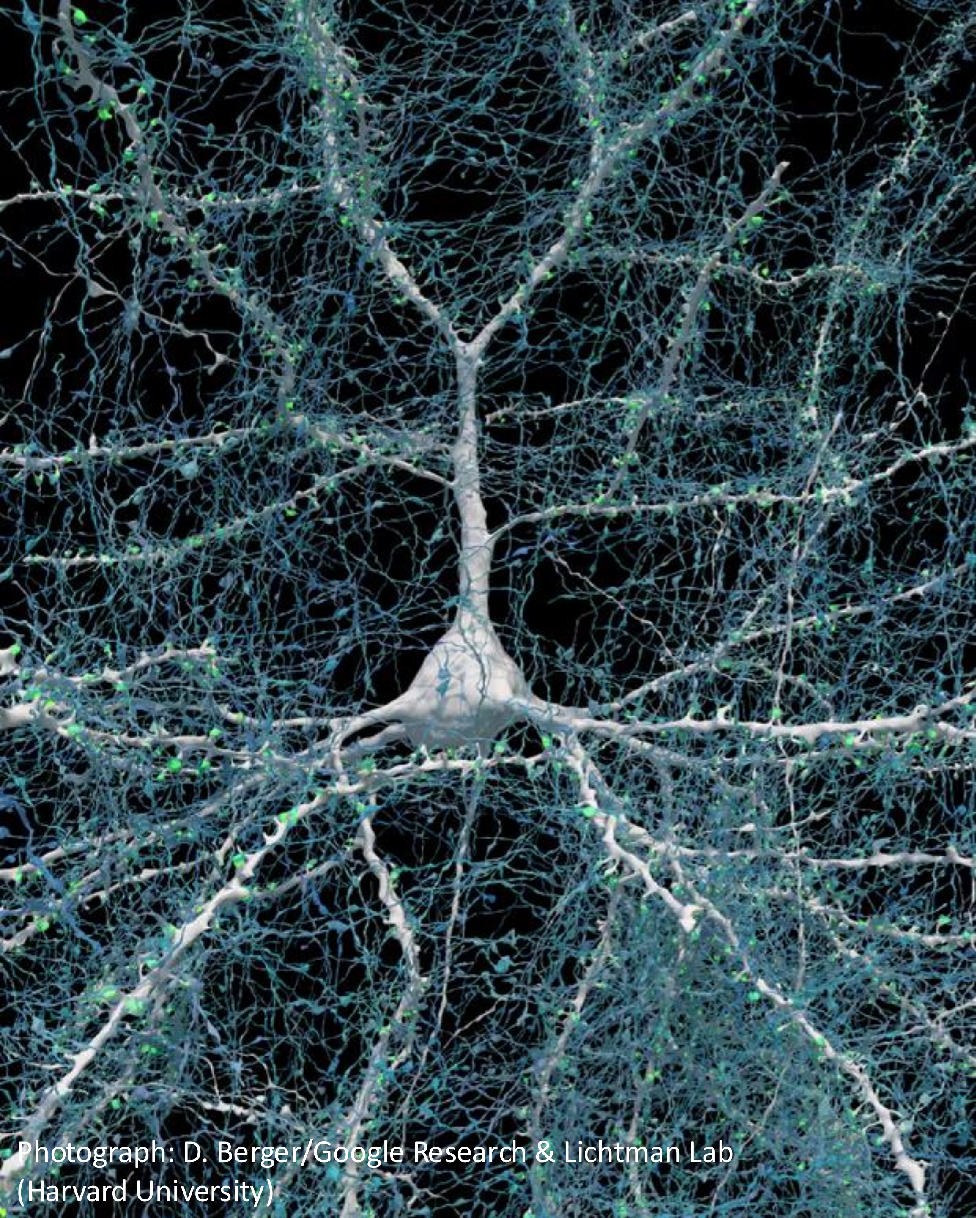
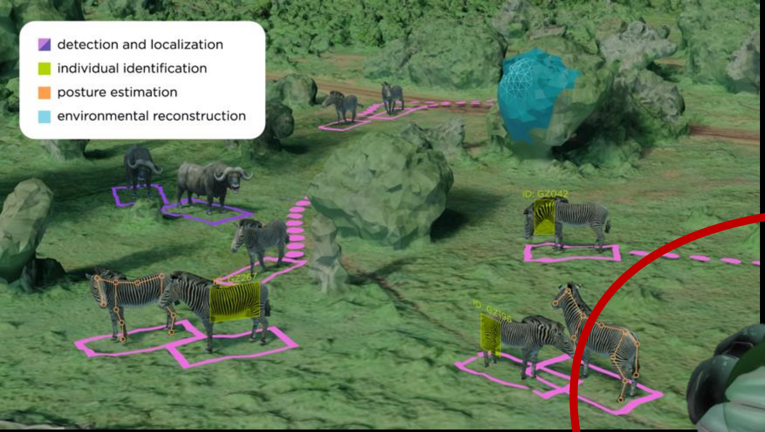

Photograph: D. Berger/Google Research & Lichtman Lab (Harvard University)

Nx-435: Emerging topics in systems neuroscience

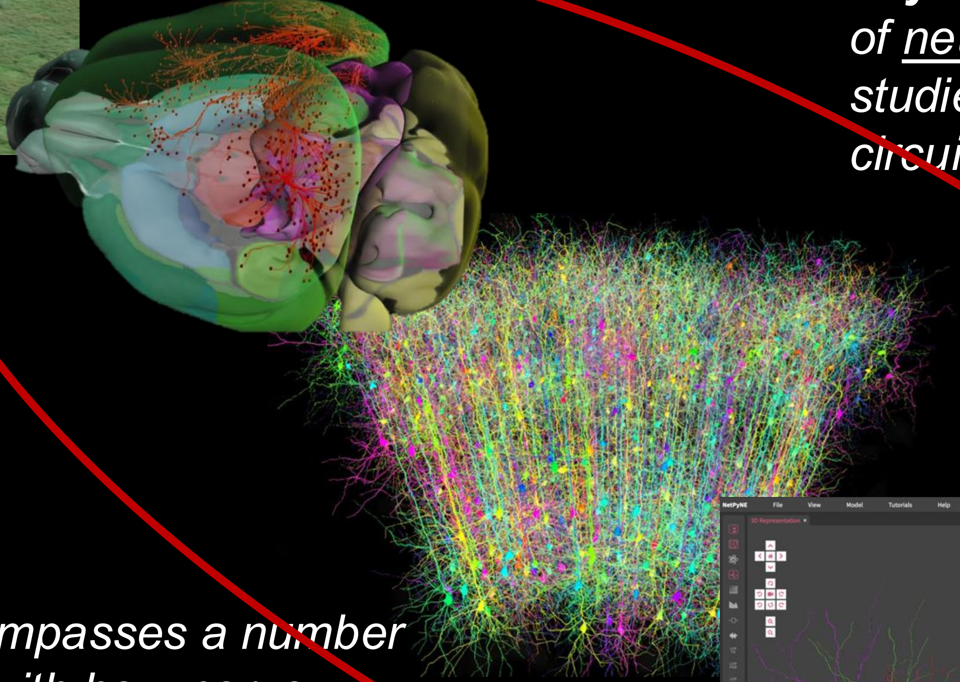
Mackenzie Mathis, PhD

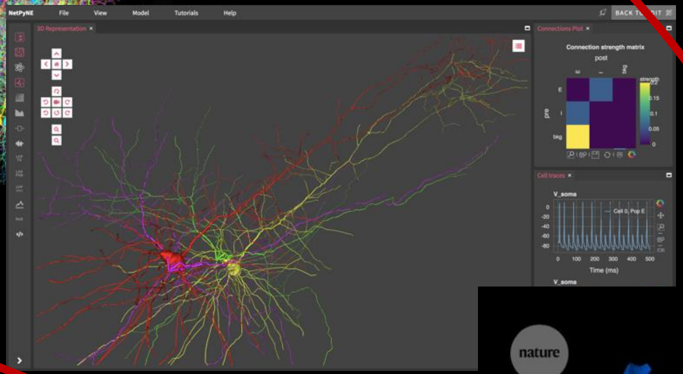
& the Teaching Team!



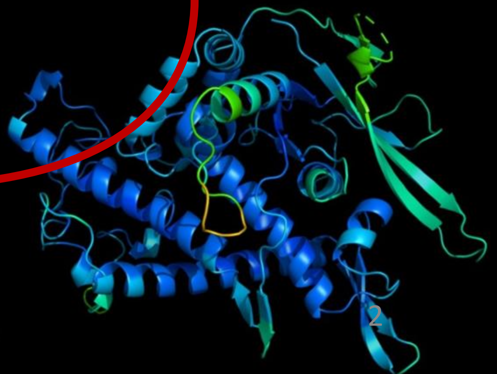
What is Systems Neuroscience?

*“**Systems neuroscience** is a subdiscipline of neuroscience and systems biology that studies the structure and function of neural circuits and systems.” - Wikipedia*

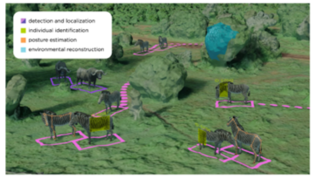


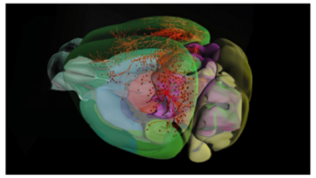


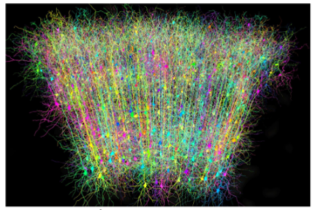
*“Systems neuroscience encompasses a number of areas of study concerned with how nerve cells behave when connected together to form neural pathways, neural circuits, and larger brain networks. **At this level of analysis, neuroscientists study how different neural circuits analyze sensory information, form perceptions of the external world, make decisions, and execute movements.**”*

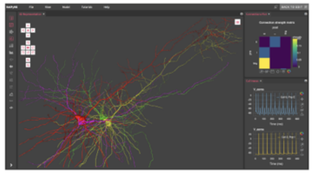


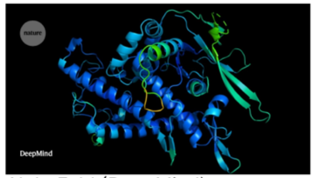
How can we study this?


Tuia et al. 2022


Allen Institute


Brainbow (Litchman Lab)


NetPyNE

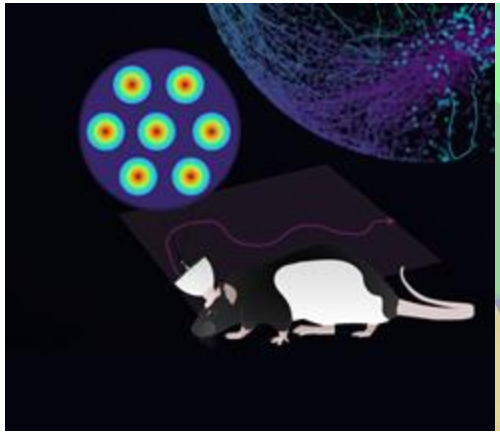

AlphaFold (DeepMind)

Level	Experimentally-derived data	Data-driven & Theory-driven models	
Environment		**multi-modal ML models**	Computation
Behavior	**video recordings, EMGs**	**computer vision & RL**	Model Behaviors
Brain	**functional imaging (2P, 1P, fMRI, EEG)**	**network neuroscience**	Algorithm
system (circuits)		**RNNs, transformers**	Control Systems
Neurons (& glia)	**pharmacology, patch clamping**	**Hodgkin-Huxley LIF (NEURON, nengo, etc)**	Neural Network models
Synapses		**ODEs, LIF**	Implementation
Genes & molecules, proteins	**RNAseq, proteomics**	**AlphaFold, gene-regulatory networks**	

Experimentally-derived data → **Data-driven & Theory-driven models**

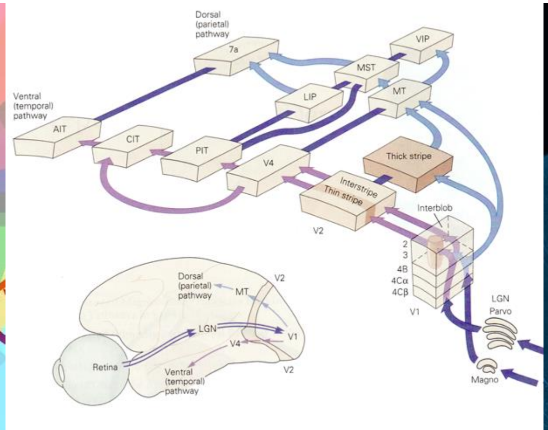
Inspired from:
Krakauer et al. Neuron 2017
Basset et al. Nature Neuro 2017
Terry Sejnowski & David Marr

