
Ways to think about the brain
www.buzsakilab.com
NYU Langone
MEDICAL CENTER

- How did we inherit our neuroscience framework?
- How did cognitive mechanisms emerge?
- What is the alternative to the blank slate model?

ACTION

Black box
Intervening variables
Information processing

Input

Learn the truth and veridical features of the world (based on Judeo-Christian views)

Output

Representation
Consciousness
Homunculus
Decision making
Free will

Internally organized patterns

output

input

Predict the consequences of actions for the survival and prosperity of the body

Buzsaki **OUP** (2019)

Black box
Intervening variables
Information processing

Input

Output

Specific to general
(e.g., binding) –
features are in the world –
representational

Representation
Consciousness
Homunculus
Decision making
Free will

Internally organized patterns

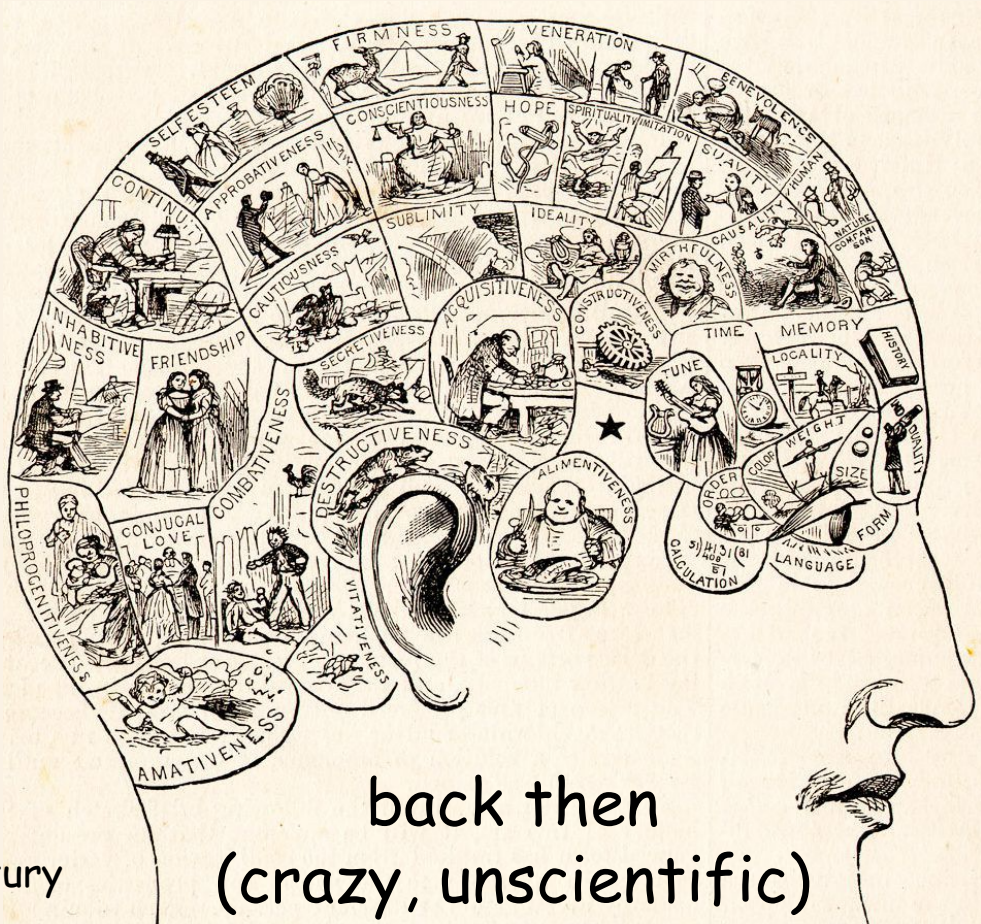
output

input

General to specific
From '*Good enough*' to
details through experience

Buzsaki **OUP** (2019)

Phrenology and neo-phrenology

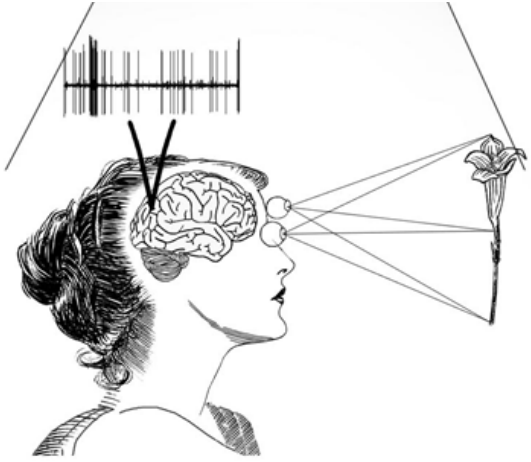


back then
(crazy, unscientific)

19th century

Outside-in framework

no grounding

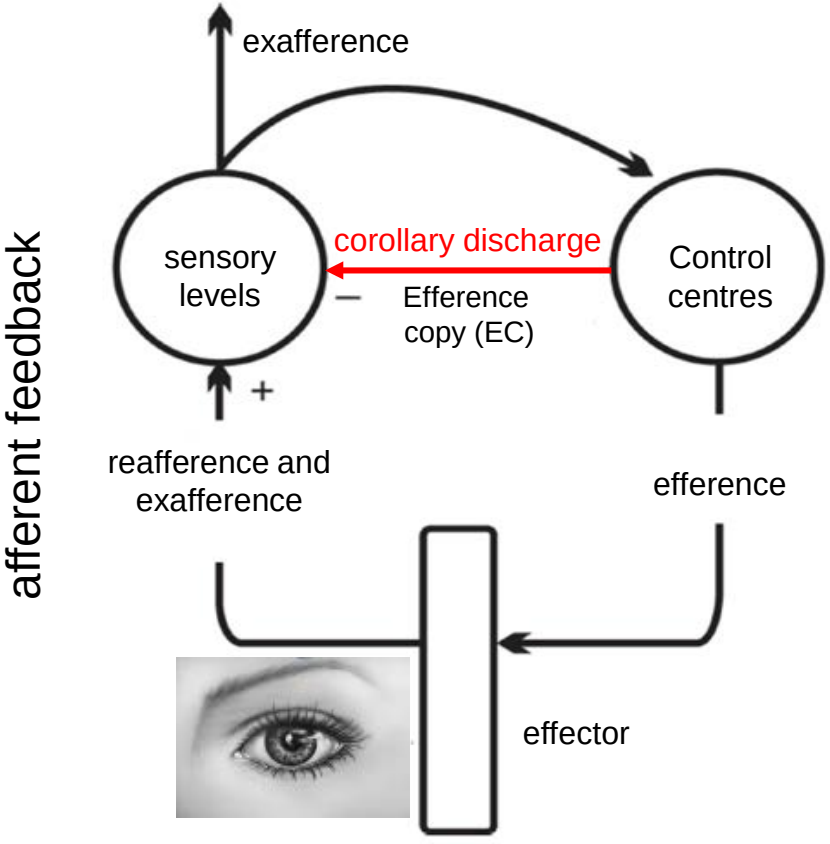


Inside-out framework

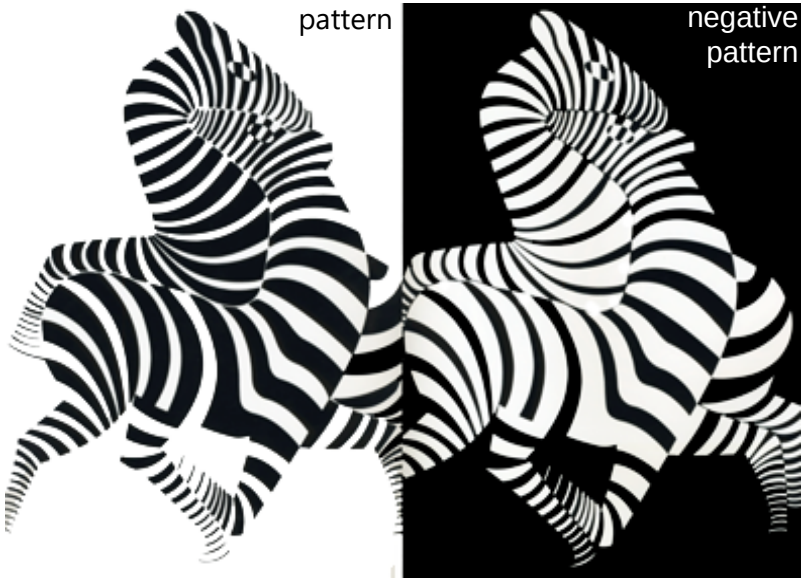
(internally organized, action based)

