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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• **Hippocampus: Introduction and early discoveries**
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The hippocampus

(Amaral and Witter 1989)
The hippocampus is highly conserved across mammals.

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

Egyptian fruit bat

Echidna (ancient egg-laying mammal)

Rat
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.

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).

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

![Diagram of the hippocampus showing DG, CA1, and CA3 regions with neuron projections marked by numbers from 2500 to 8300.](image-url)
The hippocampus is a high-level brain region

- 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 bulbs, such as dolphins

• The hippocampus and emotional processing
  • Papez circuit (1937)
  • Hippocampus as part of the Limbic System (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

John O’Keefe

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

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

- These deficits of spatial memory occur after lesions in dorsal, not ventral hippocampus.
- In rats over-trained 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

A  Male and female range size
polygamy: meadow vole  monogamy: pine vole

B  Relative hippocampal volume

- meadow vole
- pine vole

hippocampal volume

brain volume

0.06

0.05

0.04
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)

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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  - Grid cells

- *Intermezzo:* Structure-function relations in the hippocampus

- Beyond the cognitive map: Hippocampus and memory

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

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
The place fields of hippocampal place cells tile the environment.
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)

Place cells exist also in other species: Big brown bats

A single cell

More examples of place fields from 6 neurons

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

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

**Solution:** 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 (isotropic):
  Same resolution in all directions.

Yartsev & Ulanovsky
Science (2013)
Place cells in humans

Place cells in humans

Place fields rotate with the rotation of prominent external landmarks

Note that this place field is quite stable (session A vs. session C)

(Muller and Kubie 1987)
Place fields are affected by manipulations of the environment’s geometry.
Place fields, however, are not purely visual, and are not even modality-specific — they are multi-modal.

- In this experiment, the place-fields were likely determined mostly by odors 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.

G. J. Quirk, R. U. Muller, J. L. Kubie (1990)
Are place fields affected by the timing of sensory inputs? The case of bat sonar calls

Acoustic information

1 2 3

300 ms

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

Cell 1

Time-window after echolocation call →

# 1
0–78 ms
10.6 Hz

# 2
78–210 ms
10.0 Hz

# 3
210–540 ms
11.3 Hz

# 4
> 540 ms
5.1 Hz

Ulanovsky & Moss,
Hippocampus (2011)
Multiple maps are stored simultaneously in rat hippocampus

“Remapping” between representations of square and circular environments.

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.

Temporal coding of location: Theta phase precession

“Theta Phase precession”: Place cells are firing at progressively earlier and earlier phases of the cycle of the theta oscillation, as the animal runs through the place field.

Thus, spike phase relative to the theta oscillation provides information about the animal’s position (temporal code), on top of the information from the place-field (rate code).
Theta oscillation in bats is very different, casting doubt on the usefulness of theta-based temporal coding of location.

**Short theta-bouts in bats**

LFP, 5–25 Hz

200 µV

BUT: We recently found that phase precession might occur also in bat hippocampus, even in the absence of oscillations: a “non-oscillatory phase code”...

Like in humans...

(Cantero et al. 2003)

...and unlike in rats

(Hollup et al. 2001)
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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 rotate together

Head direction cells “remap” to a new random direction upon removal of cue card – but they remap together
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.
Example cells #1-3: Azimuth, Pitch, and conjunctive Azimuth x Pitch

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

About 35% of Azimuth-tuned cells were also tuned to Pitch or Roll.

Neural basis of map-and-compass navigation?

1. **Map**

2. **Compass**

   ![Head-direction cells](MBvideoHD_smaller.wmv)

   **Presubiculum (PrS)**

   **Place cells**

   **Hippocampus**

   Movie courtesy of Dori Derdikman, 2010

Ranck & Taube
JNS 1990

Movie courtesy of Tor Kirkesola, 2010
The missing link: How do you navigate to goals?

Flight room (6×5×3 m)

Recordings in hippocampal area CA1

Sarel et al., Science (2017)
Goal-Direction cells: bat hippocampal CA1 cells with tuning to the goal’s direction

Sarel et al., *Science* (2017)
Many neurons represent conjunctively the goal-direction and goal-distance: A vectorial representation of spatial goals

Sarel et al., *Science* (2017)
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Grid cells

Grid cells in medial entorhinal cortex (MEC)

Three grid-cells recorded simultaneously on the same tetrode

- 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 (all of them shift & rotate together – like remapping in head-direction cells).
The Mystery: How are the grids formed?

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')

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
Theta oscillation in the rodent entorhinal cortex

Theta in the bat entorhinal cortex...

Grid cell autocorrelation

Sleep Behav TT Ref Behav Ext Ref

Power

Frequency (Hz)

Time lag (ms)

SU MUA
Theta bouts are not required for creating the grids

Yartsev, Witter, Ulanovsky
Nature (2011)
But how are the grids formed?

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’)

**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)

Hypothesized role of grid cells in large-scale navigation

Option 1:
Very large grids for representing very large spaces


*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

**Option 2:** 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 (*Ilia Fiete et al.*)

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**Option 1:** 1-km grid for 1-km space

**Option 2:** Combinatorial grid code

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

Clearly what was found in laboratory experiments cannot work directly outdoors: You cannot tile a 20-km flyway of a bat or a 2-km runway of a rat with laboratory sized place fields (you will need $\sim 10^{12} - 10^{15}$ place cells).

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

A 200-meter long enclosure built at the Weizmann Institute to test these questions.
SUMMARY: Spatial cell types in the hippocampus and entorhinal cortex: The basic elements of the “brain navigation circuit”

Medial entorhinal cortex

Border Cells

Head-direction cells

Ranck, Taube – 1980’s

Mosers, O’Keefe, Knierim 2008

Grid cells

Place cells

O’Keefe – 1971

Hippocampus

Moser – 2005
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
- Head-direction cells → Direction

\[ \text{Map} \]

\[ \text{Compass} \]
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 Technology, Trondheim
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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 electrophysiologically 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

→ 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

- Entorhinal → CA1 connectivity: MEC (grid cells) projects to proximal CA1, whereas LEC (lateral entorhinal cortex = diffuse spatial responses) projects to distal CA1. (and a mirror-image in Subiculum.)

- 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

- 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

Henriksen et al., *Neuron* (2010)
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Coding of place is not everything: Gating of auditory responses by hippocampal place cells

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.

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

everse

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

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?

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

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

- A noted theory proposes 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

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

D1: Home on Day 1
D2: Home on Day 2

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

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

Hippocampal neural activity in humans: Beyond place cells

Quian Quiroga et al., Nature (2005)

“Jennifer Aniston cell”
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.

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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 *higher* brain area where a *simple* internal representation was found – a representation of SPACE – which is a *continuous*, *quantifiable*, and *metric* variable → Amenable to computational modeling.

• Population dynamics of hippocampal networks
Some open questions

- Hippocampus and Space:
  - **Gap in spatial scale:** Are place cells and grid cells relevant at all for large-scale navigation in the wild?
  - **Neural basis of goal-directed navigation:** Vectorial goal-direction and goal-distance cells... BUT: How do you plan your route optimally, or avoid obstacles, or re-orient when the way is lost?
  - **Hippocampus: Space versus memory?** Perhaps the hippocampus is a sequence encoder, which can bind sequences of events:
    - Spatial sequences $\rightarrow$ Spatial memory
    - Temporal sequences $\rightarrow$ Episodic memory
  - **Hippocampus: Past vs. Future:** Remembering the past vs. Planning the future.

Thank you!

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