Memory systems

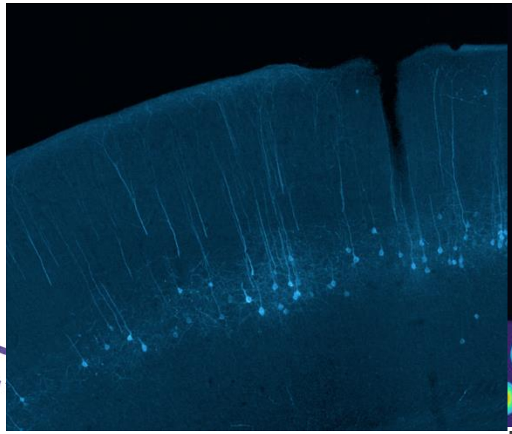


Decision-making

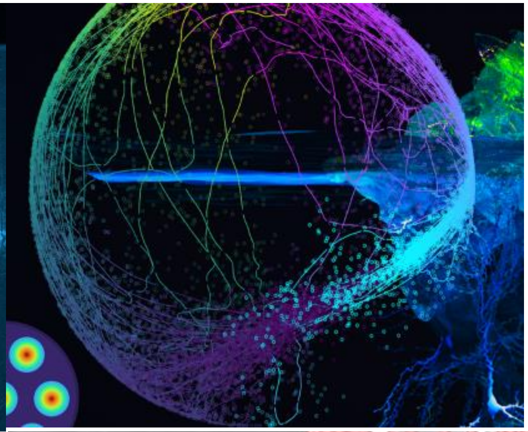
Visual systems

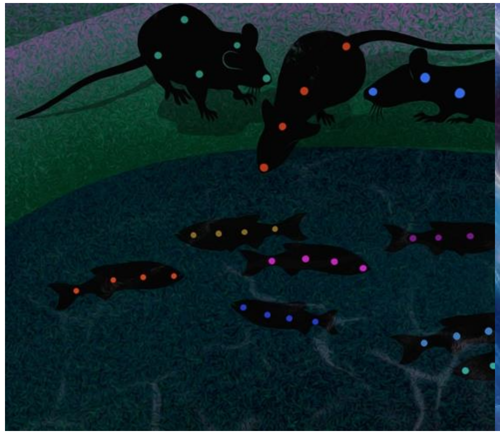


Motor systems



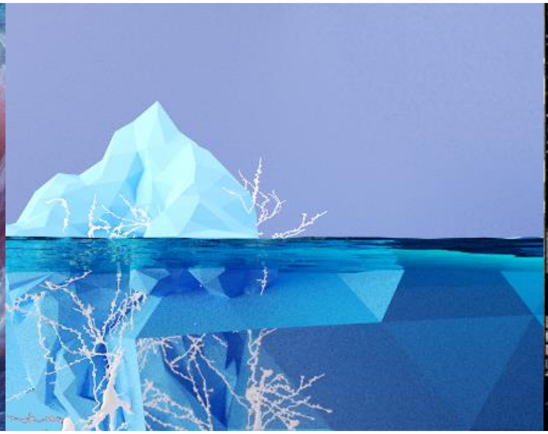
Neural Data Analysis



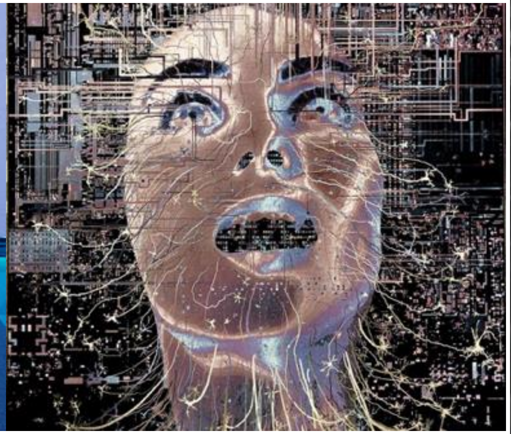


Behavior Analysis

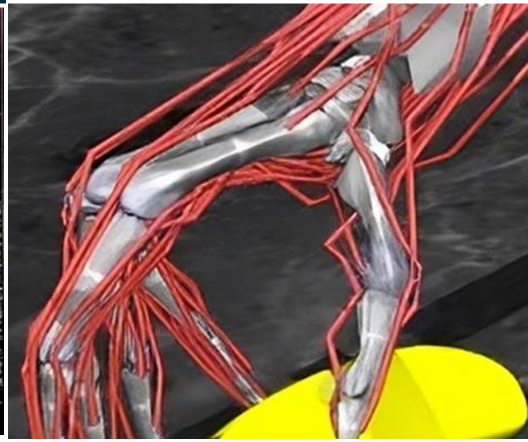
Encoding of Space



NeuroAI



BCIs for systems neuro



Skill learning

Cognition Motor systems

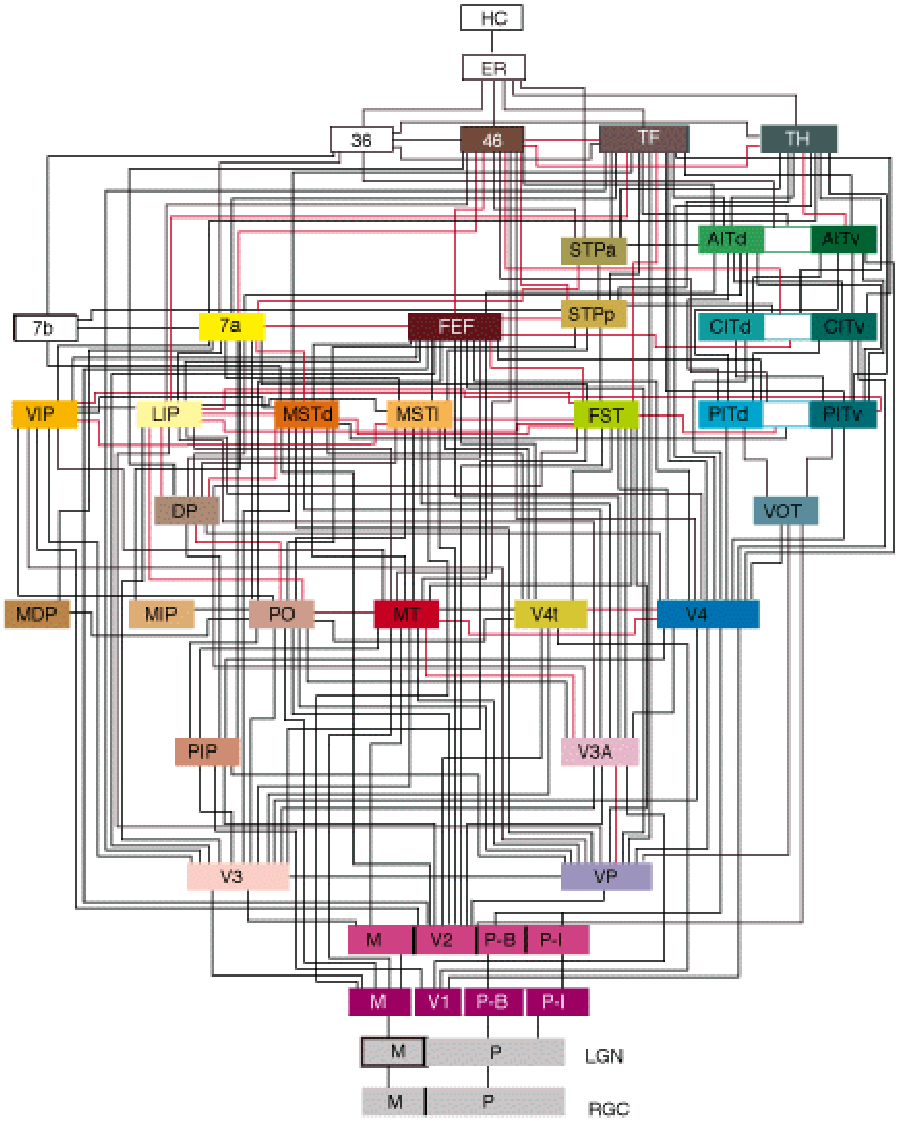
Memory systems

Encoding of Space

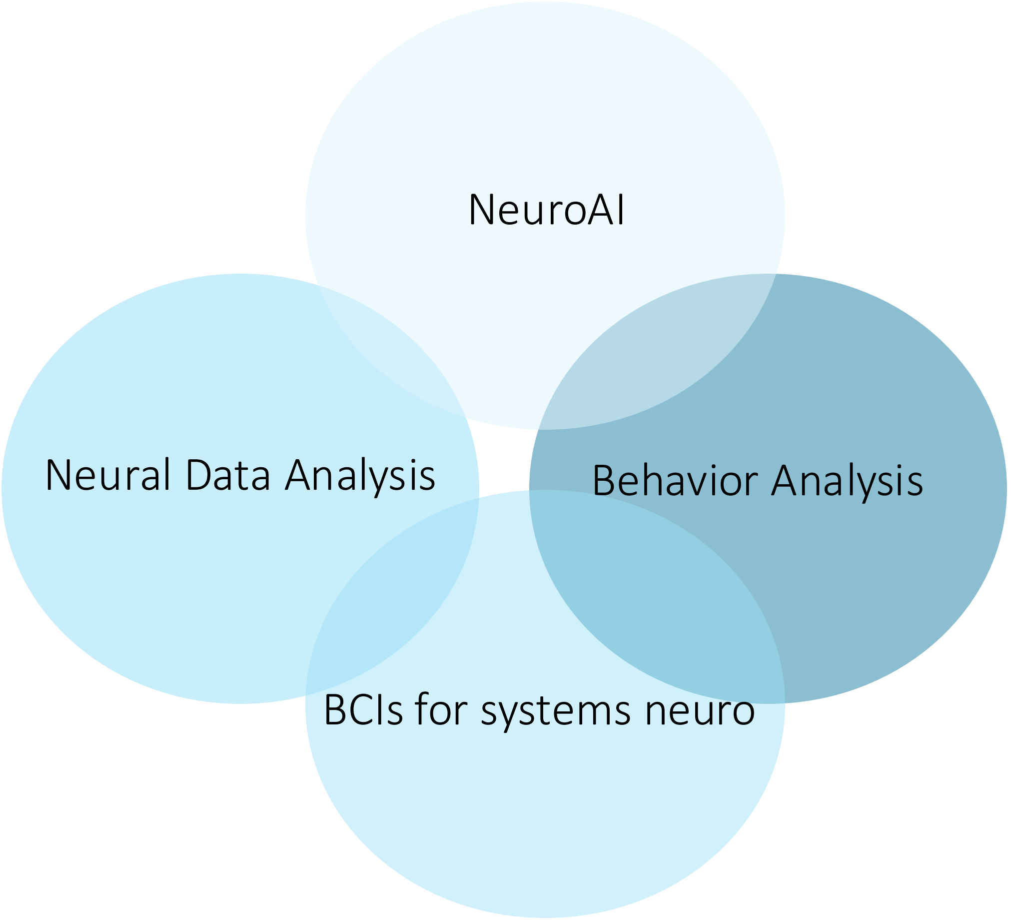
Decision-making

Visual systems

“thinking & acting”



Felleman and Van Essen *Cerebral Cortex* 1991



Final course logistics:

- Final exam is the same style as the Quiz
  - You can bring a A4 double side sheet of notes

- Please take the **“course survey”** on Moodle! 🙏

What’s new in systems neuroscience in 2025 …

Article | Open access | Published: 03 February 2025

Left–right-alternating theta sweeps in entorhinal–hippocampal maps of space

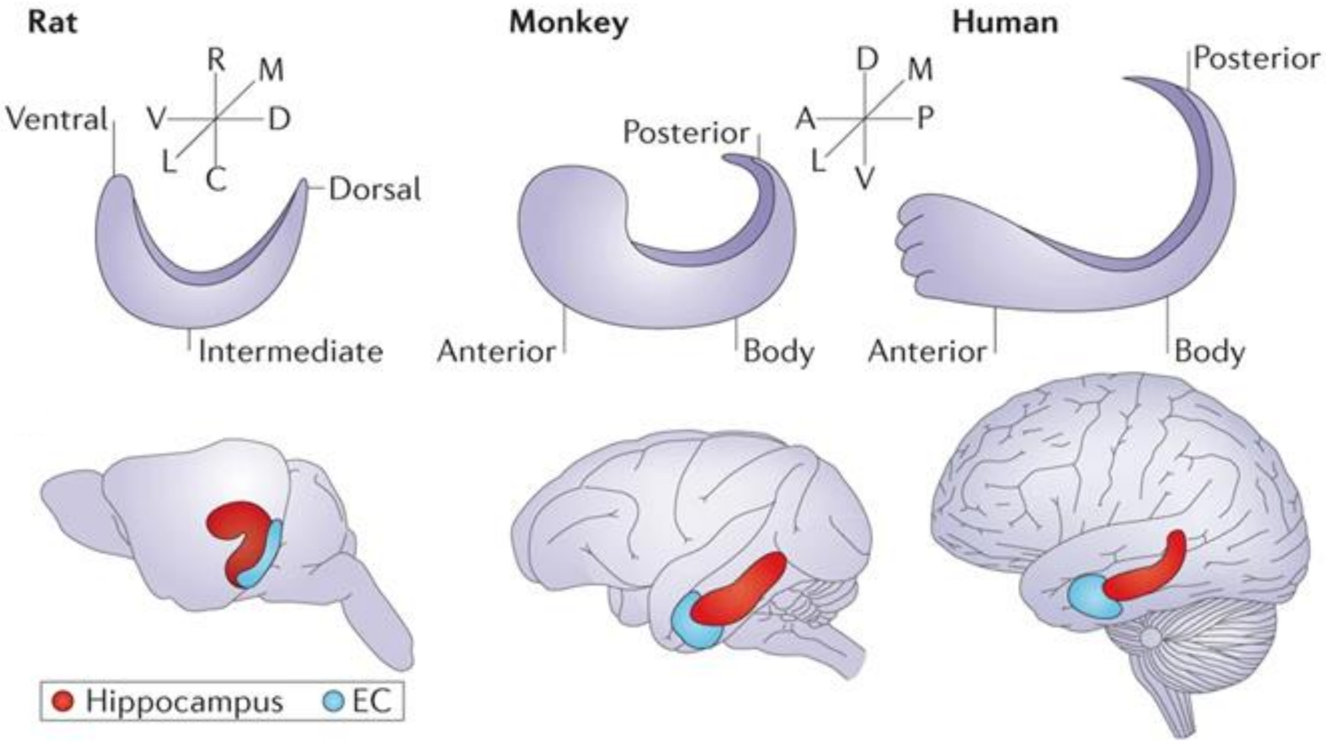
Abraham Z. Vollan, Richard J. Gardner, May-Britt Moser & Edvard I. Moser

Nature **639**, 995–1005 (2025) | Cite this article

27k Accesses | **146** Altmetric | Metrics

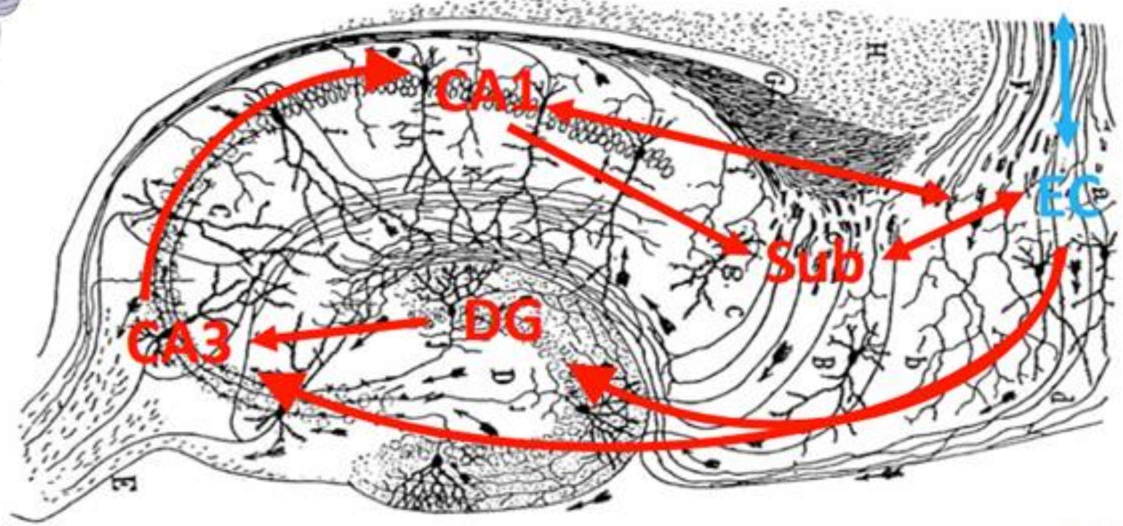
Nature 2025

Recap - The Hippocampus



The hippocampus is a **highly conserved brain structure** across all mammals, including humans