“I am … ons”

Grounding mechanism: Corollary discharge



comparator
efference – afference

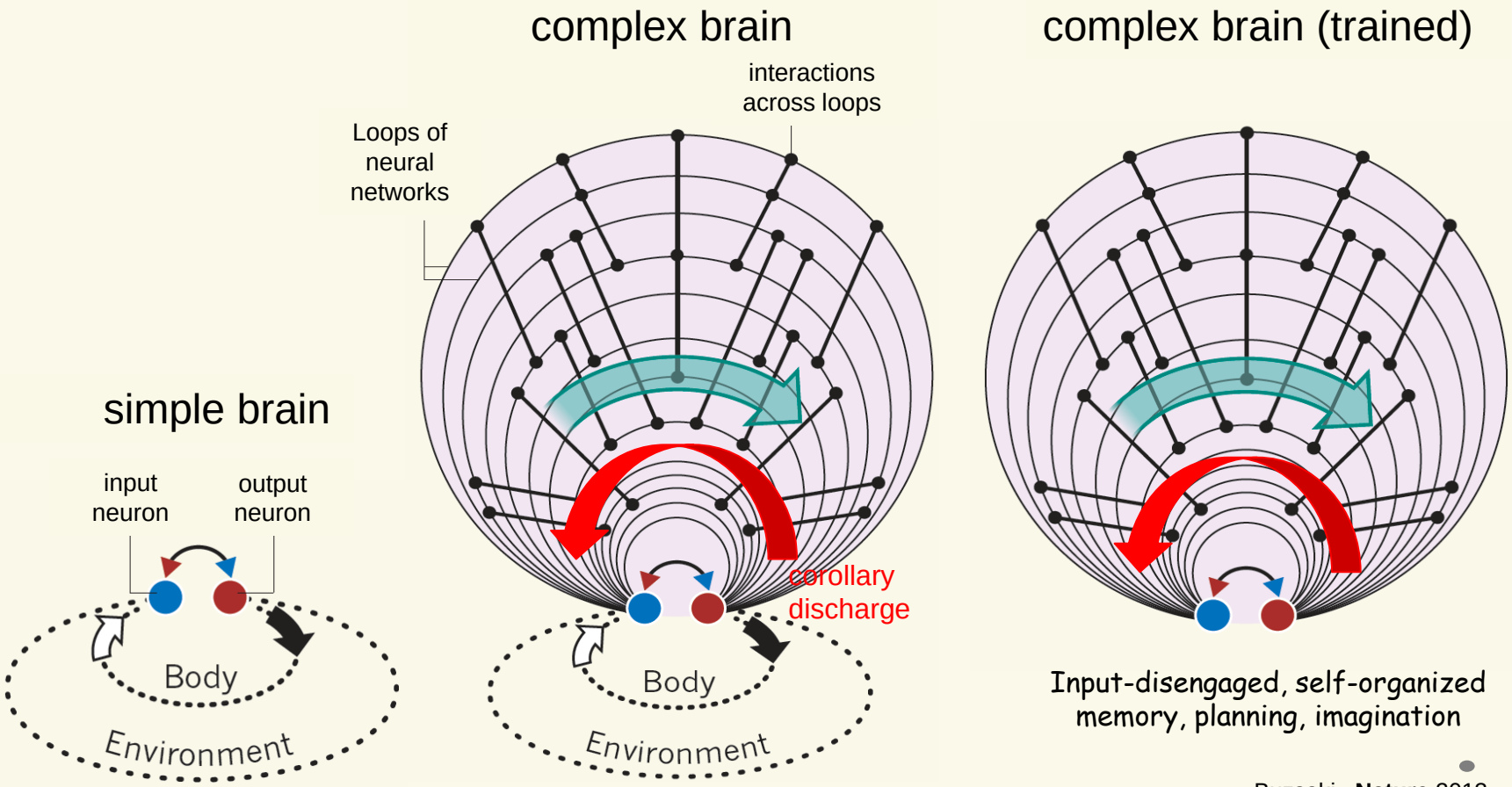


"I am the agent of change"

Von Holst, Mittelstaedt (1950)
Sperry (1950); Sokolov (1963)

- How did we inherited today’s neuroscience framework?
- How did cognitive mechanisms emerge?
- What is the alternative to the blank slate model?

Cognition is internalized action

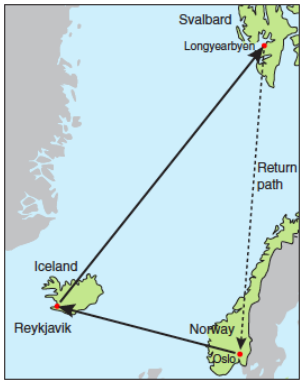


Buzsaki, **Nature** 2013

Internalization of navigation: memory

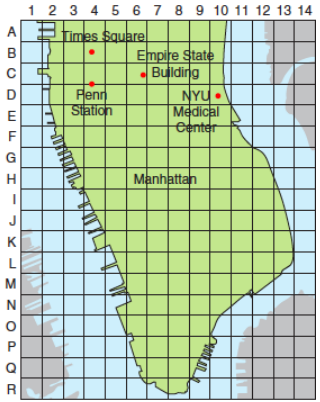
Navigation → **Memory** (mental navigation)

Dead-reckoning path integration
(self-referenced)
displacement
duration velocity



Episodic
(self-referenced)

Map-based
(allocentric)
Set of positions
time is stripped off



Semantic
(allocentric)

Buzsaki **Hippocampus** (2005)
Buzsaki, Moser E **Nature Neurosci** (2013)

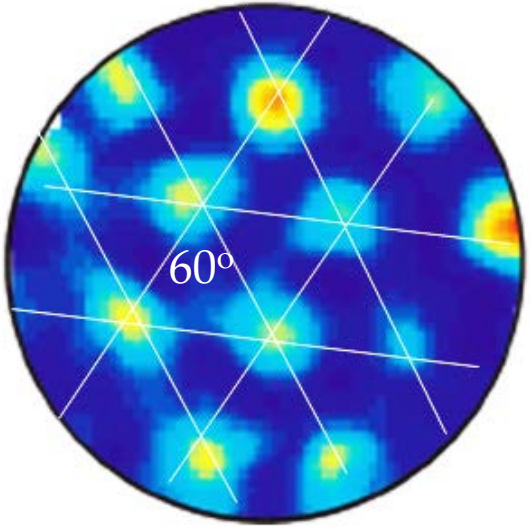
Elements of navigation
(the map metaphor)

Head directions cells

Ranck (1984)

no prize

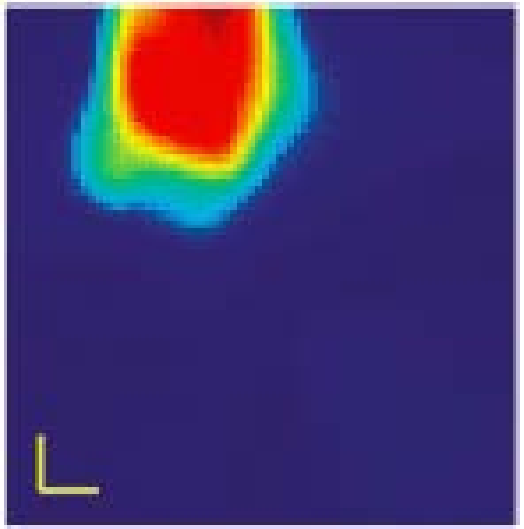
Grid cells



Moser group (2005)

