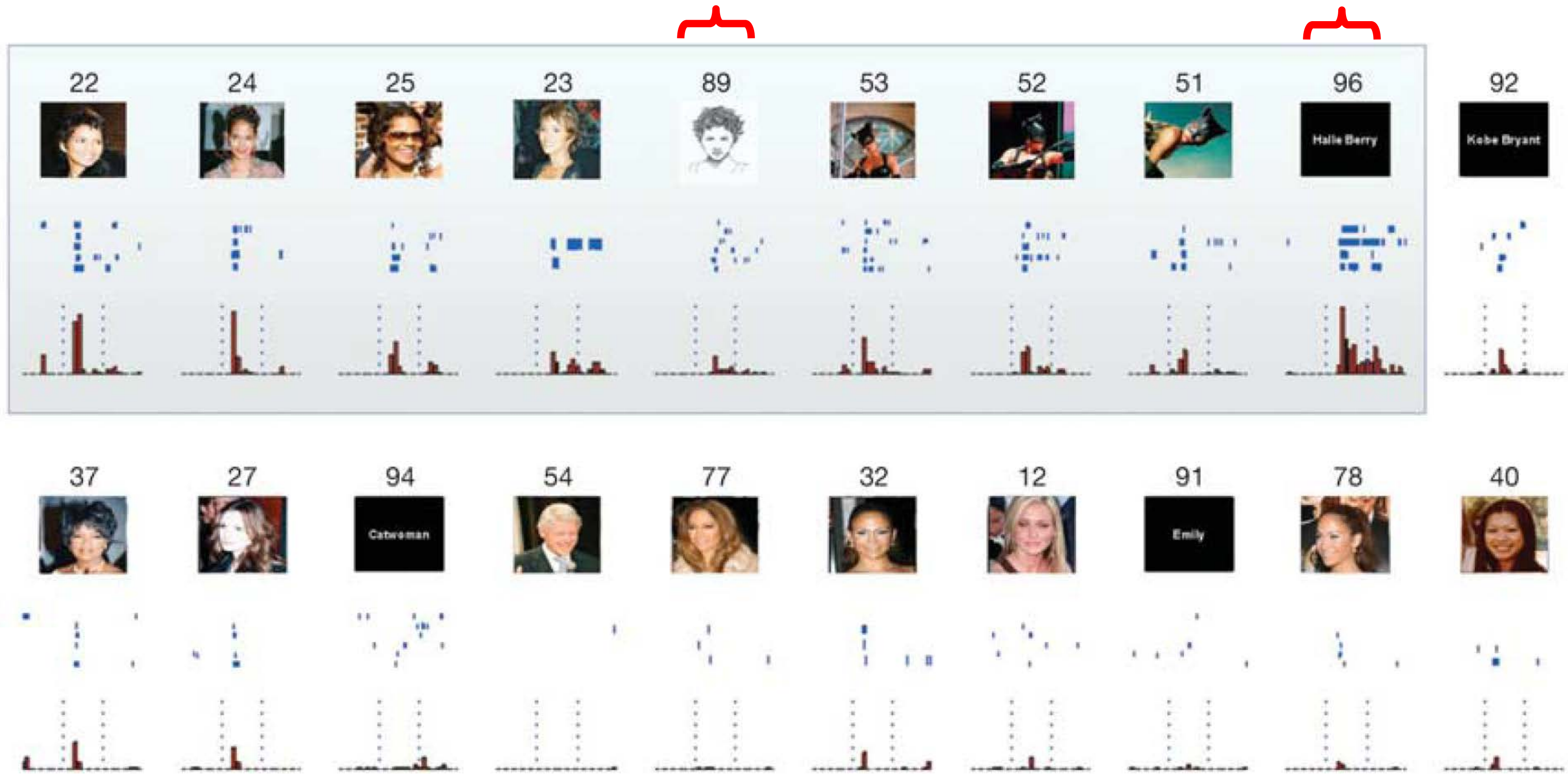
Hippocampal neural activity in humans: Beyond place cells