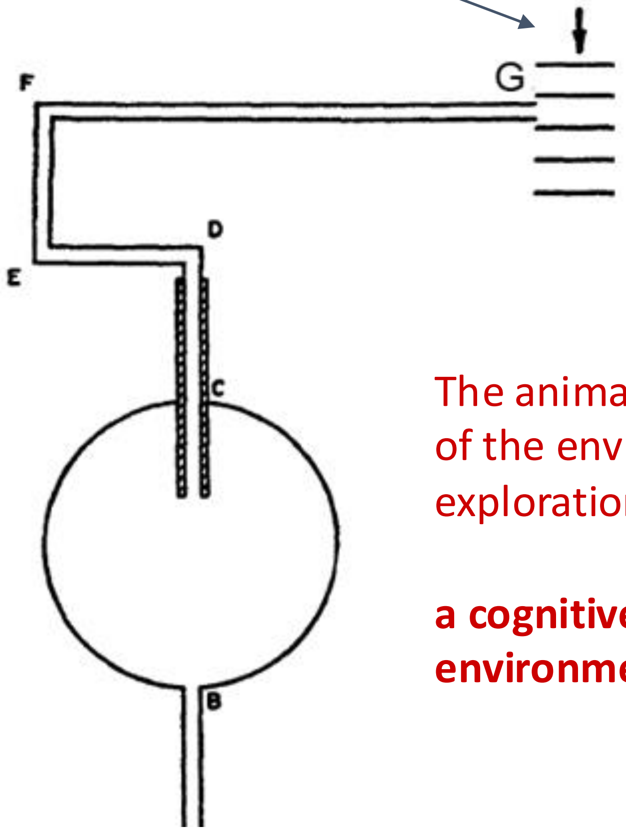
Primarily **uni-directional processing loop**: entorhinal cortex -> hippocampus -> entorhinal cortex



EC -> Entorhinal cortex
Ca1: Cornu Ammonis 1
Ca3: Cornu Ammonis 3
DG: Dentate Gyrus
Sub: Subiculum

The cognitive map

Food reward



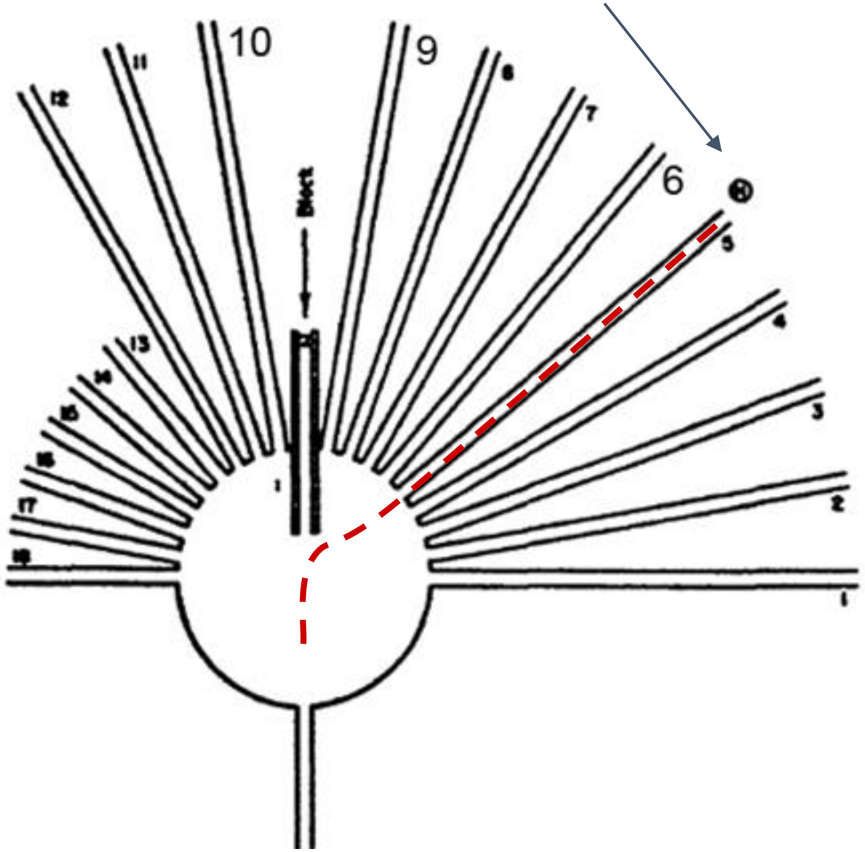
Initial training setup

The animal acquires a structure of the environment during initial exploration

a cognitive map of the environment

Test setup

Food reward



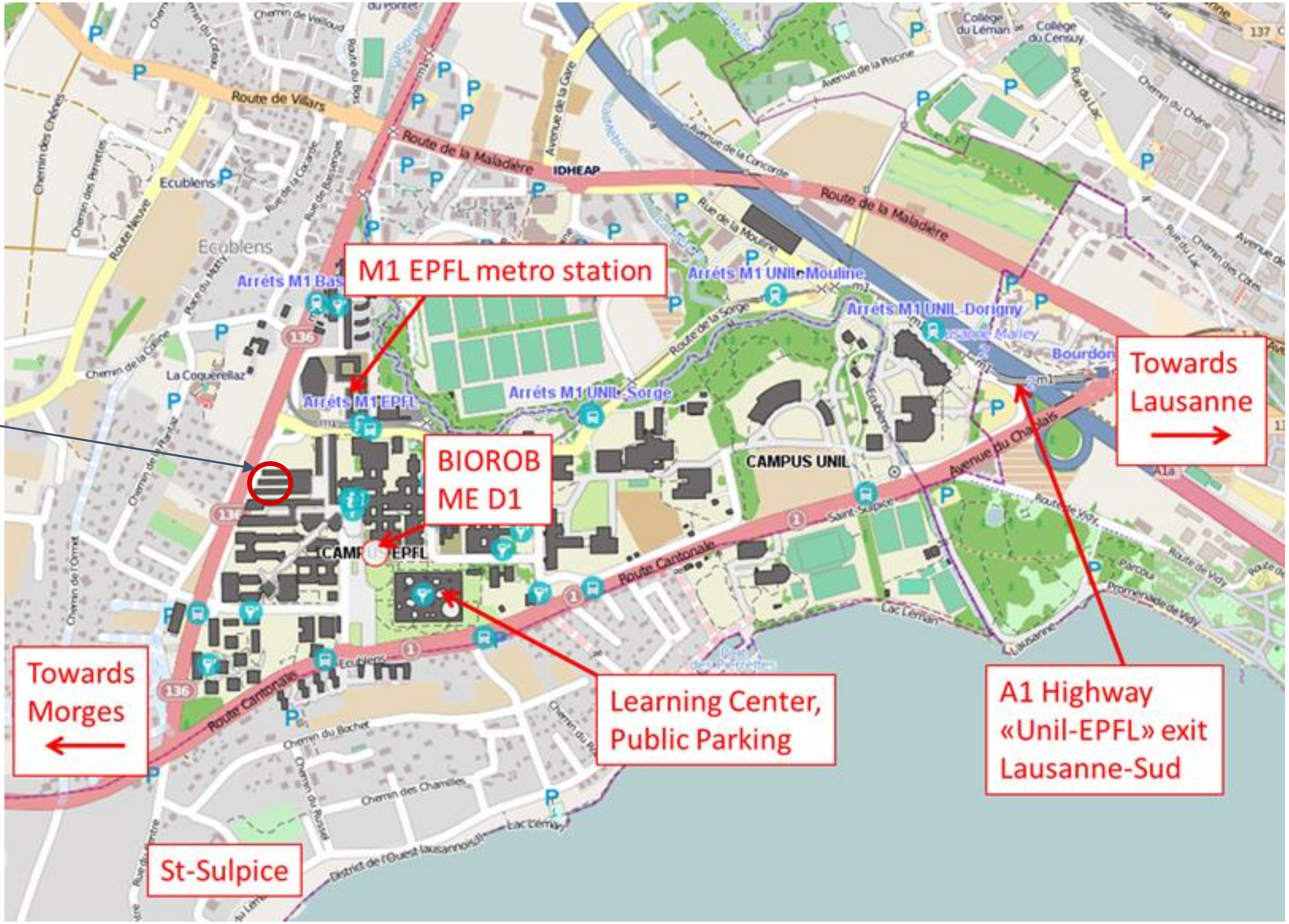
Tolman, Ritchie, Kalish 1946
Edward C. Tolman, 1948

The cognitive map

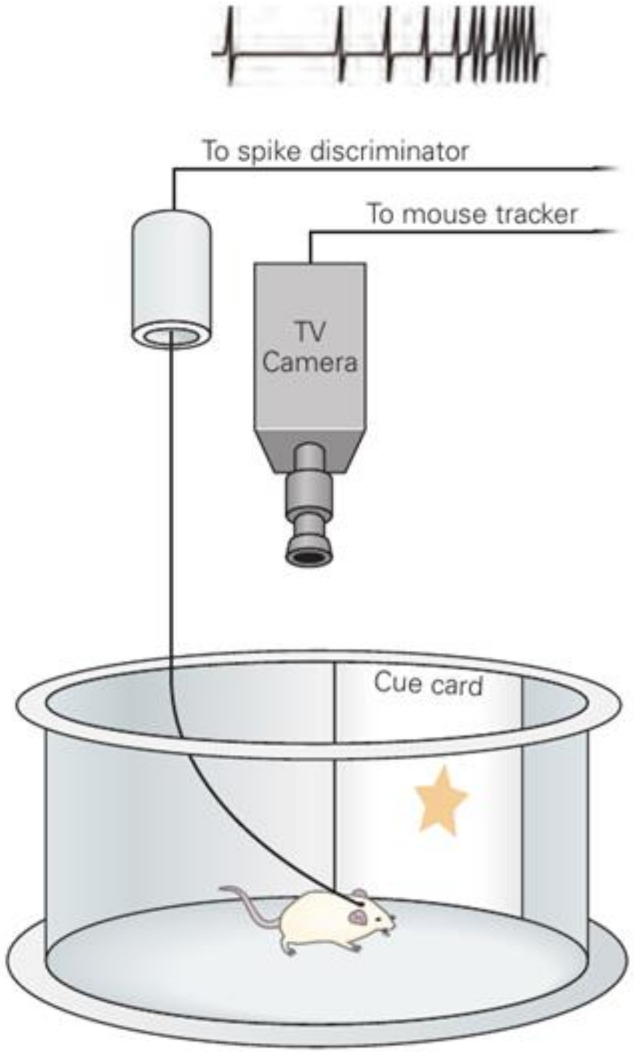
You are here

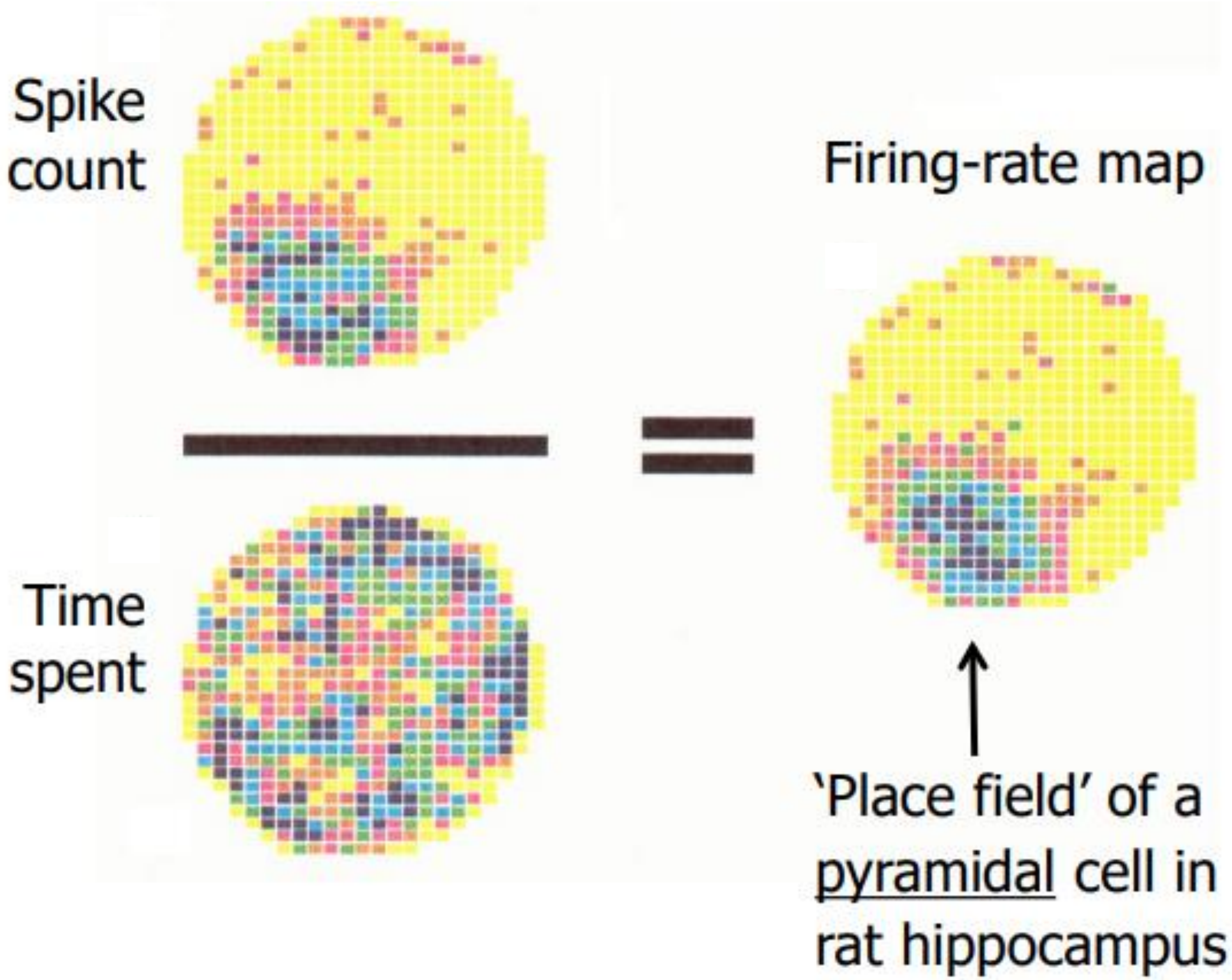
How do you know?