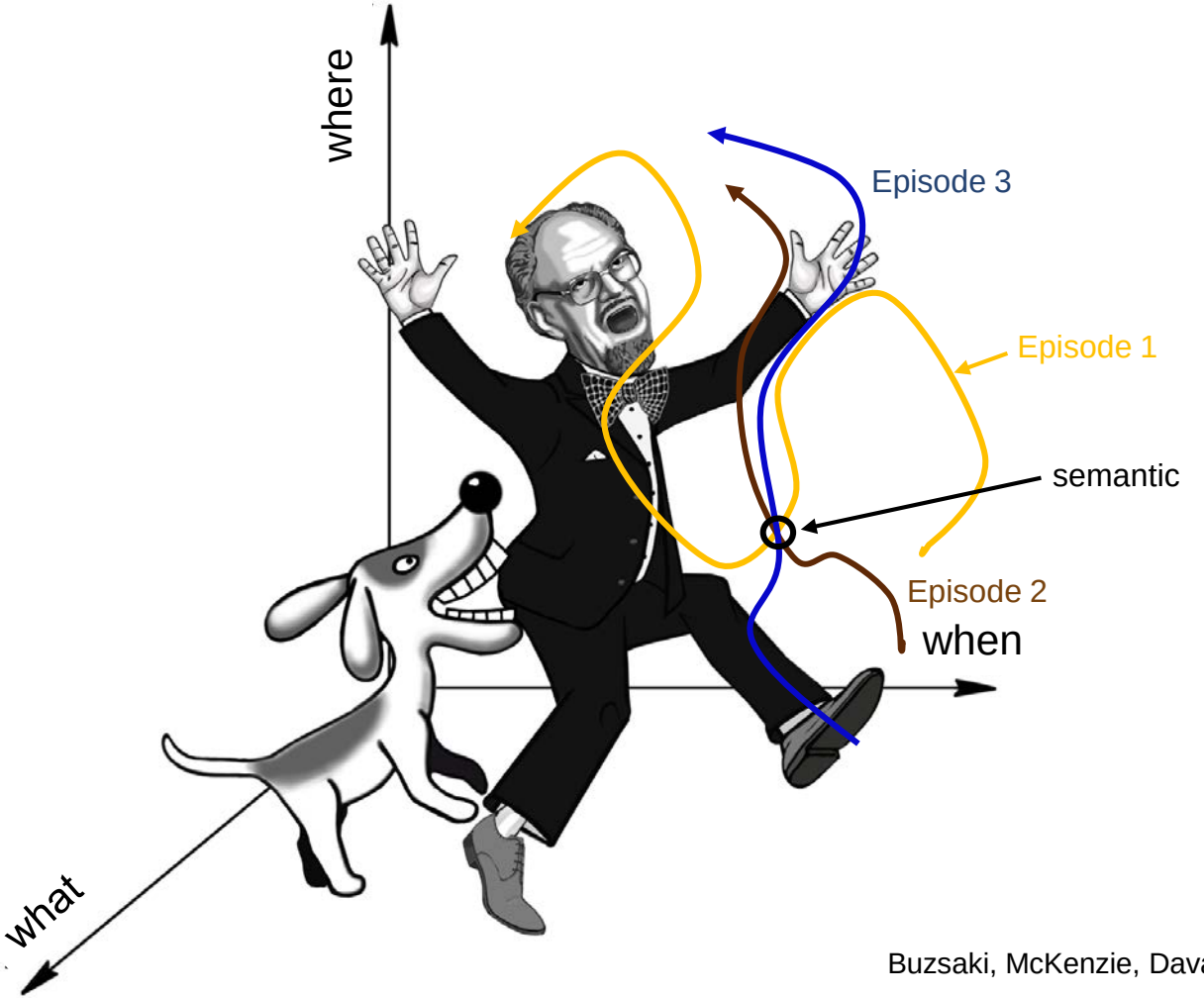
Nobel Prize 2014

Place cells



O'Keefe (1971)

Nobel Prize 2014



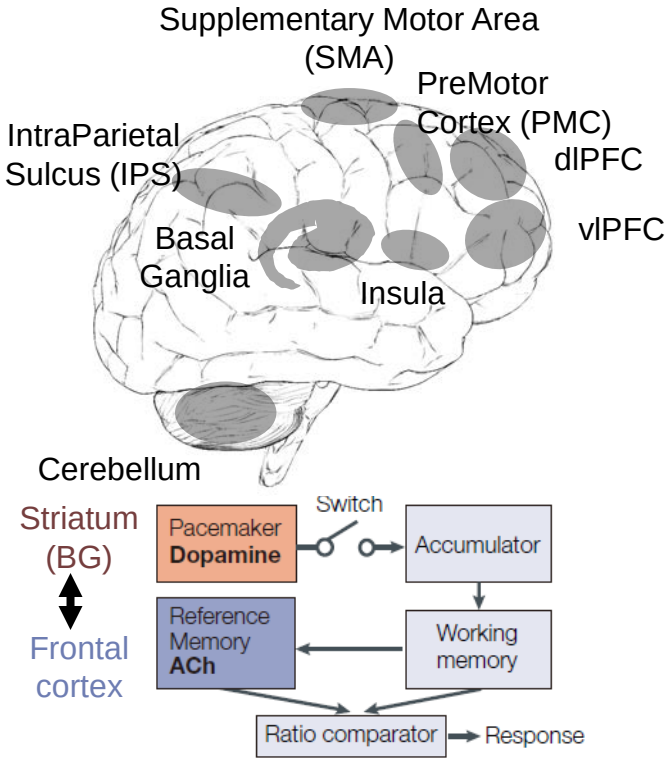
Episodic memory:

What happened to me **where** and **when**?

Buzsaki, McKenzie, Davachi **Ann Rev Psychol** (2022)

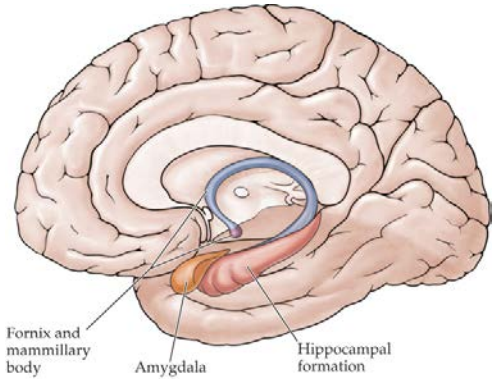
Newtonian, Kantian neuroscience

Time



Buhusi, Meck **Nat Rev Neurosci** (2005)

Space



Maguire (2000)

