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
• 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
- Echidna (ancient egg-laying mammal)
- Rat

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.

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”)
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
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

• 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

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

Egocentric navigation: Based on body’s self coordinates ("left/right")

Richard Morris
(original finding: 1982)
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

![Diagram showing male and female range sizes under polygamy and monogamy, with corresponding hippocampal volume graphs.]
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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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

Place cells exits 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?
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

Jacobs et al, PNAS (2010)
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

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

- 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
Multiple maps are stored simultaneously in rat hippocampus

“Remapping” between representations of square and circular environments.

Wills et al., Nature (2005)
Multiple maps are stored simultaneously in the hippocampus

<table>
<thead>
<tr>
<th>SQUARE</th>
<th>1.7</th>
<th>2.6</th>
<th>3.5</th>
<th>4.4</th>
<th>CIRCLE</th>
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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 position: 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).
BUT: No theta oscillations in bat neurons (nor in humans)

Yartsev et al., *Nature* (2011)
Eliav et al., *Cell* (2018)
No movement-related oscillations at any frequency

• 67% of rat neurons (273/409) are significantly oscillatory – almost all at ~8 Hz.
• 0% of bat neurons (0/166) are significantly oscillatory in the 1–20 Hz range.

→ Does this mean there is no temporal coding (phase coding) in bats?
A twist in the story

Eliav et al., *Cell* (2018)
Nonoscillatory phase-locking in bats

- 44% of bat CA1 principal neurons (19/43) show significant nonoscillatory phase-locking.
- In the time-domain, these neurons are nonoscillatory.

Eliav et al., *Cell* (2018)
Nonoscillatory phase-coding of the animal’s position

- 38% of bat CA1 neurons (16/42) show significant nonoscillatory phase-coding of position.

Eliav et al., *Cell* (2018)
Conclusion: The importance of the Comparative Approach

- Analysis of in vivo data from bats did not reveal movement-related oscillations at any frequency – neither in grid cells, nor place cells, nor interneurons (“theta cells”) – neither in 2D nor in 3D flight.

- In rodents – 3 phenomena that are coupled together:

<table>
<thead>
<tr>
<th>Rodents:</th>
<th>Bats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oscillations (theta)</td>
<td>X Oscillations (theta)</td>
</tr>
<tr>
<td>Synchronization</td>
<td>✓ Synchronization</td>
</tr>
<tr>
<td>Coding (of position)</td>
<td>✓ Coding (of position)</td>
</tr>
</tbody>
</table>

- The comparative approach allows to identify what is invariant across species – and what is not.

- We predict similar nonoscillatory coding also in humans (which lack theta).
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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

Fields rotate with cue card

Fields shift after cue card removal
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
Yarasev, Witter, Ulanovsky
Nature 2011
3-D head direction cells in bats

Euler Angles

3D head-direction cell

Neural basis of map-and-compass navigation?

1. **Map**
   - **Place cells**
   - **Hippocampus**

2. **Compass**
   - **Head-direction cells**
   - **Presubiculum (PrS)**

Ranck & Taube
JNS 1990

Movie courtesy of Tor Kirkesola, 2010

Movie courtesy of Dori Derdikman, 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

Zero preferred angle

Non-zero preferred angle

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.
Support for the attractor network model of grid cells comes from the finding that grid cells are organized in \textit{discrete} 'modules'.

Stensola et al., \textit{Nature} (2012)

2-D grid cells in bats

Yartsev et al., *Nature* (2011)
3-D grid cells in bats

Gily Ginosar
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
  - Grid cells

- **Hippocampus**
  - Place cells

**Place cells**: Ranck, Taube – 1980’s

**Grid cells**: Mosers – 2005

**Border Cells**: Mosers, O’Keefe, Knierim – 2008

**Head-direction cells**: Mosers – 2005

**Medial entorhinal cortex**: Ranck, Taube – 1980’s

**Hippocampus**: O’Keefe – 1971
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
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
- **Goal-direction cells** → Goals

Map

Compass

"Waze"
BUT: How are large-scale spaces encoded in the brain?

Geva-Sagiv, Las, Yovel, Ulanovsky
• Nature Rev. Neurosci., 2015
• PNAS, 2011
1. Developing on-board 16-channel neural logging system
1. Developing on-board 16-channel neural logging system
2. Large-scale precise localization system

BeSpoon, Inc.

- 10-cm precision
3. Large behavioral setup
Preliminary results

- Food rewards at both ends
- Direct flights from start to end
- 100 laps / session (20 km / 1.5 hrs)

→ Utilizing the bat’s flight-speed to measure the representation of large spaces.

- Flight speeds: 7-8 m/s
Example cell from dorsal CA1

Properties of this spatial code:
• Large fields
• Multiple fields
• Multi-scale
Properties of this spatial code:

• Large fields
• Multiple fields
• Multi-scale

→ Looks very different from place cells recorded in small lab setups!
**Mechanism:** How can such a multi-scale firing come about? \( \text{CA3} \rightarrow \text{CA1} \).

**Function:** What is the computational advantage of such a multi-field, multi-scale code? Hierarchical coding?

Properties of this spatial code:
- Large fields
- Multiple fields
- Multi-scale

→ Looks very different from place cells recorded in small lab setups!
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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.

Moita et al., Neuron (2003)
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

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")

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

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

~200 neurons recorded simultaneously with electrophysiology

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

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). ➔ Social cells? Concept Cells?
Social place-cells in the bat hippocampus
Bats are highly social mammals
A delayed-match-to **place** task

**Step 1: Other bat flying**

Wireless neural recordings in the hippocampus
A delayed-match-to **place** task

**Step 2: Implanted bat flying**

- Wireless neural recordings in the hippocampus
- Average delay: 12.7 seconds.
**A delayed-match-to place task**

Step 1: Other bat flying

- **Attention**: The implanted bat has to attend to the location of the other bat.
- **Behavioral ‘space clamp’**:
  - The implanted bat is stationary when the other bat is flying.
  - We used an accelerometer to rule out miniature head movements.
Example of a social place-cell in bat CA1

Omer et al., Science (2018)
Example of a place-cell in bat CA1

Observer flying

Demonstrator flying

Omer et al., *Science* (2018)
Example of a CA1 neuron tuned to both Observer flying and Demonstrator flying.

Omer et al., *Science* (2018)
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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? How are large-scale spaces represented in the brain?
  - **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.

- **The Social Hippocampus.**

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Thank you!

Nachum Ulanovsky

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