You have a cognitive map of the EPFL campus with **place cells** encoding specific places within it



Place cells in hippocampal subfield CA1



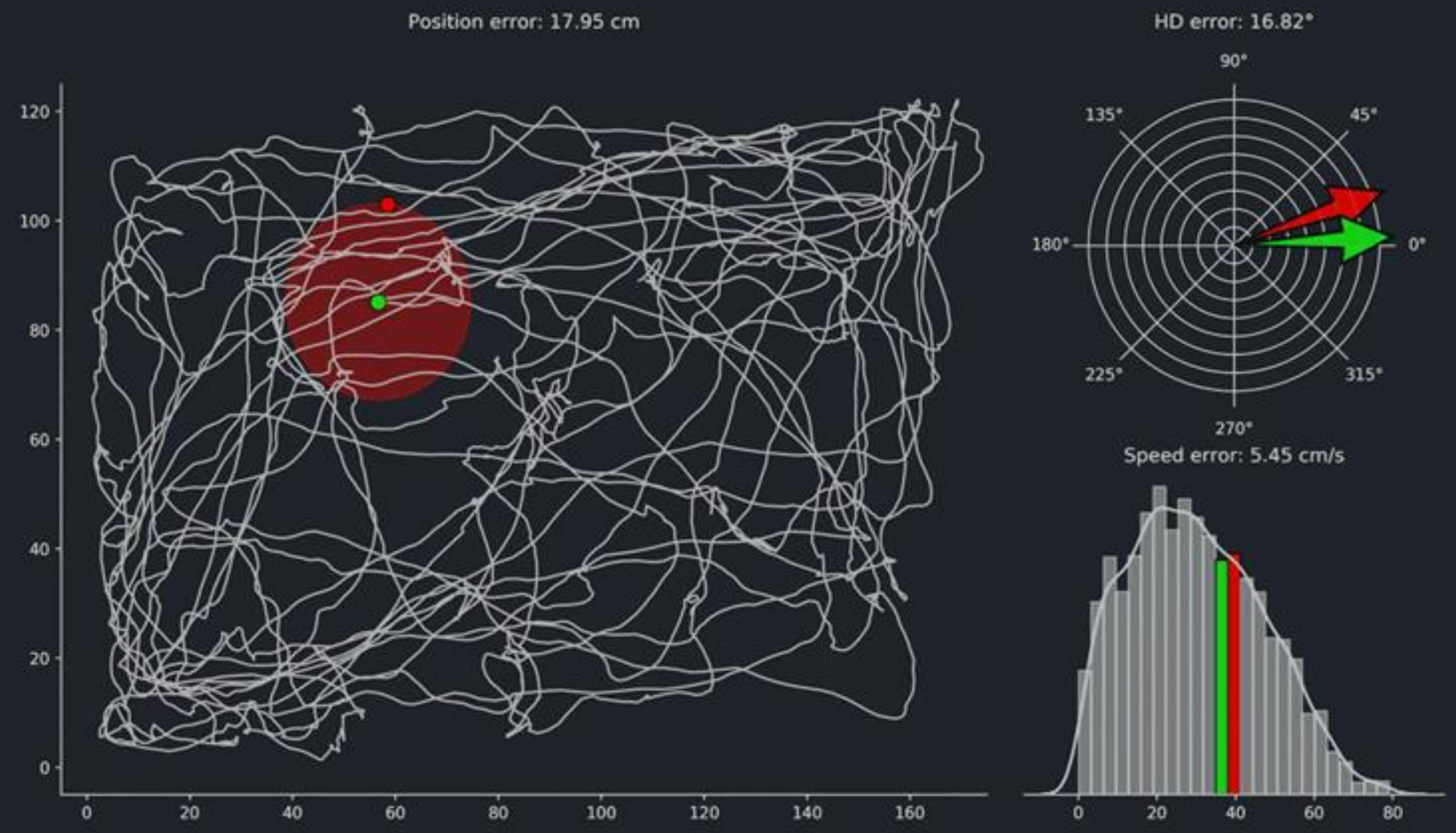


O'Keefe et al. 1971
O'Keefe & Nadel, 1978

Decoding multiple behaviors from raw neural activity

Position

$$\mathcal{L}p(y_p, o_p) = \sqrt{\sum_{i=1}^{N}(o_p - y_p)^2}$$



Head Direction

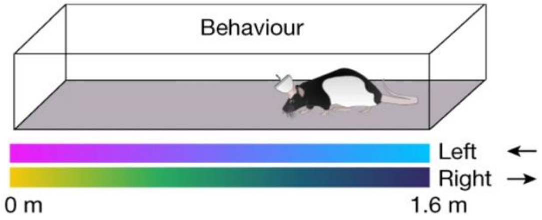
$$\mathcal{L}_h(y_h, o_h) = \min[(o_h - y_h)^2, (o_h - y_h)^2 + \pi, (o_h - y_h)^2 - \pi]$$

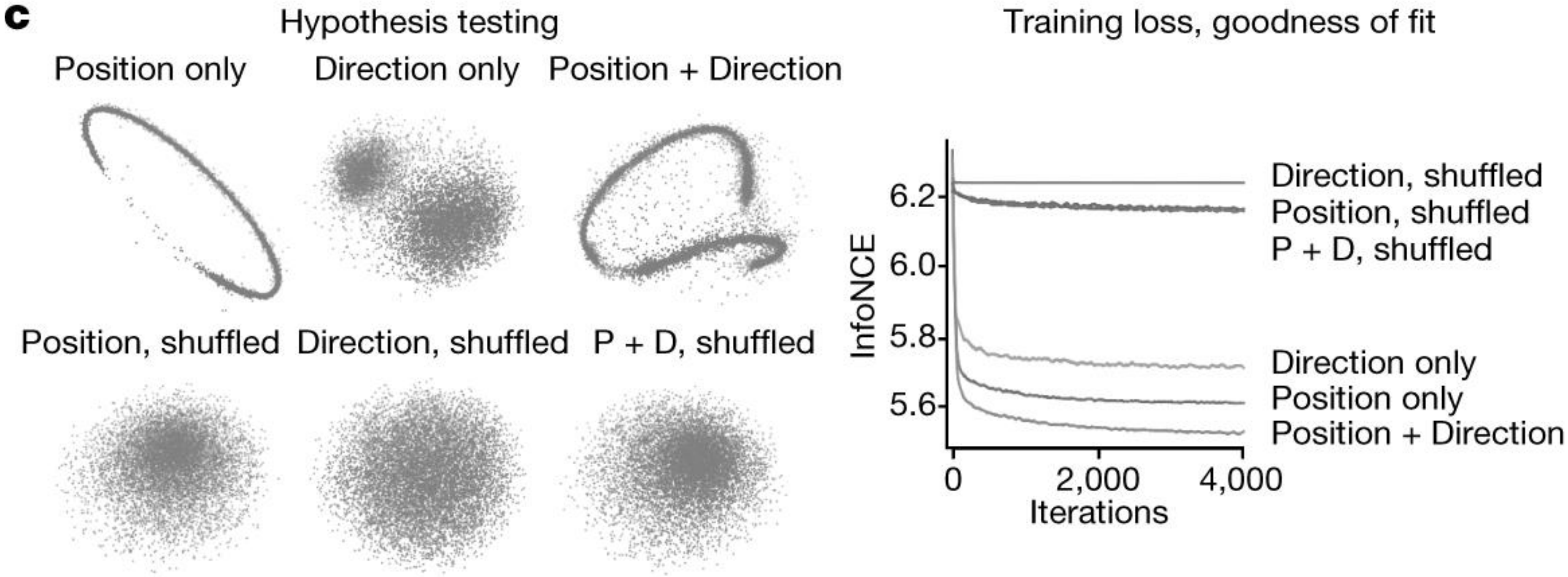
Speed

$$\mathcal{L}_s(y_s, o_s) = \frac{1}{N}\sum_{i=1}^{N}(o_s - y_s)^2$$

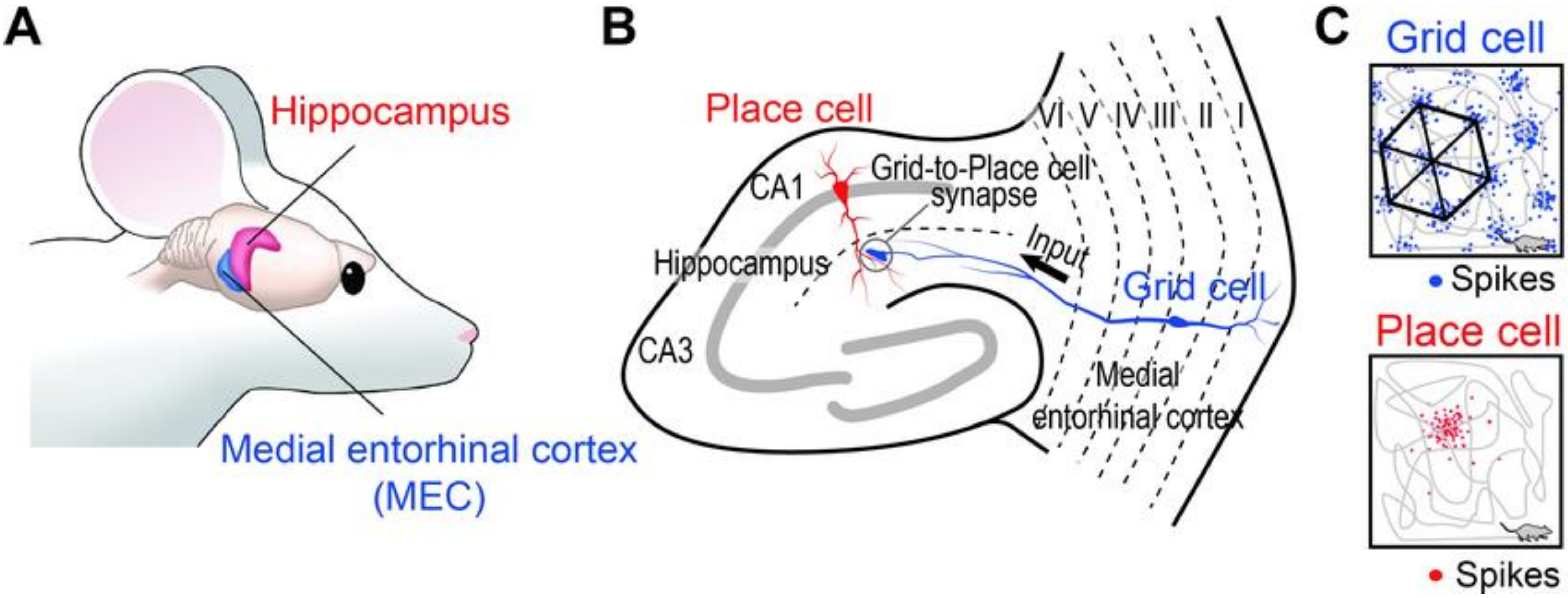
Frey et al. 2021

Using CEBRA for testing positional encoding in the hippocampus





Grid-cell & place-cell anatomy

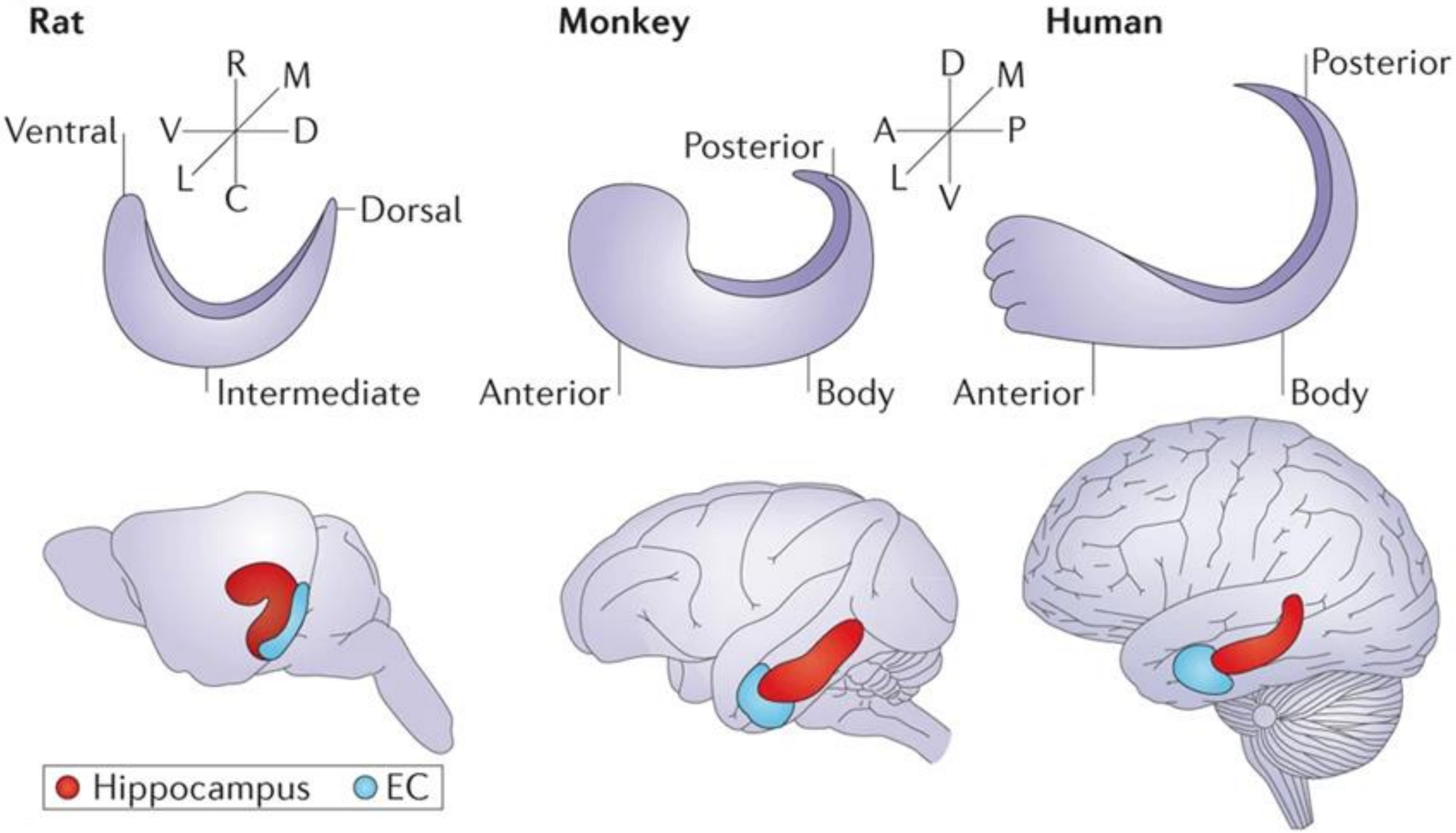


Park et al. 2019

Grid cells in entorhinal cortex (EC)