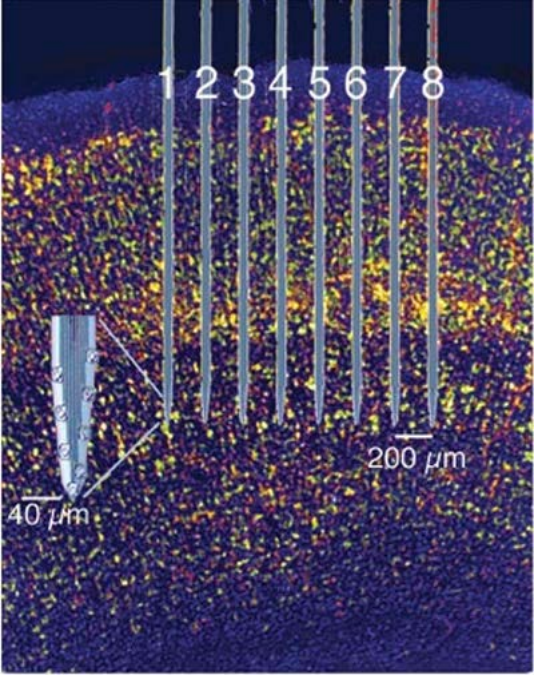
Challenge to neuroscience

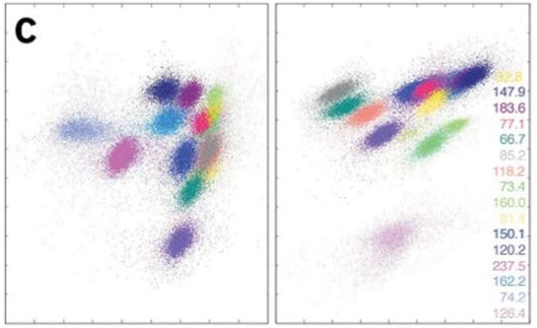
Carlo Rovelli

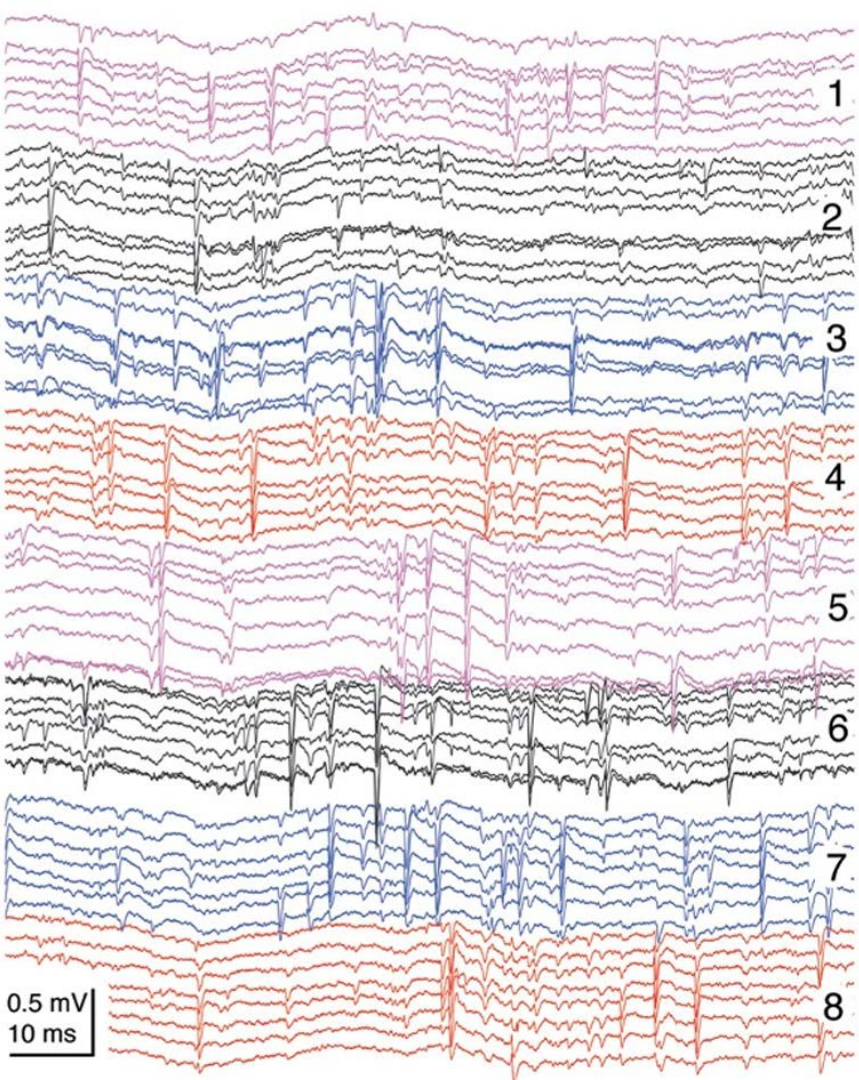
in contemporary physics:

"*there is no longer space* which 'contains' the world,
and *there is no time* 'in which' events occur."

Carlo Rovelli (2016)





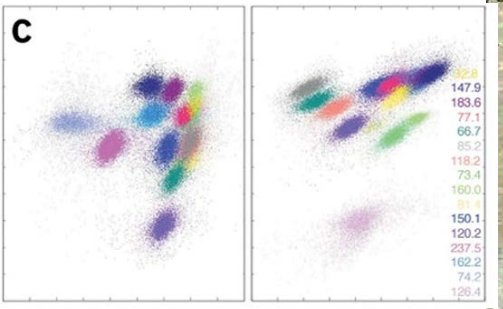


Separation (clustering) of individual neurons

Challenge:

An unsolved mathematical clustering problem

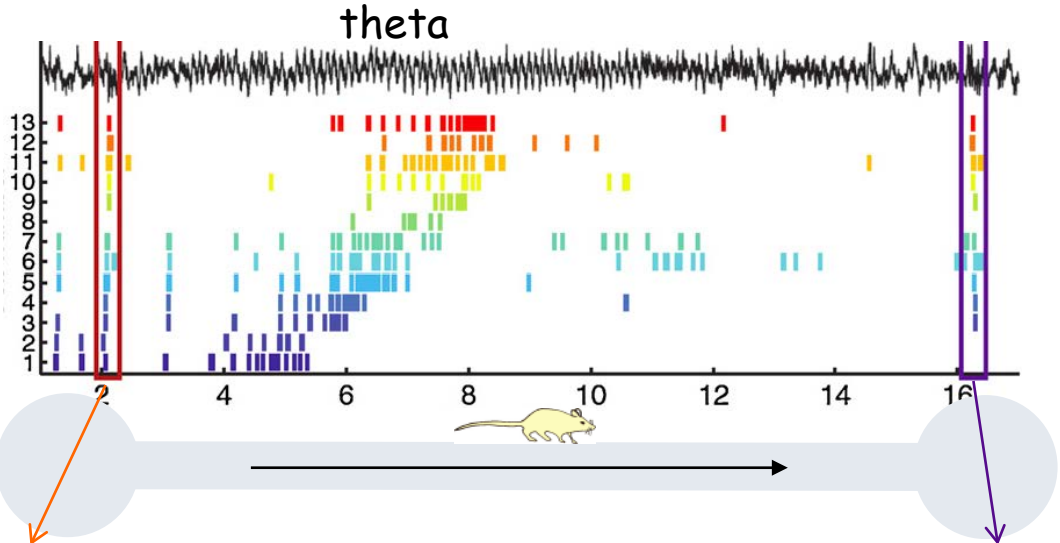
Cluste

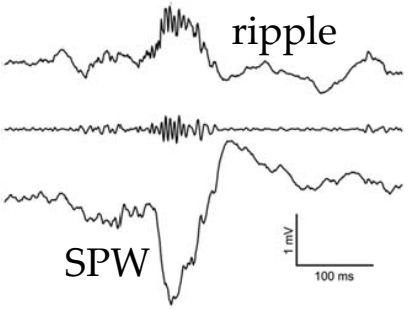


Clustering by function
(flight dynamics)

Spacetime warping of waking sequences by sharp wave-ripples

Kamran Diba





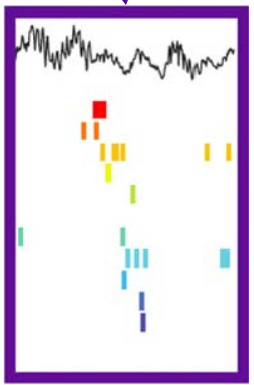
SPW-R

Forward

(planning, prediction, future)

Reverse

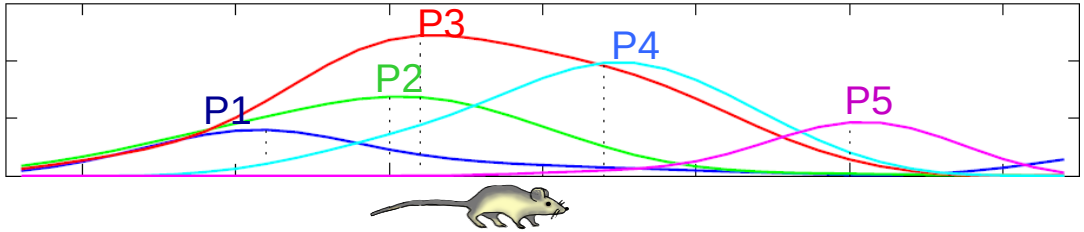
(memory, postdiction, past)