"Jennifer Aniston cell"

Quian Quiroga et al., *Nature* (2005)

Hippocampal neural activity in humans: Beyond place cells



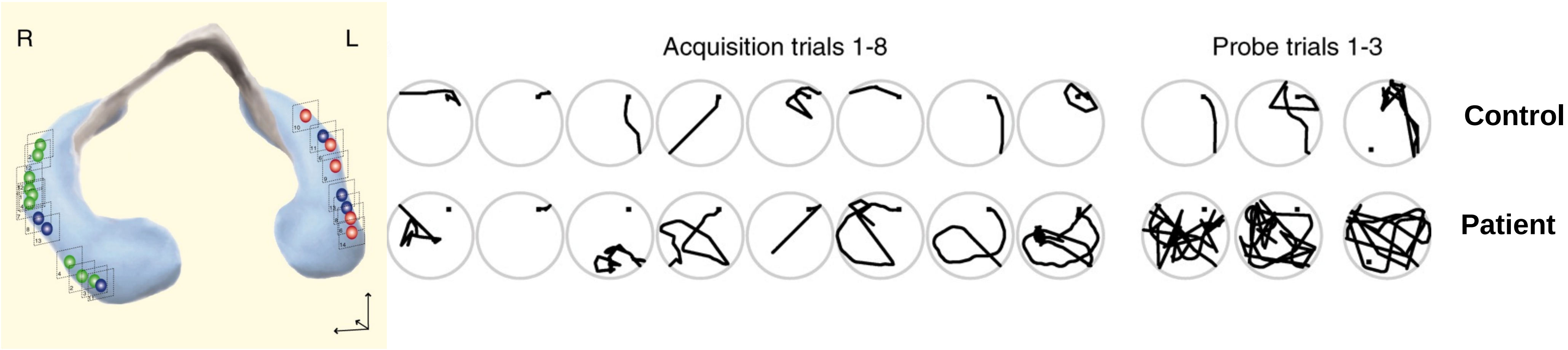
"Halle Berry cell"

Quian Quiroga et al., *Nature* (2005)

Although place-cells were found in human hippocampus (epileptics undergoing electrophysiological recordings as preparation for surgery), hippocampal neurons in humans can also show completely different activity patterns – highly specific responses to very different instantiations of the same famous human (or the same famous building).

Hippocampus: Beyond place cells

- H.M. was impaired generally in declarative memory – was unable to learn and remember hardly any new facts (*semantic memory*) or new events (*episodic memory*), including inability to learn new spatial routes – but his deficit was not specific to space.
- Spatial deficits in a virtual Morris watermaze task are clearly present in human patients with focal lesions in CA1 (a condition called “Transient Global Amnesia”) – but these patients have other memory deficits as well.



T. Bartsch et al. *Science* (2010)

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Instead of Summary:
Some reasons for studying the hippocampus

- Crucial for memory
- Clinically: The most important area of the brain (Alzheimer's, epilepsy...)
- Memory is a convenient *higher brain function* to study, because you can *quantify* memory performance: So the hippocampus is a convenient starting place for studying higher brain functions more generally
- Beautifully-structured and orderly anatomy (much more than in neocortex)
- Easy to study the basic physiology and molecular properties of hippocampal neurons: Much simpler than in the neocortex
- A <u>higher</u> brain area where a <u>simple</u> internal representation was found – a representation of SPACE – which is a <u>continuous</u>, <u>quantifiable</u>, and <u>metric</u> variable → Amenable to computational modeling.
- Population dynamics of hippocampal networks

Some open questions

- Hippocampus and Space – Gap in spatial scale: No place-cells or grid-cells were measured so far in kilometer-sized environments: Are these cells relevant at all for large-scale navigation in the wild?
- Hippocampus: Space versus memory? Perhaps the hippocampus is a sequence encoder, which can bind sequences of events:
  - Spatial sequences → Spatial memory
  - Temporal sequences → Episodic memory
- Past (memory) versus Future (planning, predictive coding)?

Thank you !

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