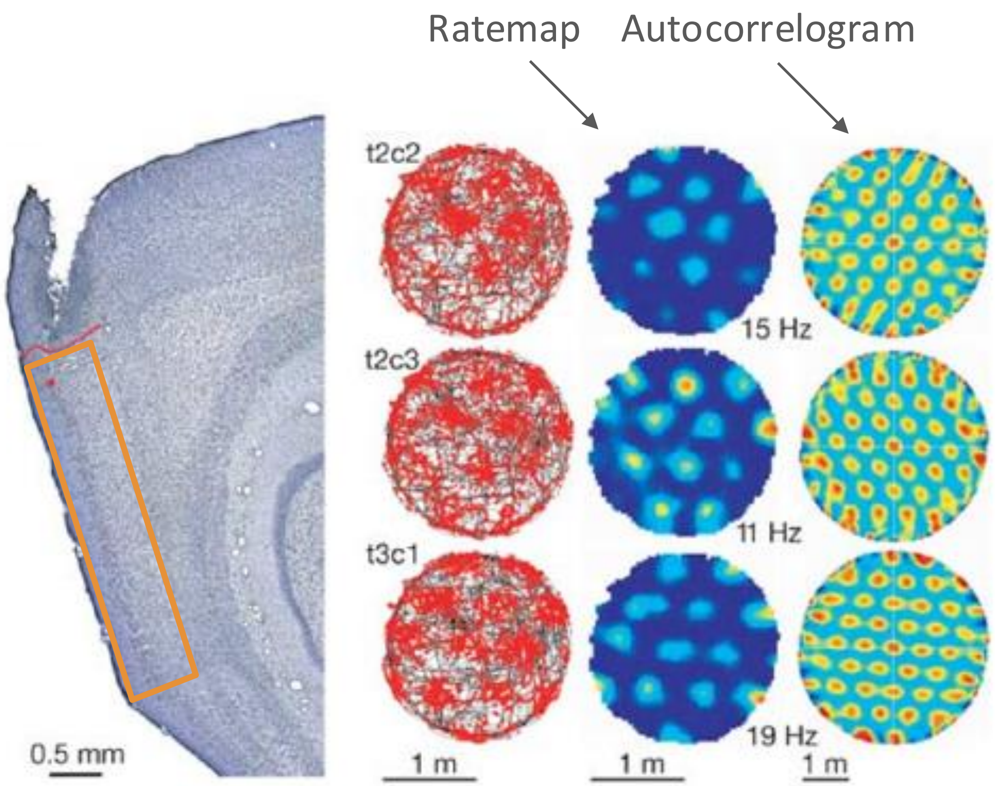
Place and Head direction cells are found in hippocampus (and other areas)

Grid cells are found in entorhinal cortex

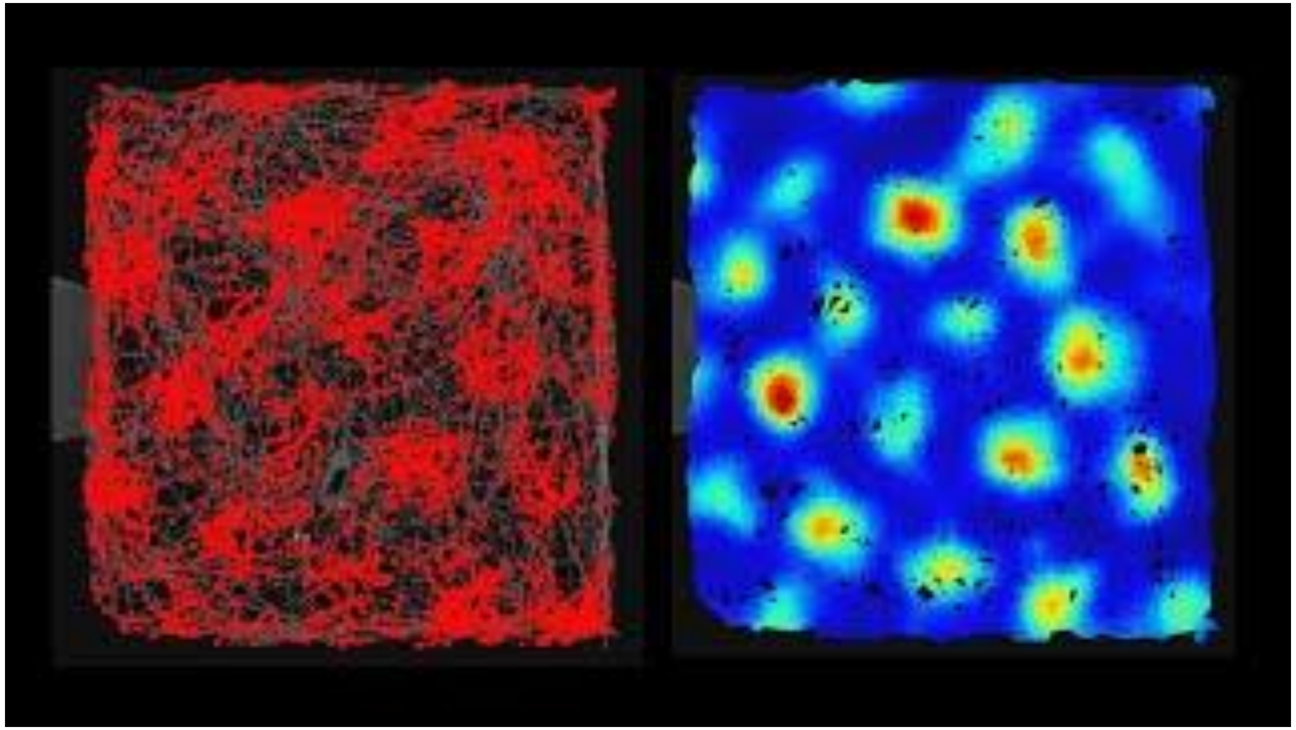


Strange et al. 2014

Grid cells in entorhinal cortex (EC)



Hafting et al. 2005



Grieves, Jefferey 2020

Grid cells in entorhinal cortex respond to multiple spatial locations in a unique triangular grid pattern.

Theta sweeps …

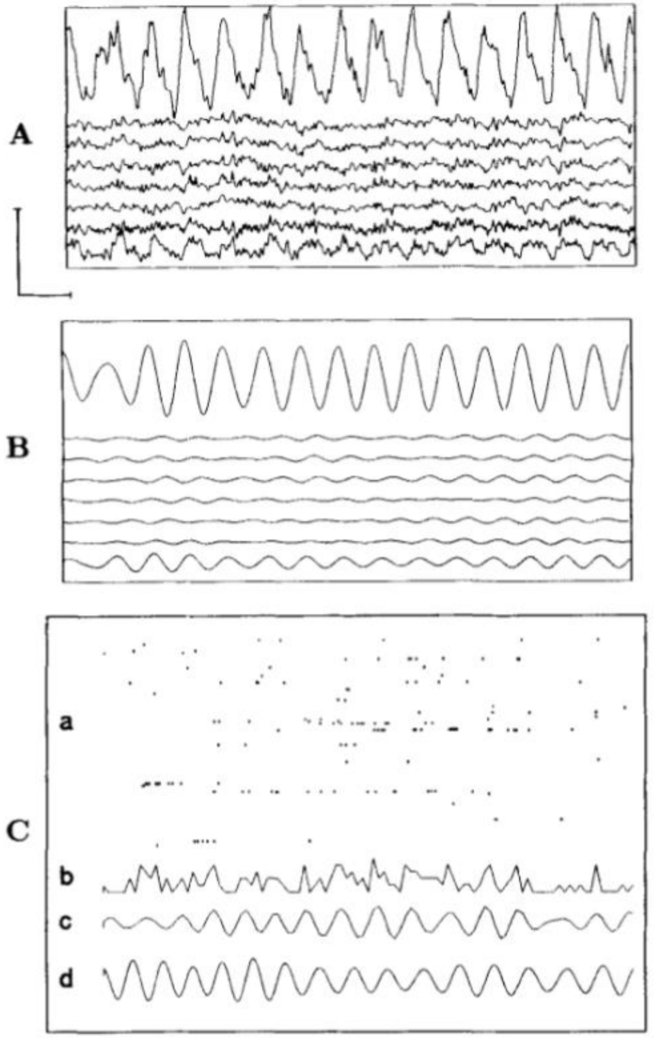
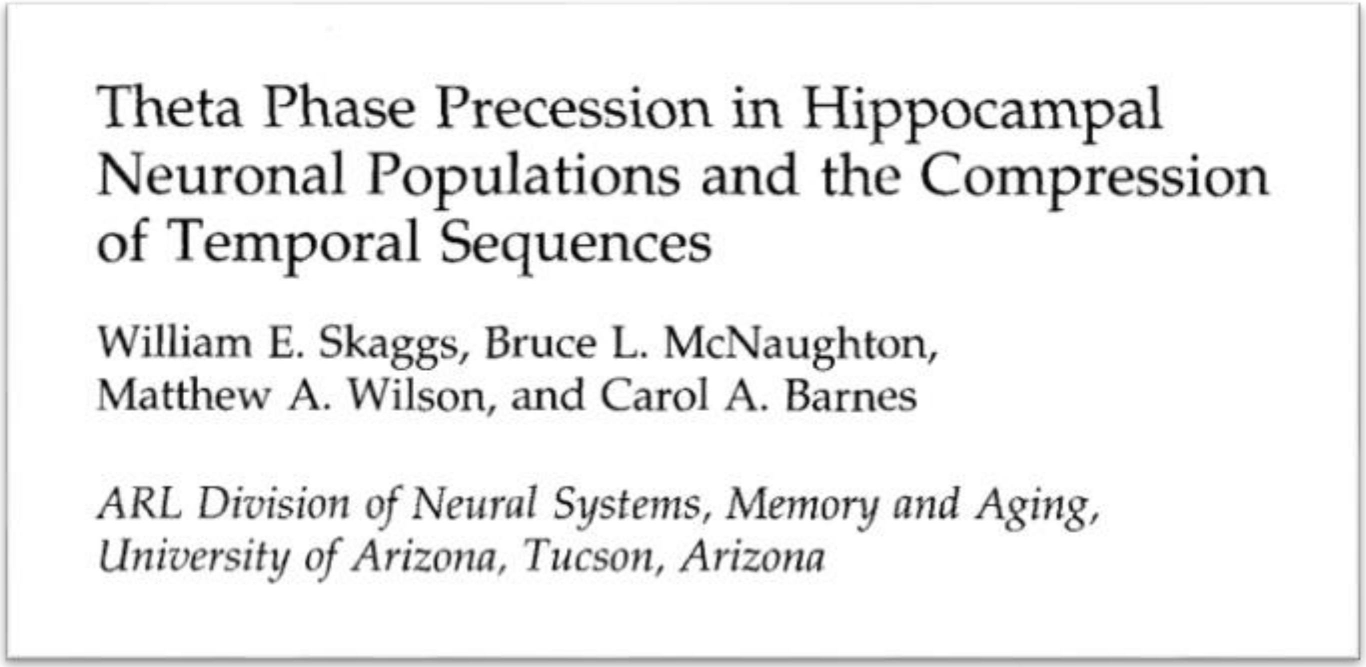


FIGURE 2. Examples of raw and filtered EEG, together with CA1 pyramidal cell population activity. A: A typical example of EEG recorded simultaneously from eight electrodes, one located several hundred μm below the CA1 layer (top trace), the other seven located in or near the CA1 layer, in a rat running on the triangle maze. Filter bandpass: 1–100 Hz. Scale bar: 1 mV, 200 ms. B: The EEG signal from A, digitally filtered with a bandpass of 6–10 Hz. The peaks of the reference channel (top trace) were used to compute phases of the theta cycle for the analyses performed here. C: Example



Theta Phase Precession in Hippocampal Neuronal Populations and the Compression of Temporal Sequences

William E. Skaggs, Bruce L. McNaughton, Matthew A. Wilson, and Carol A. Barnes

ARL Division of Neural Systems, Memory and Aging, University of Arizona, Tucson, Arizona

The **theta cycle** is a rhythmic oscillation in the 4–12 Hz range observed in the hippocampus during active behaviors

Article

Constant Sub-second Cycling between Representations of Possible Futures in the Hippocampus

Kenneth Kay [1 2 4], Jason E. Chung [1 2], Marielena Sosa [1 2], Jonathan S. Schor [1],
Mattias P. Karlsson [1 2], Margaret C. Larkin [1 2], Daniel F. Liu [1 2],
Loren M. Frank [1 2 3 5]