SPW-R

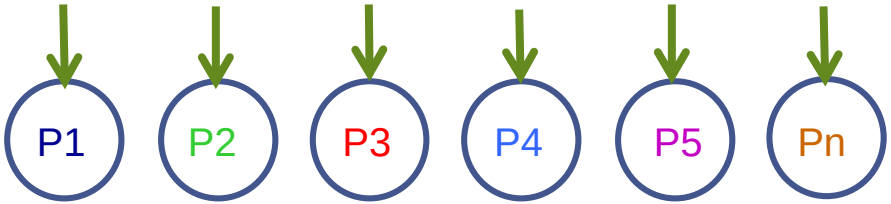
Diba, Buzsaki **Nature Neurosci** 2007

Two ways of inducing neuronal assembly sequences



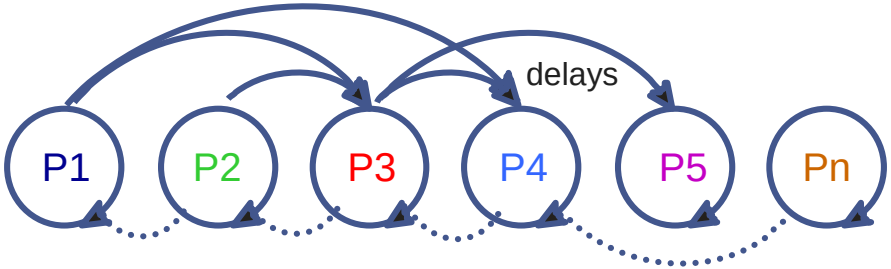
Imposed by upstream mechanisms
(cues, path integration)

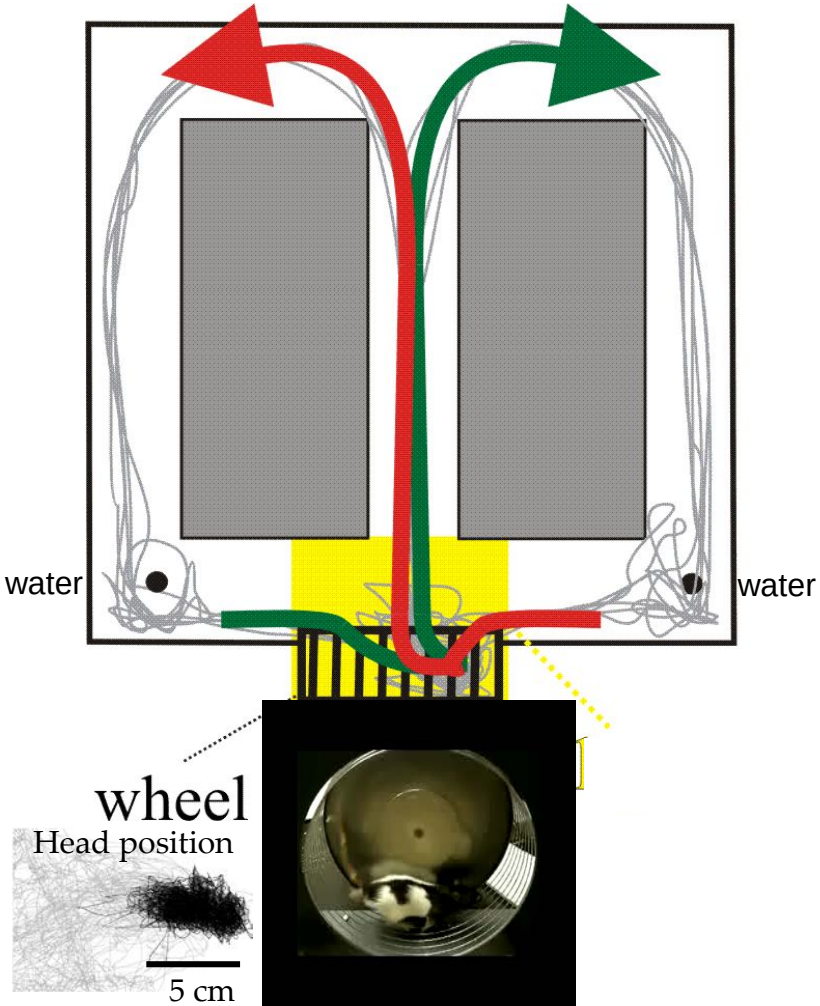
Outside in



Internal dynamics

Inside out



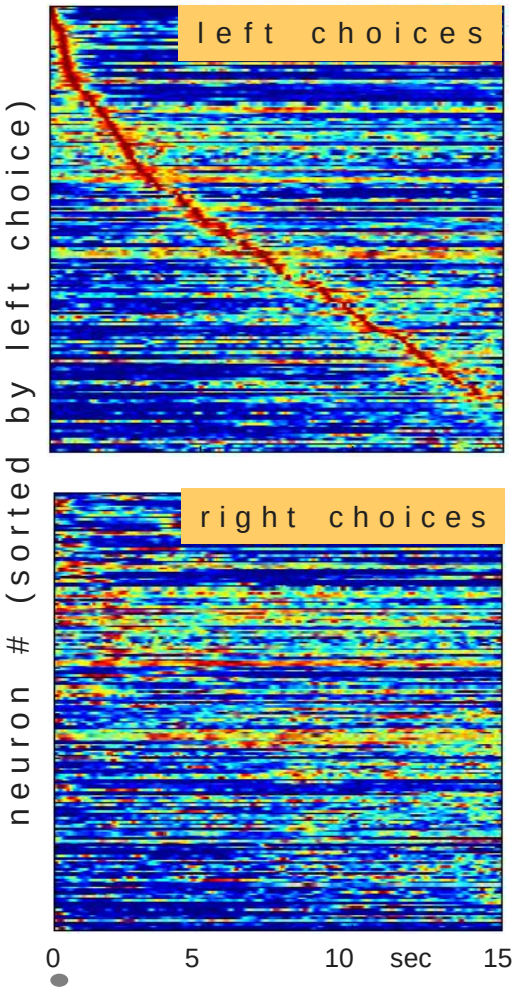


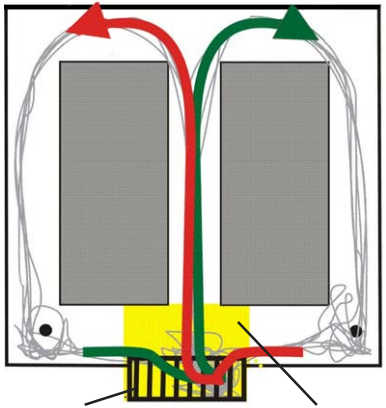
Eva Pastalkova

Zero displacement

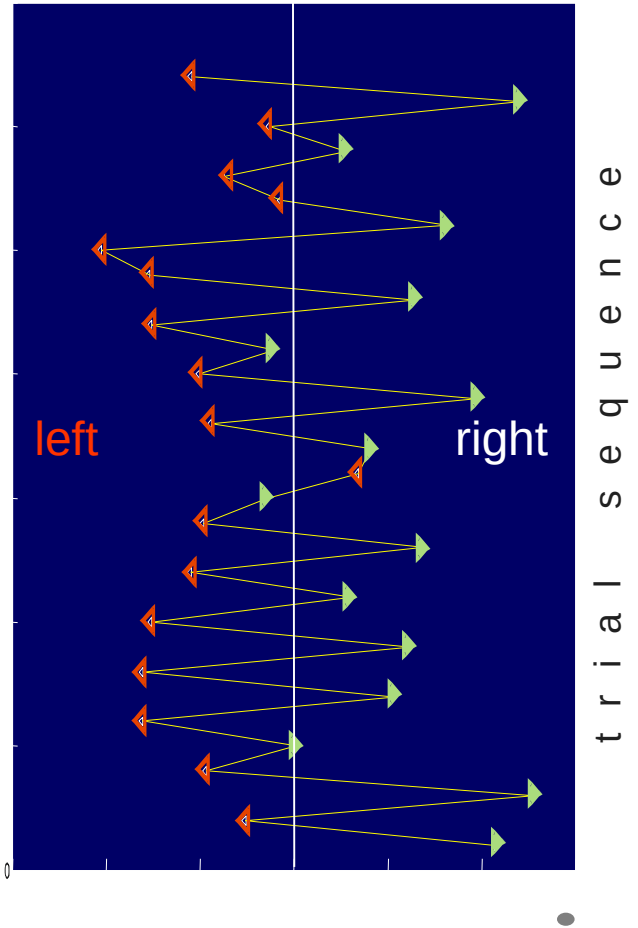
During wheel running, external and bodily cues are stationary – firing pattern changes must reflect internal readout

Pastalkova, Itzkov, Amarasingham,Buzsáki, **Science** (2008)

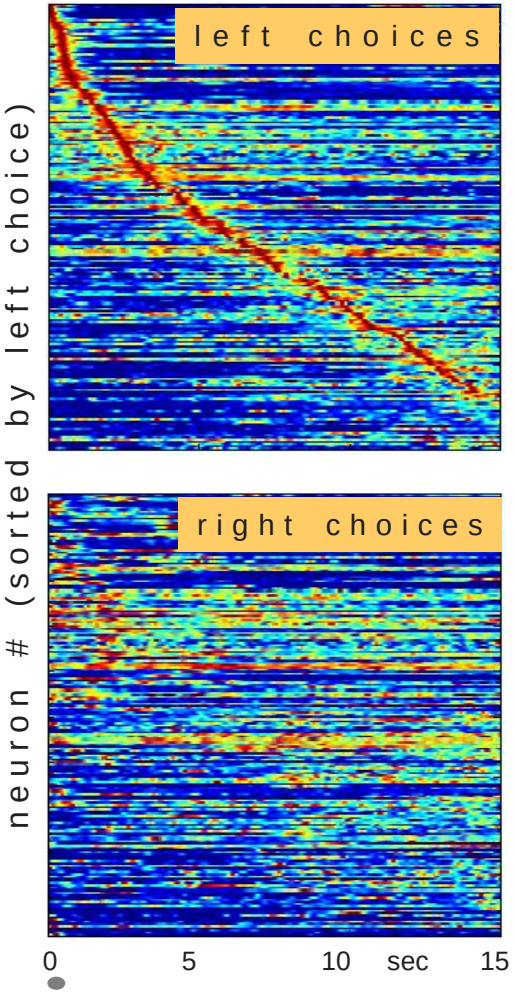


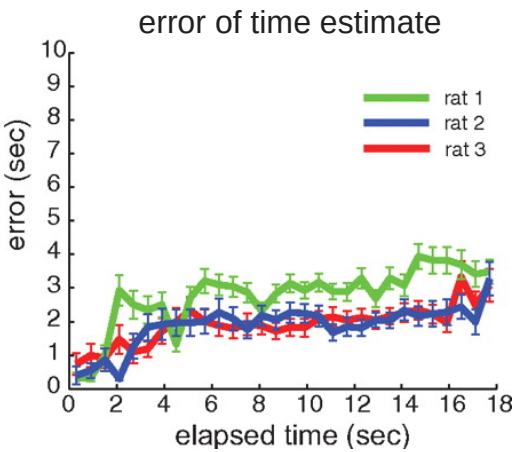


Choice prediction



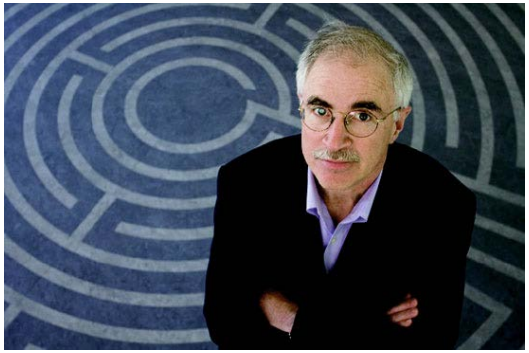
Pastalkova, Itzkov, Amarasingham, Buzsáki **Science** (2008)





Cell assembly sequences in the hippocampus keep track of time

Itzkov, Curto, Pastalkova, Buzsáki **J Neurosci** (2009)

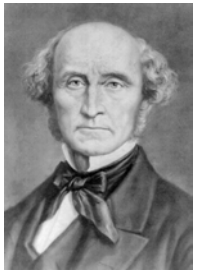


TIME CELLS

Howard Eichenbaum **Nat Rev Neurosci (**2014)

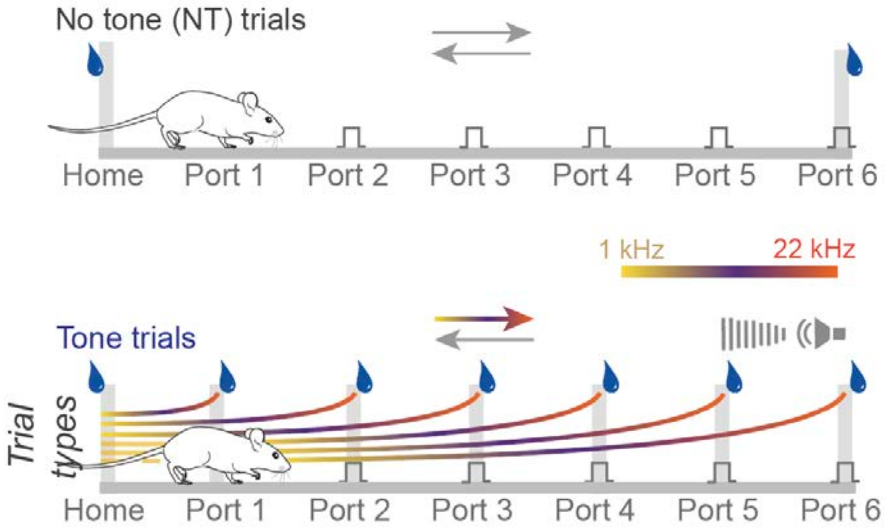
Pastalkova, Itzkov, Amarasingham, Buzsáki **Science** (2008)

"He who knows only his side of the case, knows little of that"



John Stuart Mill

Acoustic Cue-guided Navigation Task



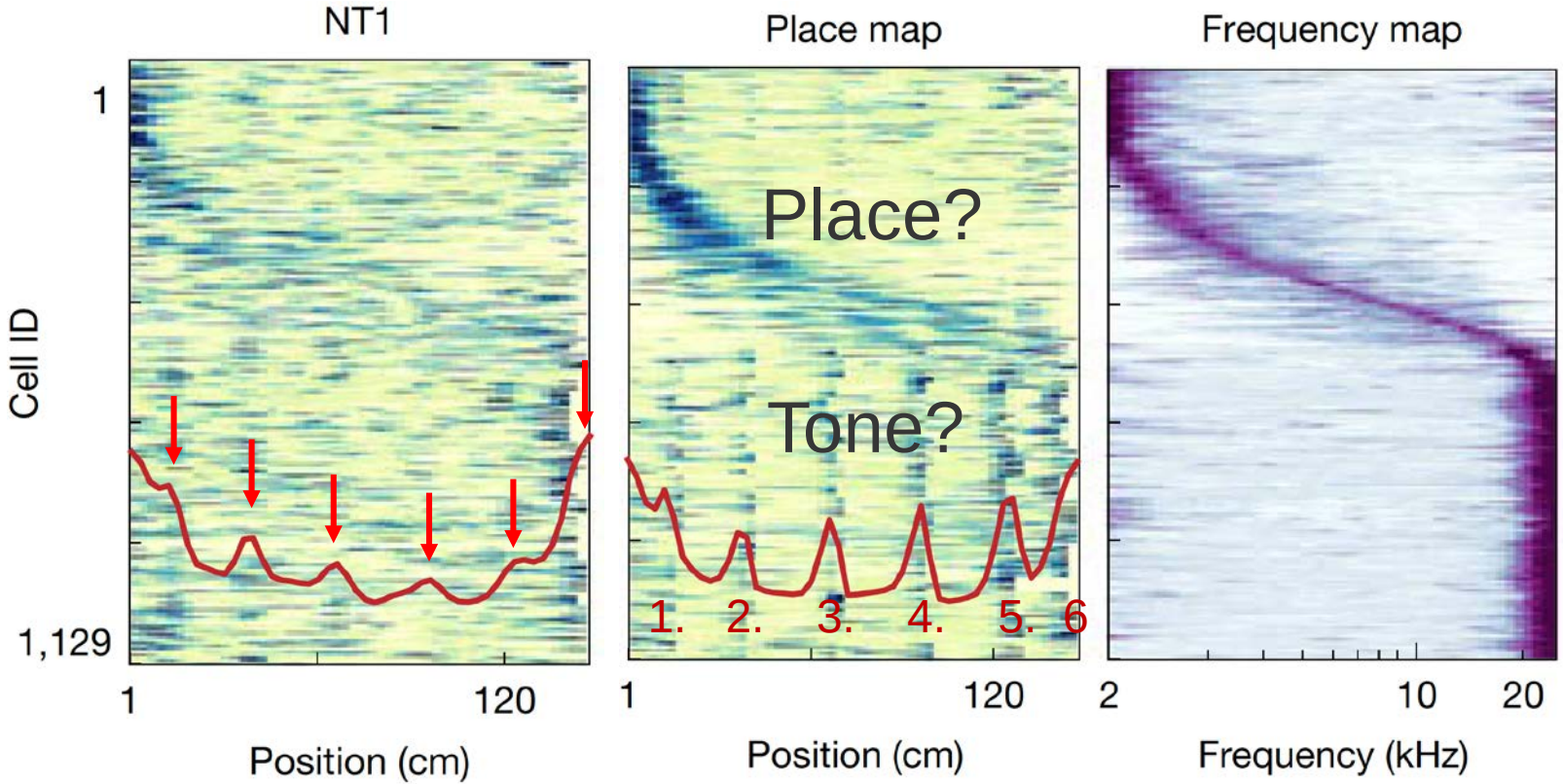
(10 trials)