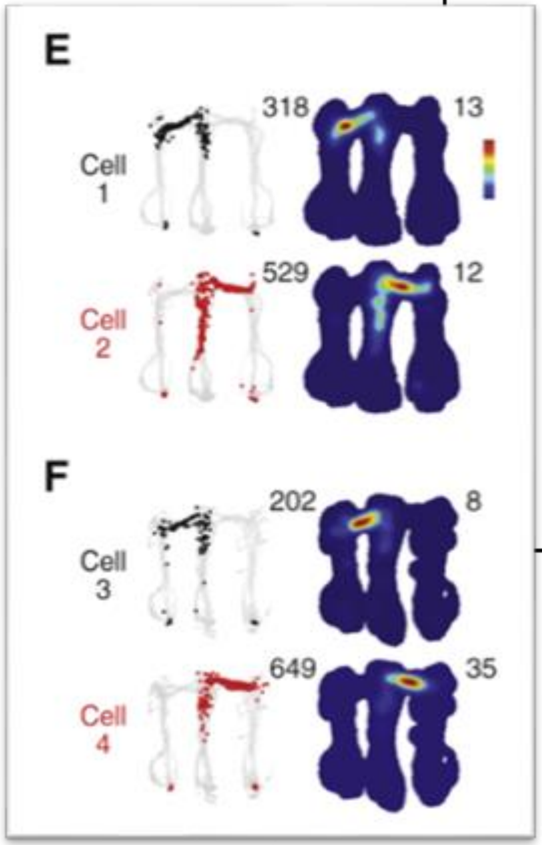
Highlights

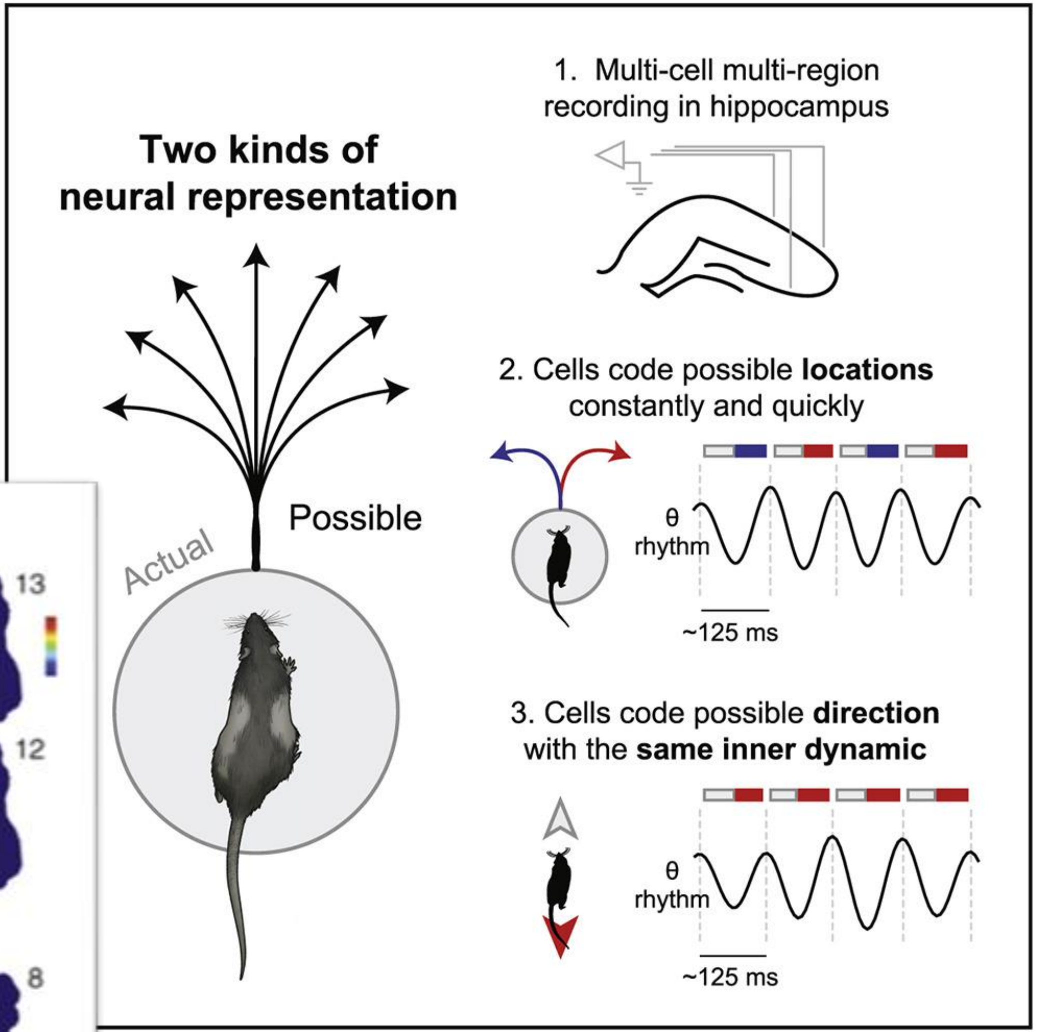
•Firing across hippocampal neurons can regularly "take turns" (cycle) every ~125 ms

•Cycle firing is seen at single-cell, cell-pair, and population levels

•Cycle firing encodes hypothetical experience, including multiple possible futures

•Cycle coding generalizes across representational correlates, implying common process





Volume 180, Issue 3, 6 February 2020, Pages 552-567.e25

But is there an experience-independent spatial sampling mechanism?

nature > articles > article

Article | Open access | Published: 03 February 2025

Left–right-alternating theta sweeps in entorhinal–hippocampal maps of space

Abraham Z. Vollan, Richard J. Gardner, May-Britt Moser & Edvard I. Moser

Nature **639**, 995–1005 (2025) | Cite this article

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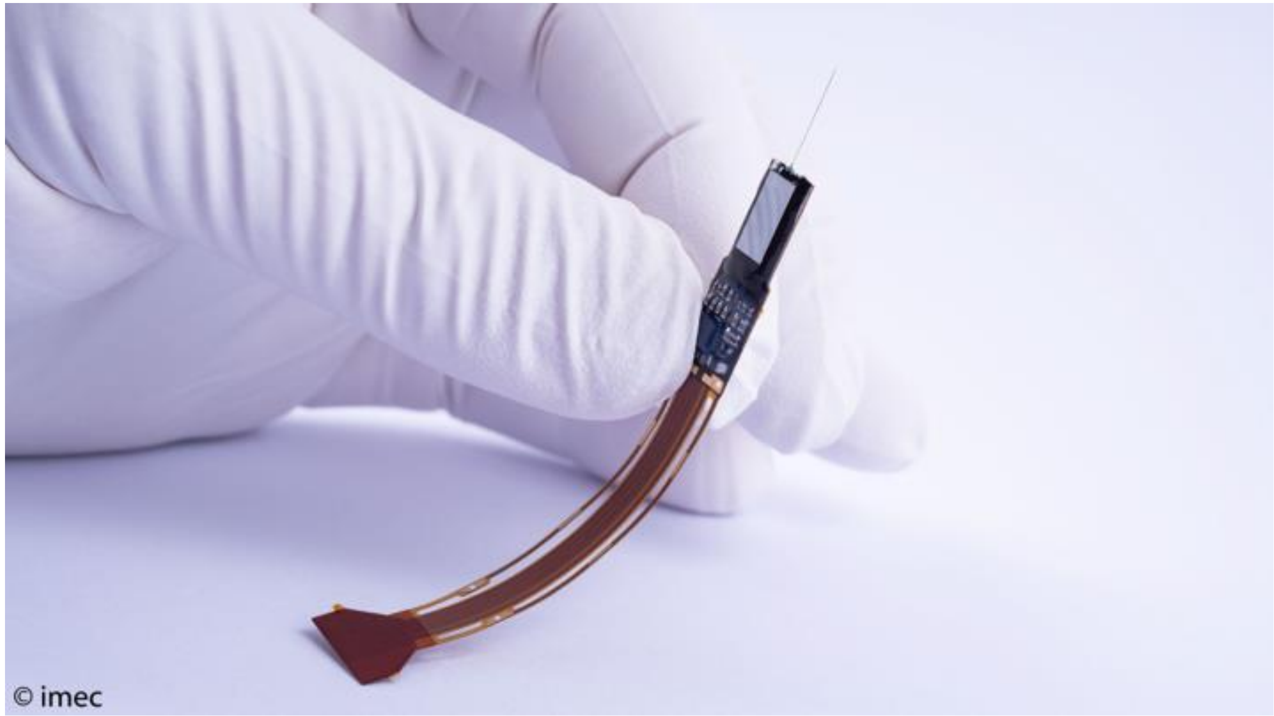
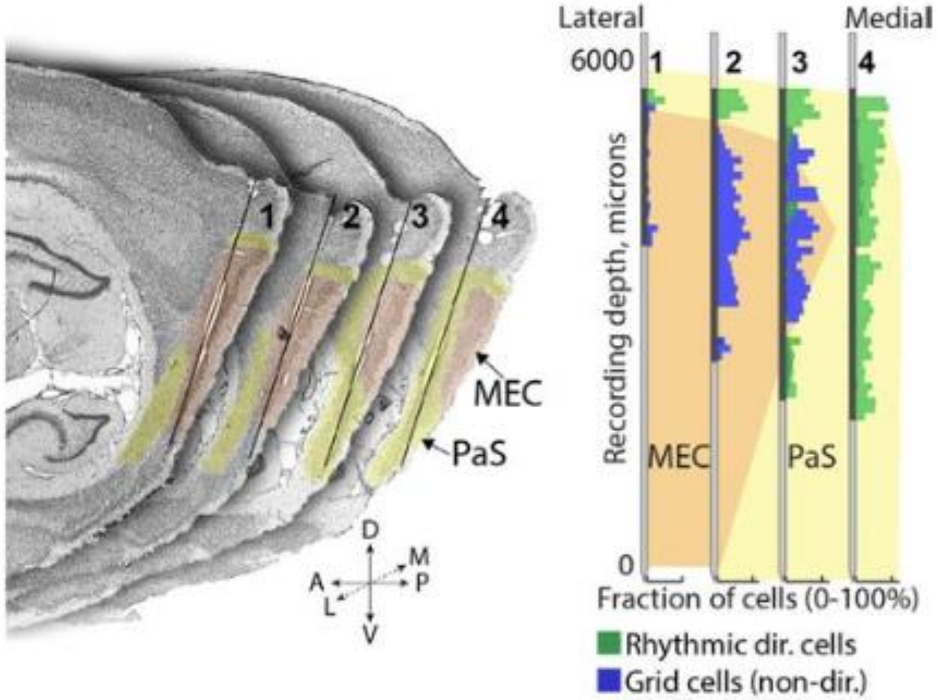
Nature 2025

The major claim:

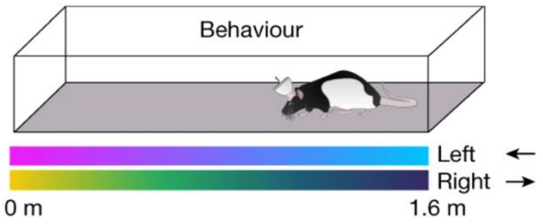
"…. **we show in freely moving rats, that within individual theta cycles, ensembles of grid cells and place cells encode a position signal that sweeps linearly outwards from the animal's location into the ambient environment, with sweep direction alternating stereotypically between left and right across successive theta cycles** "

Method: high density Neuropixels recordings (were key!)