(70-80 trials)

Ipshita Zutshi

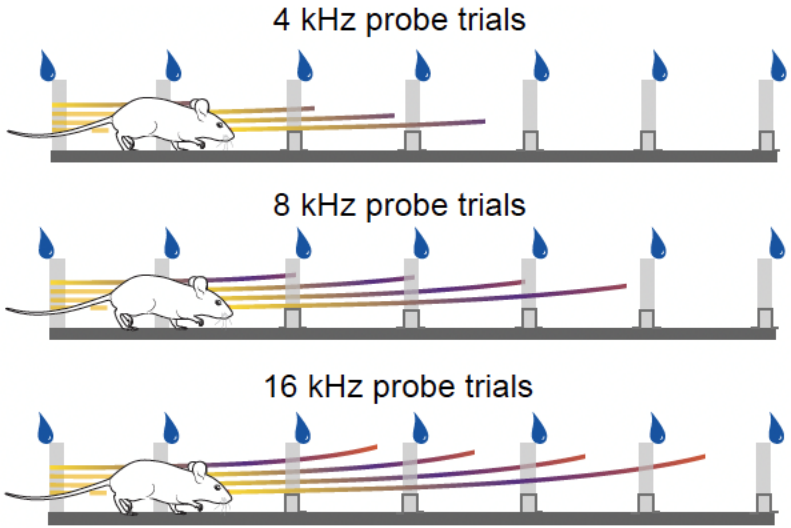
Zutshi, Apostolelli, Yang, Zheng, Tora, Balzani, Williams, Savin, Buzsáki **Nature** 2025

What features drive the neurons?

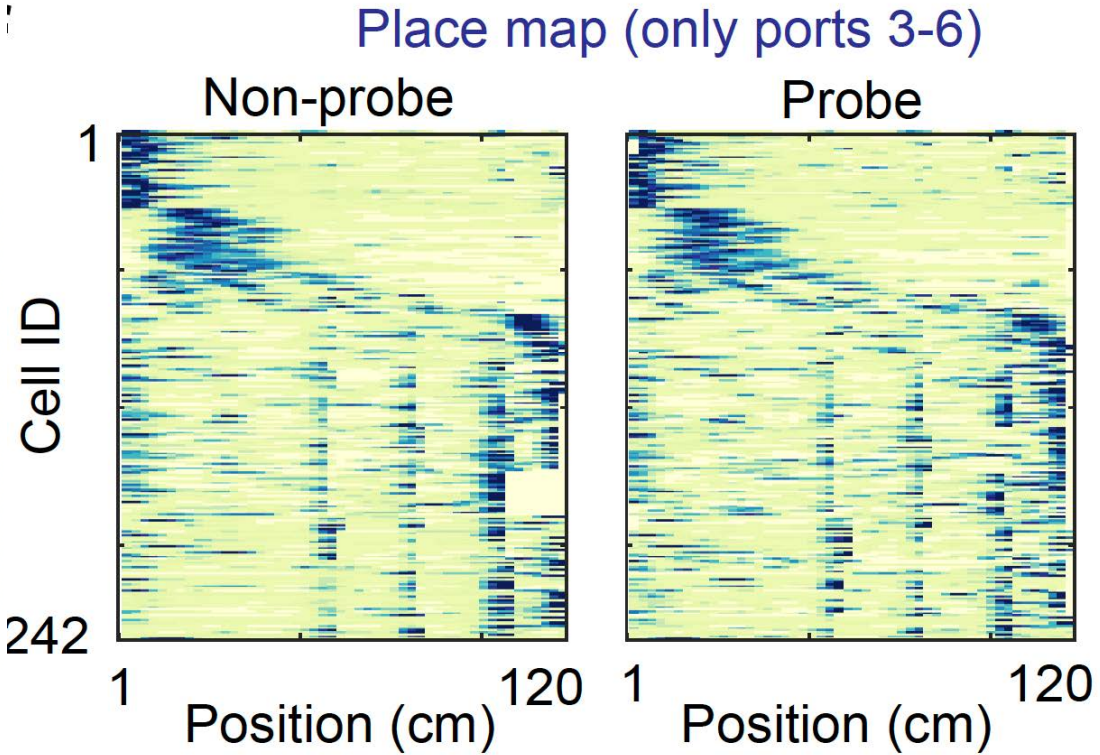


Zutshi, Apostolelli, Yang, Zheng, Tora, Balzani, Williams, Savin, Buzsáki **Nature** 2025

What features drive the neurons?

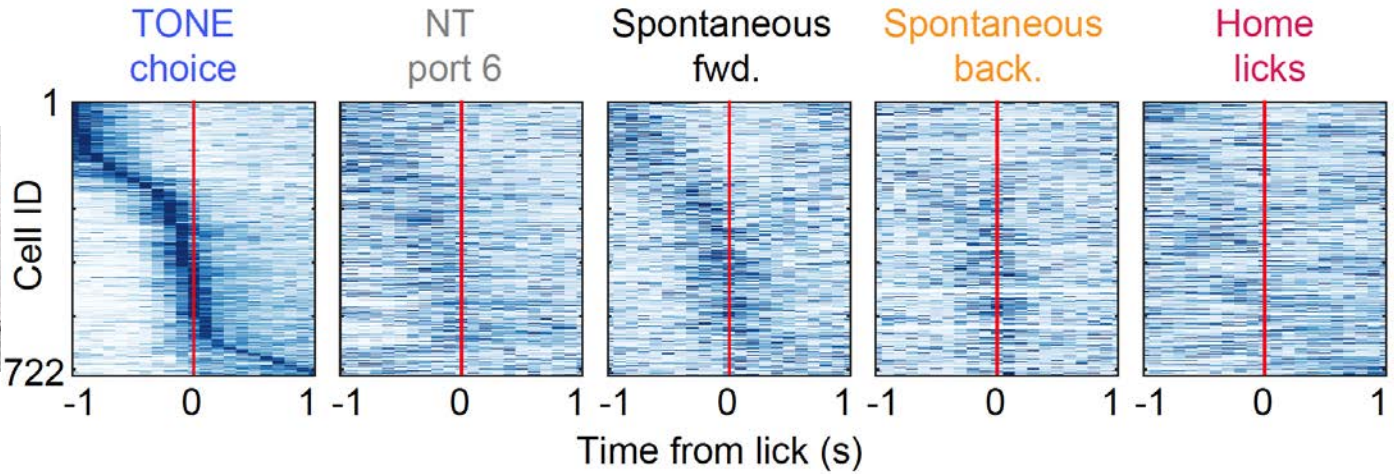


~~Sound~~

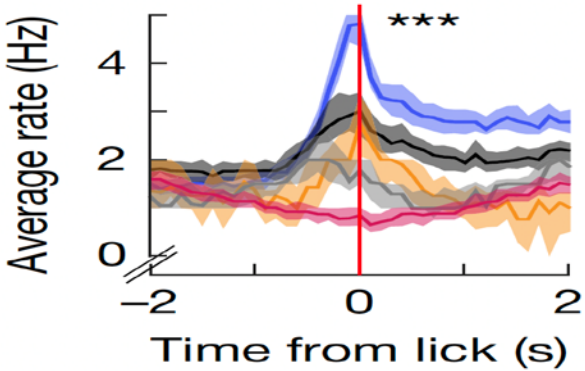


Zutshi, Apostolelli, Yang, Zheng, Tora, Balzani, Williams, Savin, Buzsáki **Nature** 2025

What features drive the neurons?