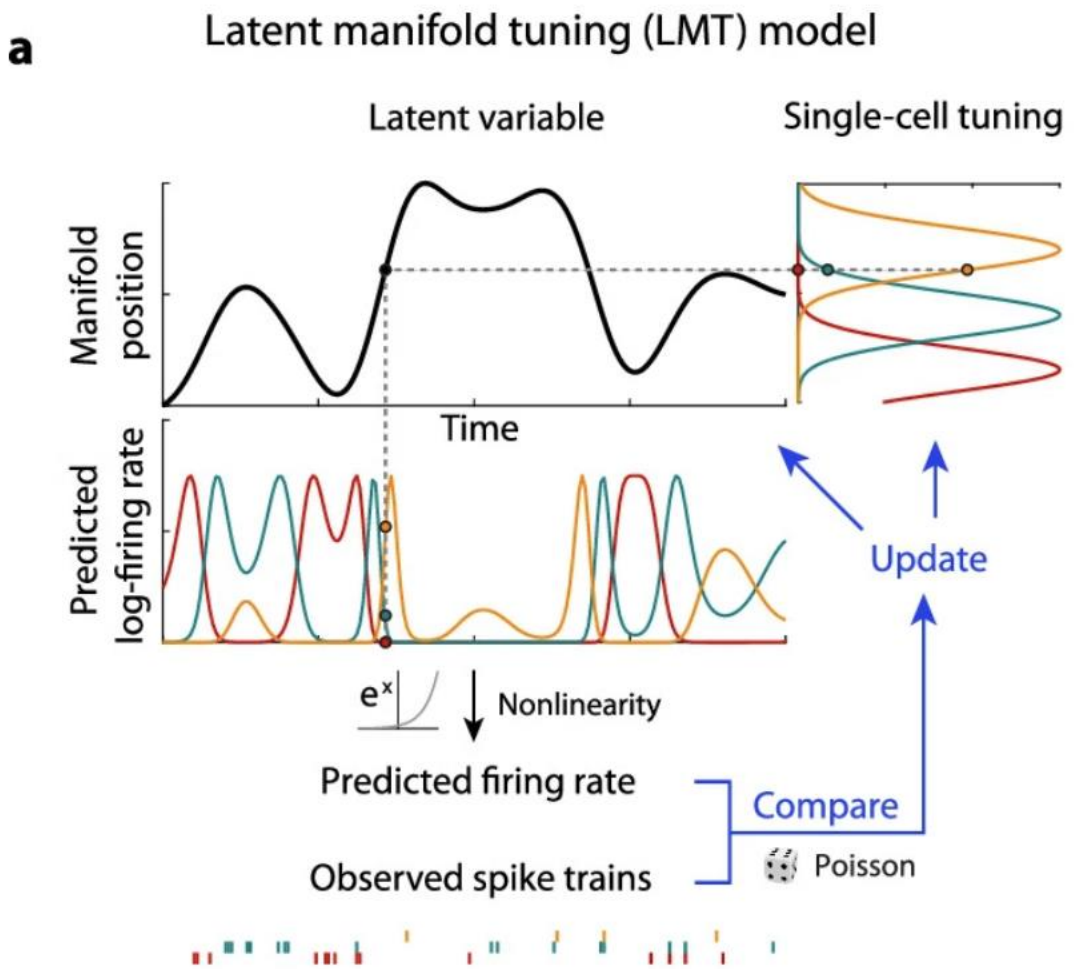




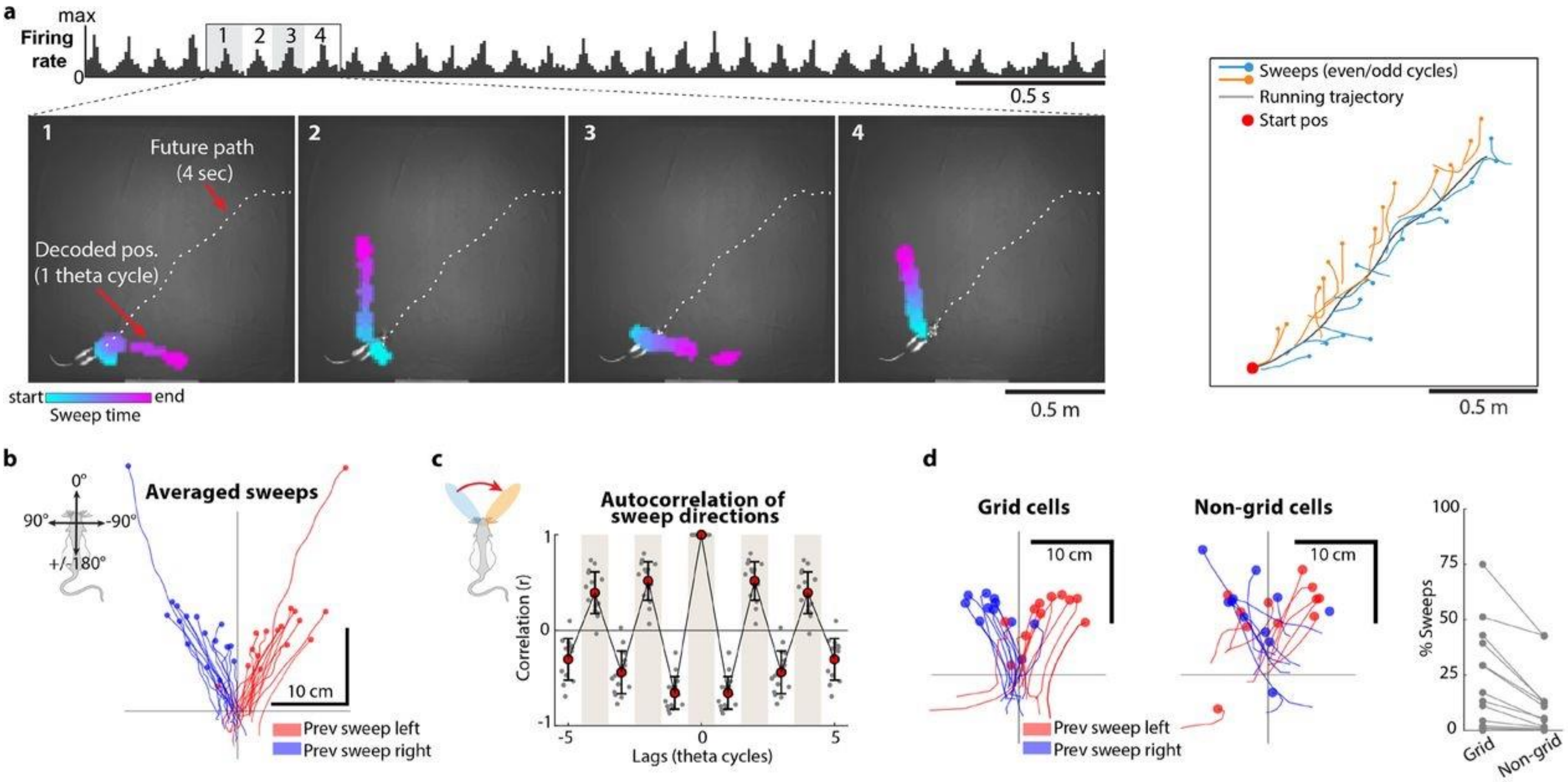
Method: latent variable modeling plus GLM



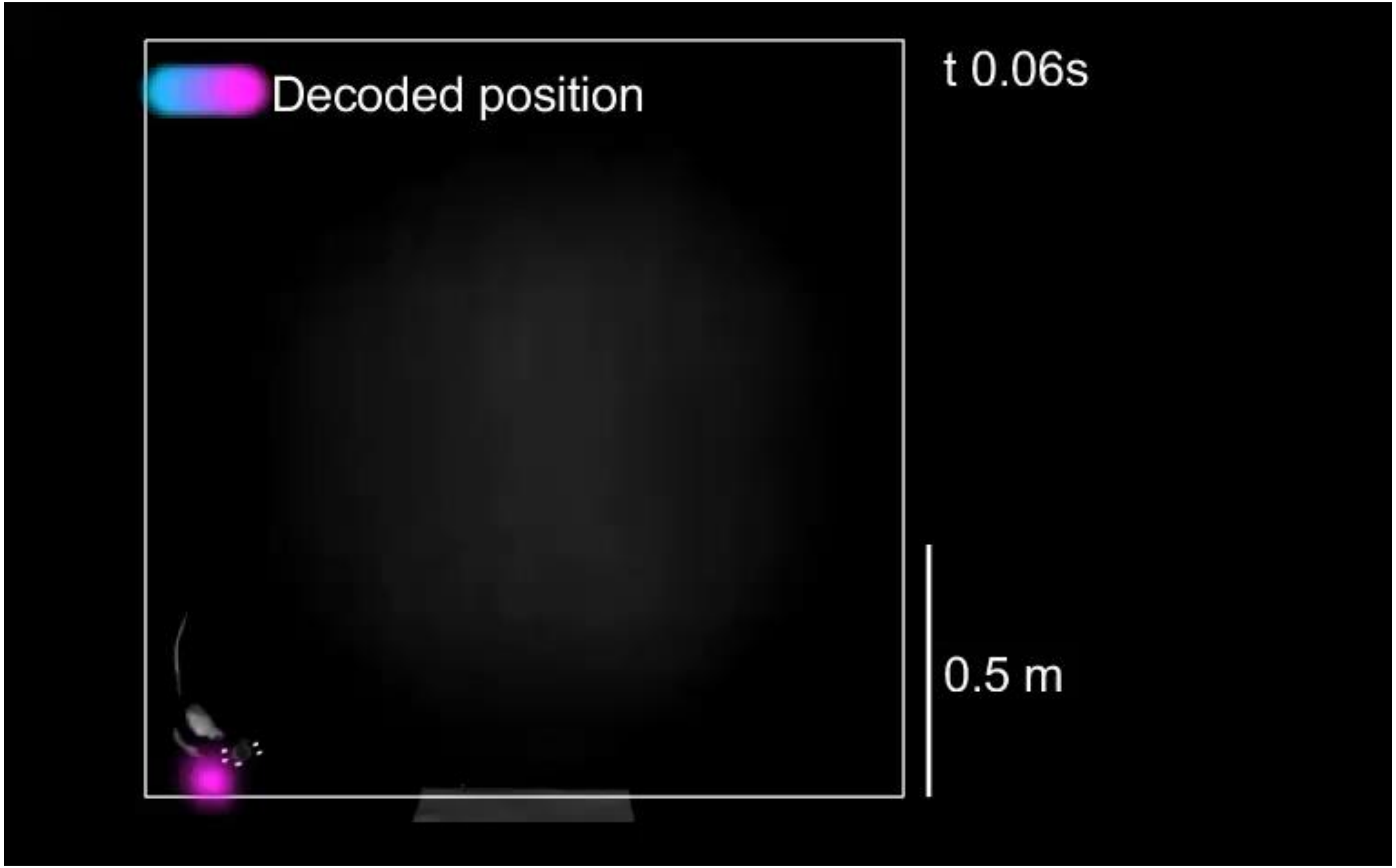
Nice "trick": expand the latent manifold beyond what is known (in position)



Grid cells and place cells sample ambient space with alternating "sweeps"

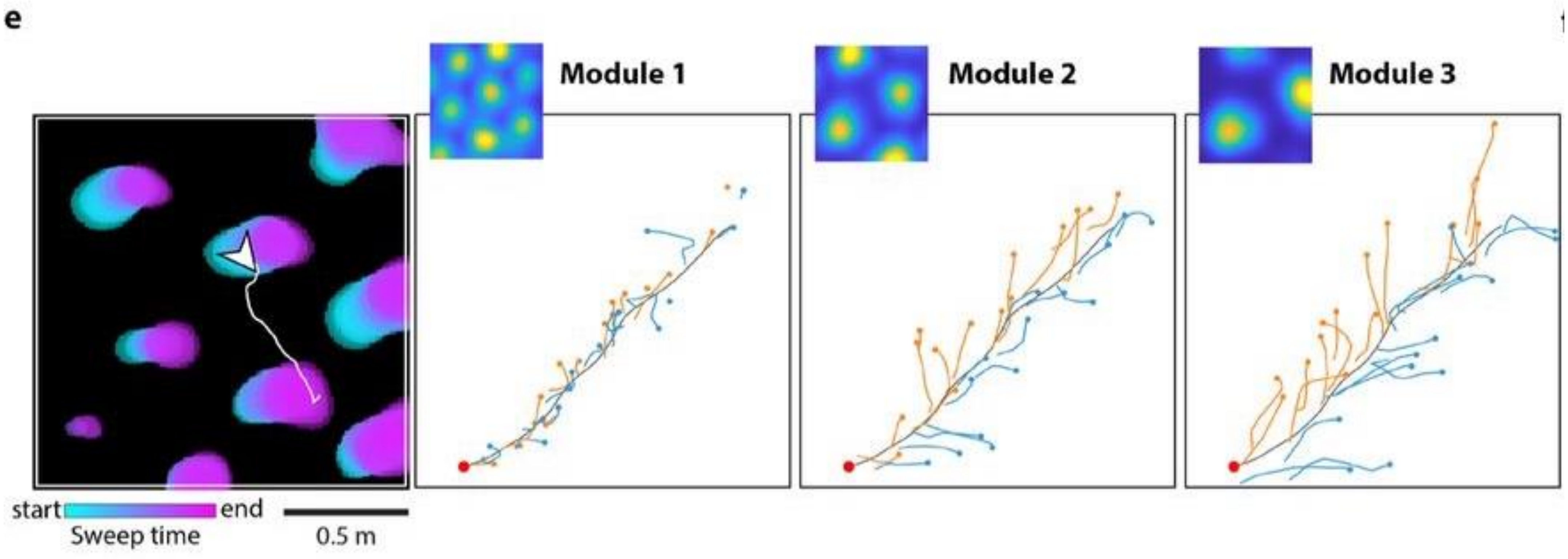


Grid cells and place cells sample ambient space with alternating “sweeps”

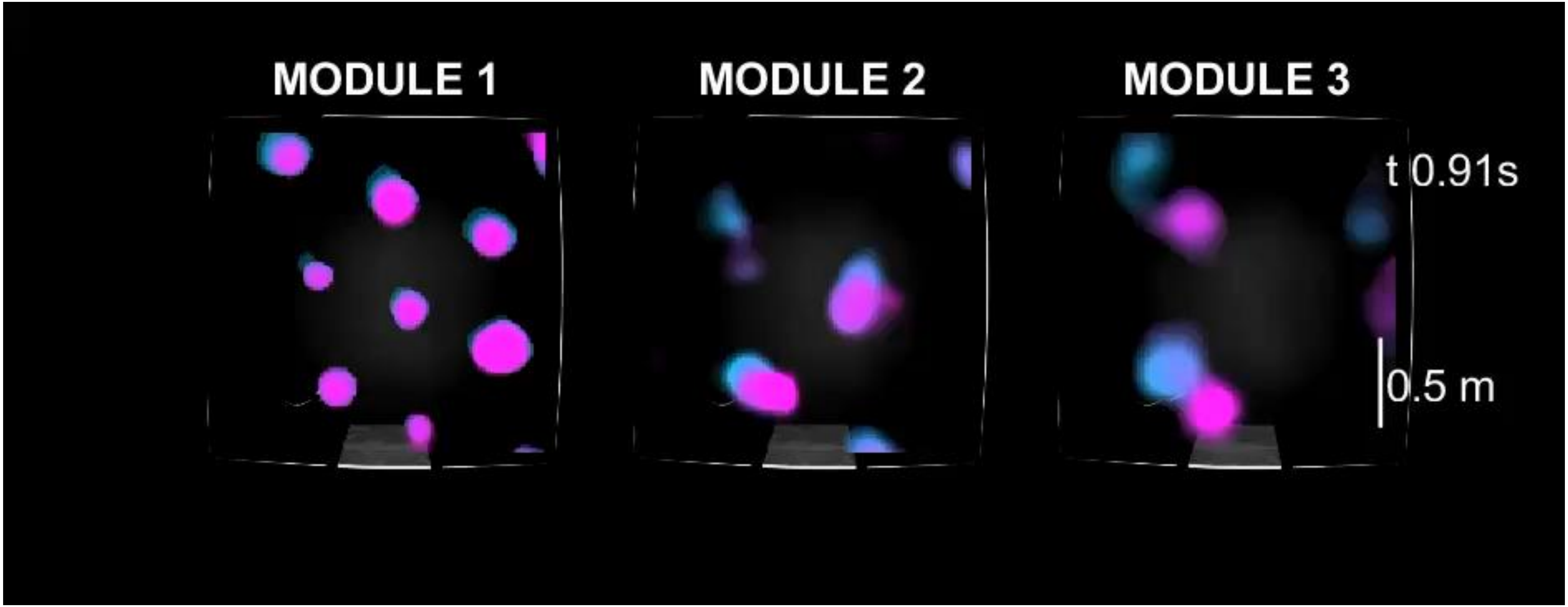


Sweeps were detected in 72.9 ± 3.4% (mean ± s.e.m.) of the theta cycles in rats with more than a thousand cells (3 rats). In the full sample (16 rats, mean of 769 cells), sweeps were detected in 48.0 ± 1.3% of theta cycles.

Grid cells and place cells sample ambient space with alternating "sweeps"



Grid cells and place cells sample ambient space with alternating “sweeps”

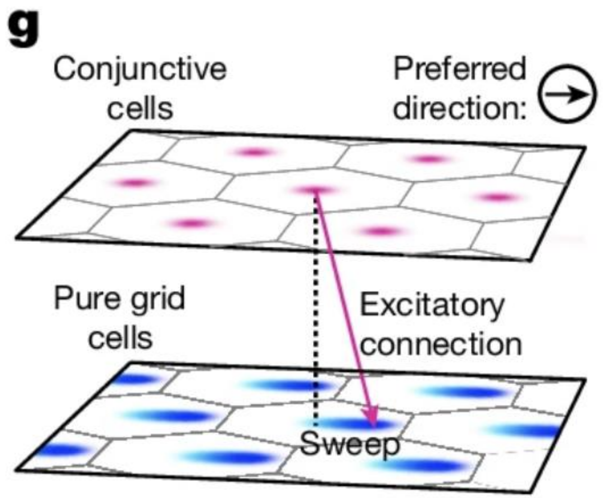


Sweep lengths scaled with the spacing of the grid modules

Restricting the analysis to **grid cells revealed a stronger presence of sweeps relative to non-grid cells** in EC

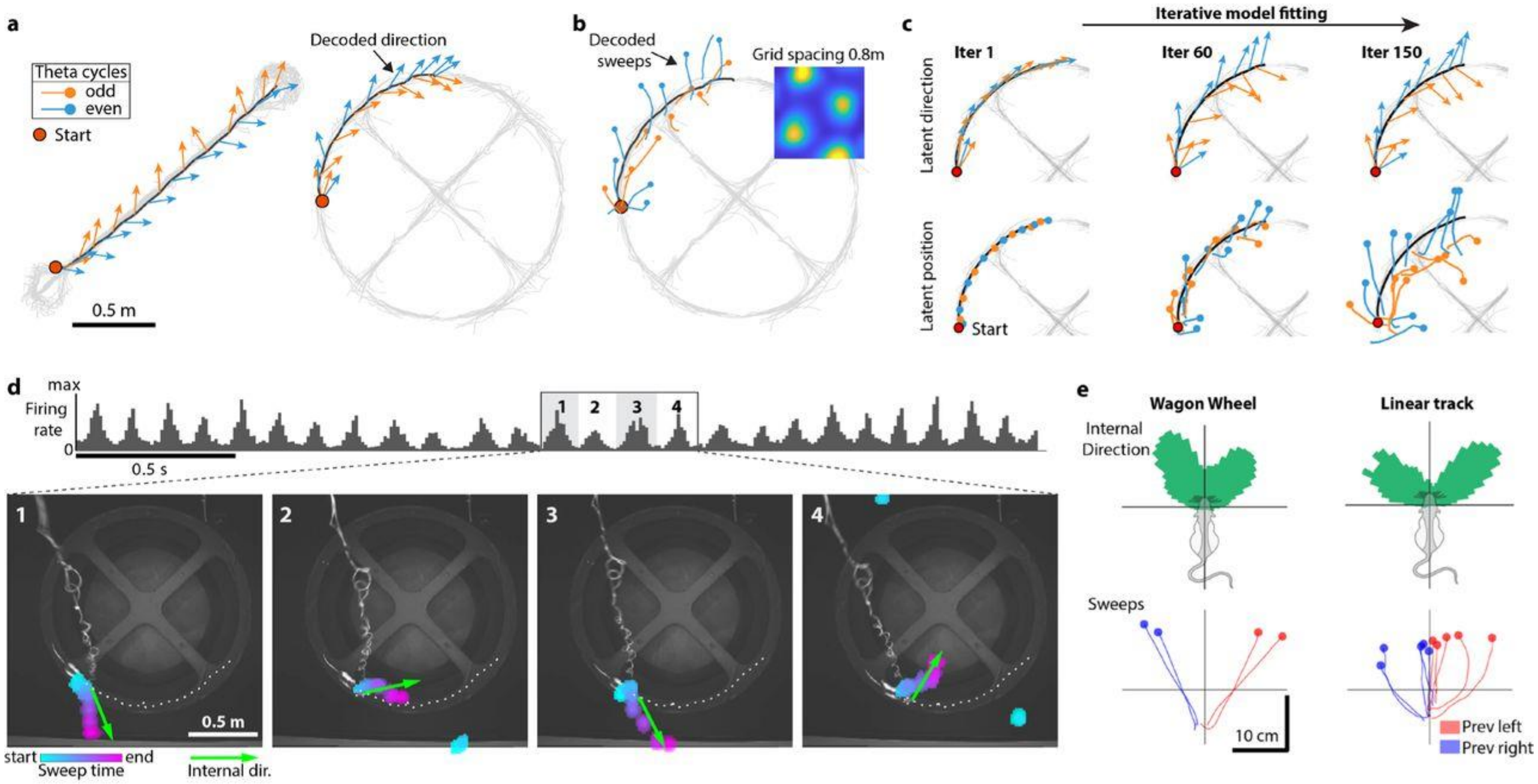
Place cell sweeps were delayed compared to simultaneously recorded EC, raising the possibility that hippocampal place cell sweeps are inherited from entorhinal grid cells

Strong **correspondence between sweep direction in grid cells and the direction encoded by theta-modulated directional cells**



the findings support the notion that sweep direction is determined by activation of internal direction cells, via a layer of conjunctive grid cells

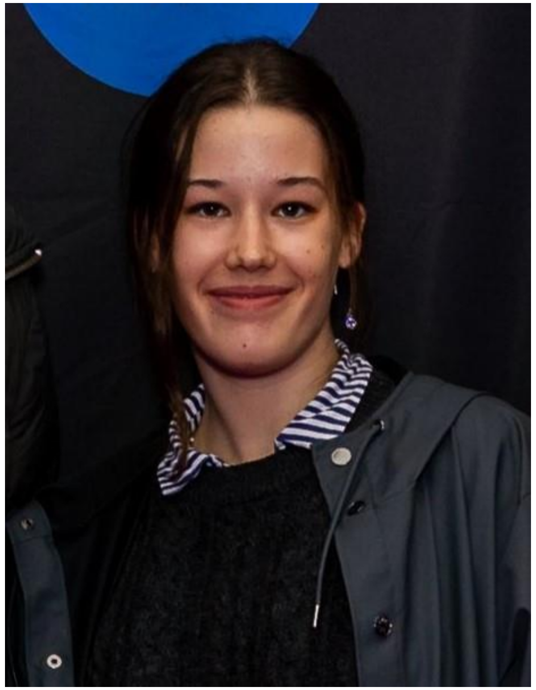
Sweeps extend to never-visited locations



Taken together, these findings show that a seamless map of ambient space – including grid cells, internal direction cells and place cells – is unfolded independently of whether the animal ever visits the locations covered by the sweep signals.

Huge thanks to the TAs 🎉


EDEE PhD candidate

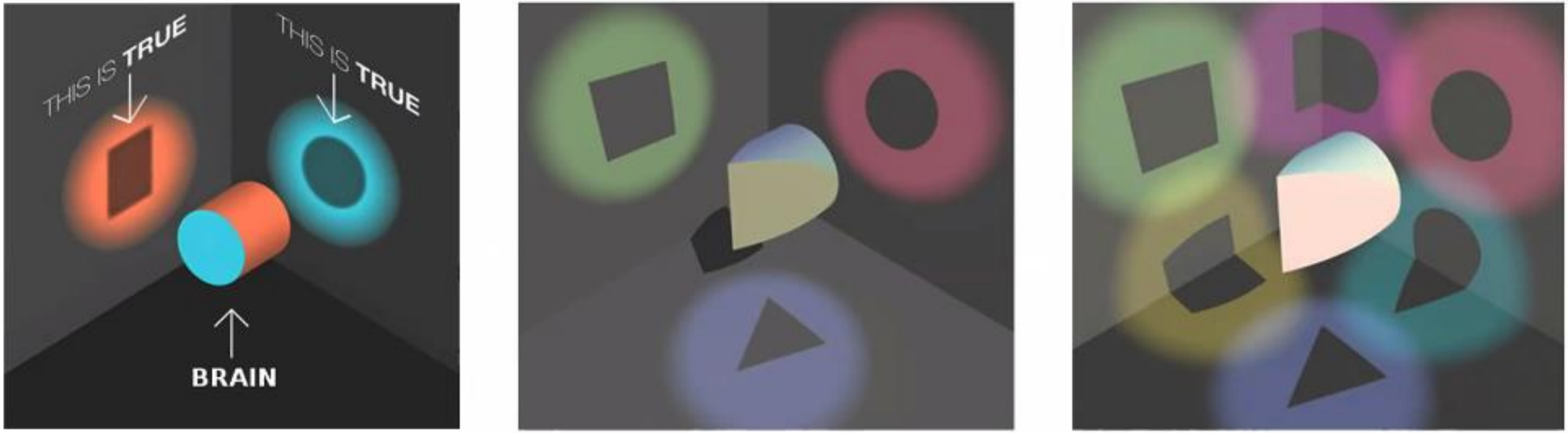

EDNE PhD candidate

- **Célia Benquet**
- **Myriam Hamon**

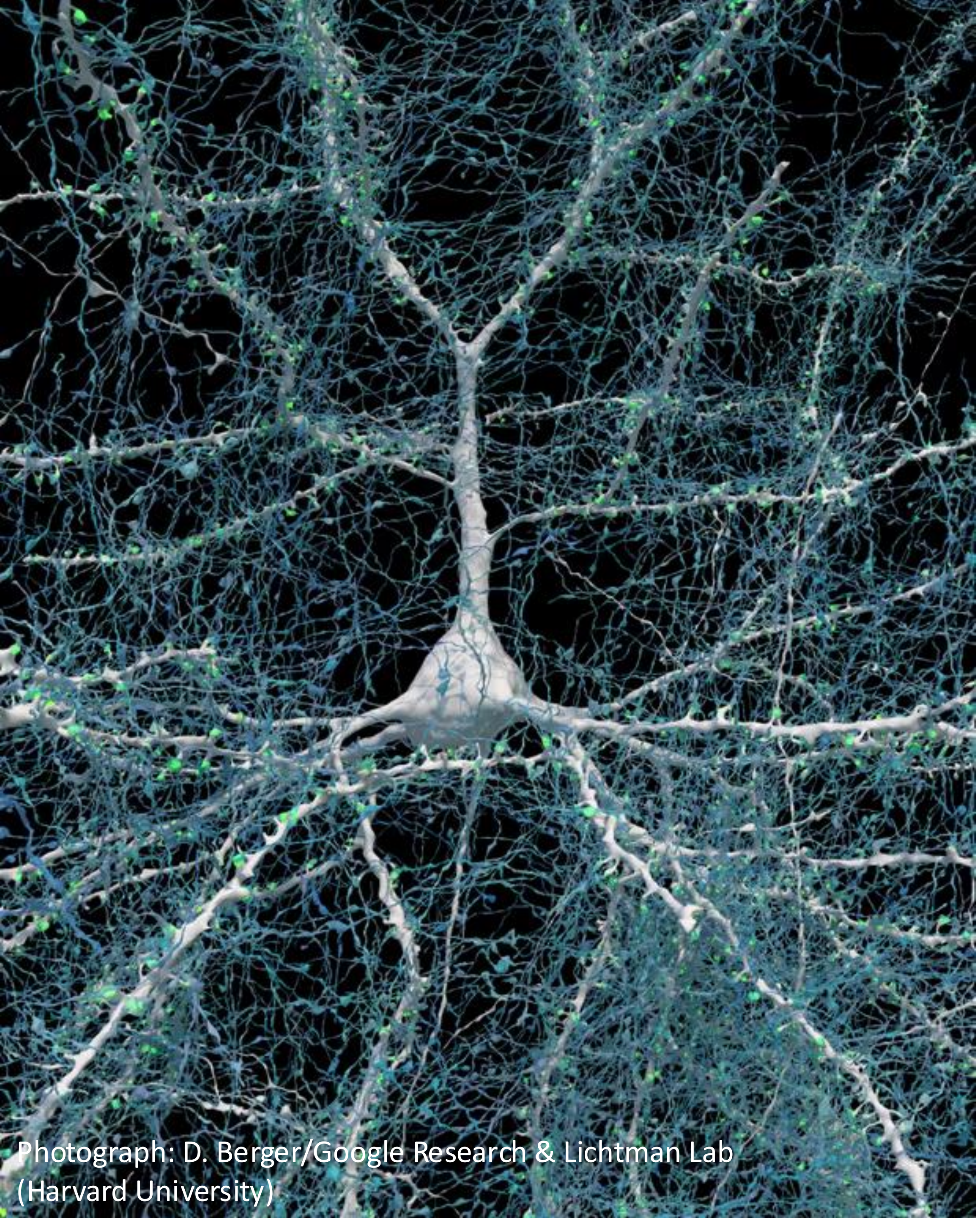
- **Spencer Bowles (a lecture on BMIs + hands-on expts!)**

- **Thomas Sainsbury (a lecture on fish & vision + hands-on expts!)**

Remember, we are just at the starting line for many key questions....



Cartoon courtesy of Adrian Roggenbach



Photograph: D. Berger/Google Research & Lichtman Lab (Harvard University)

Thank you!

Abstract

Place cells in the hippocampus and grid cells in the entorhinal cortex are elements of a neural map of self-position[1–5]. To benefit navigation, this representation must be dynamically related to surrounding locations[2]. A candidate mechanism for linking places along an animal's path has been described in place cells, where the sequence of spikes within each cycle of the hippocampal theta oscillation encodes a trajectory from the animal's current location towards upcoming locations[6–8]. In mazes that bifurcate, such trajectories alternately traverse the two upcoming arms as the animal approaches the choice point[9,10], raising the possibility that the trajectories express available forward paths encoded on previous trials[10]. However, to bridge the animal's path with the wider environment, beyond places previously or subsequently visited, an experience-independent spatial sampling mechanism might be required. Here we show in freely moving rats, that within individual theta cycles, ensembles of grid cells and place cells encode a position signal that sweeps linearly outwards from the animal's location into the ambient environment, with sweep direction alternating stereotypically between left and right across successive theta cycles. These sweeps were accompanied by, and aligned with, a similarly alternating directional signal in a discrete population of parasubiculum cells with putative connections to grid cells via conjunctive grid×direction cells. Sweeps extended into never-visited locations that were inaccessible to the animal and persisted during REM sleep. Sweep directions could be explained by an algorithm that maximizes cumulative coverage of surrounding space. The sustained and unconditional expression of theta-patterned left-right-alternating sweeps in the entorhinal-hippocampal positioning system provides an efficient 'look-around' mechanism for sampling locations beyond the travelled path.