~~licking~~



Zutshi, Apostolelli, Yang, Zheng, Tora, Balzani, Williams, Savin, Buzsáki **Nature** 2025

What do the 'task-relevant' cells respond to?

Possibilities:

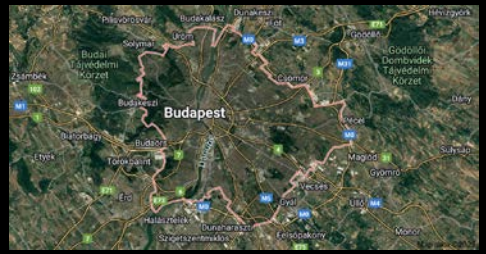
- Space
- Time
- Auditory frequency
- preparation to lick
- Deceleration
- Context
- Head turns
- Reward consumption
- Goals

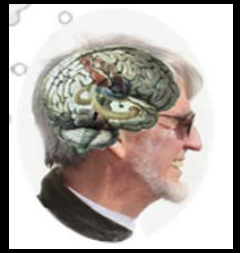
What do the 'task-relevant' cells respond to?

Possibilities:

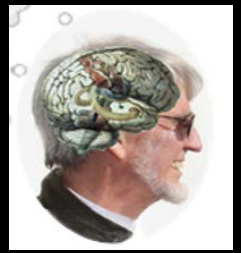
- ~~Space~~
- ~~Time~~
- ~~Auditory frequency~~
- ~~preparation to lick~~
- ~~Deceleration~~
- ~~Context~~
- ~~Head turns~~
- ~~Reward consumption~~
- Goals

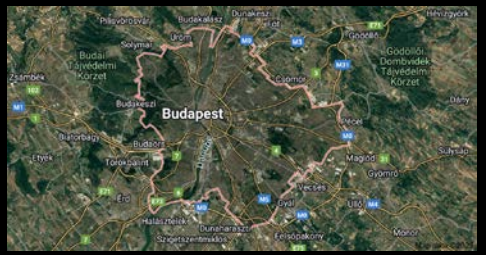
Represent the world





Construct the world

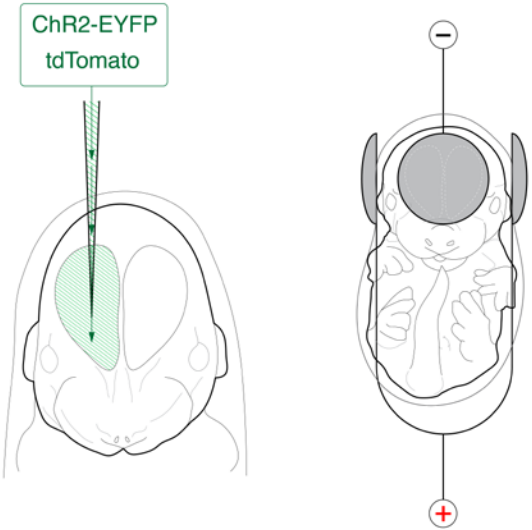


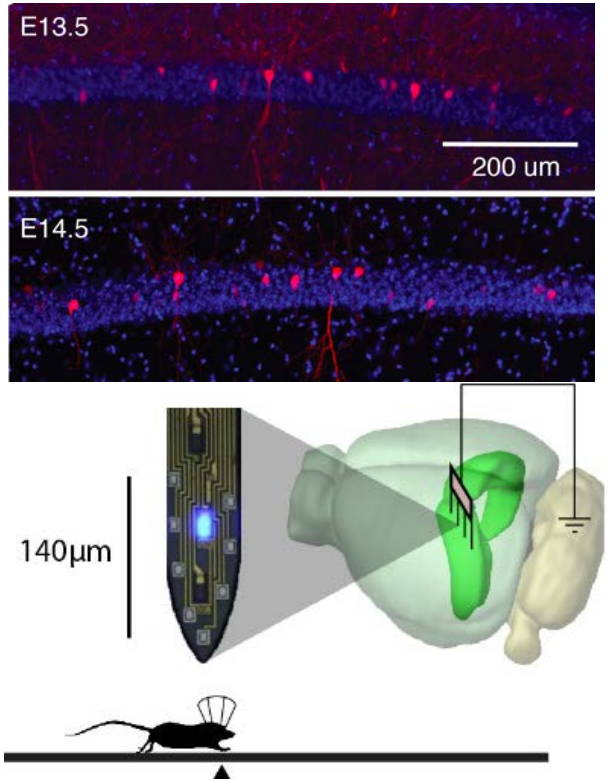


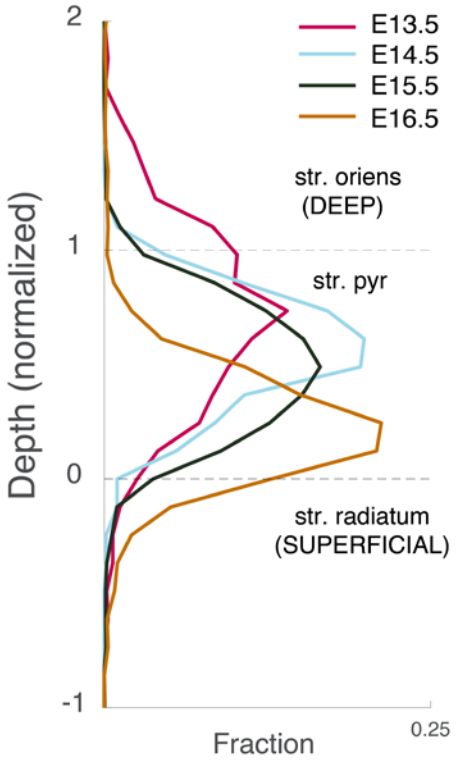
"Departing from the notion of 'representation' of external stimuli or 'mapping' the environment onto the hippocampus, we hypothesize that its **internally-generated dynamics are projected onto the animal's niche to make sense of the world through its prospective actions."**

- How did we inherited today’s neuroscience framework?
- How did cognitive mechanisms emerge?
- Experience: ‘writing in’ or ‘unmasking’?

Developmental origin of circuit configuration





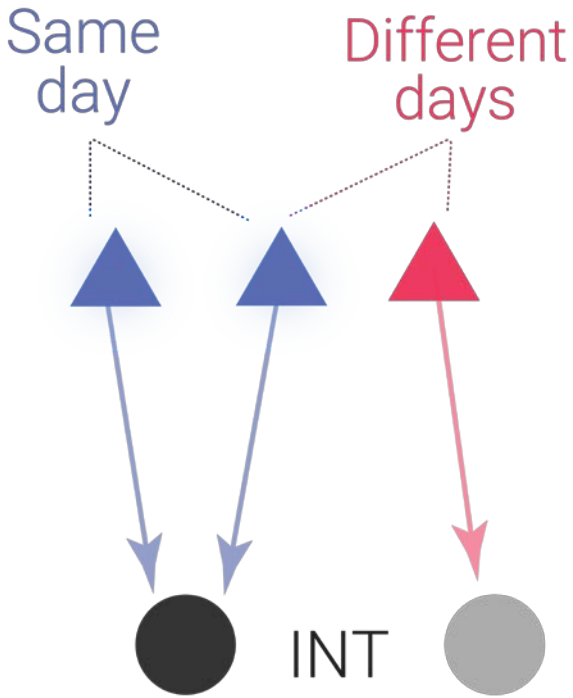


Roman Huszar

Euisik Yoon

Huszár, Zhang, Blockus, Buzsáki **Nature Neurosci** 2022

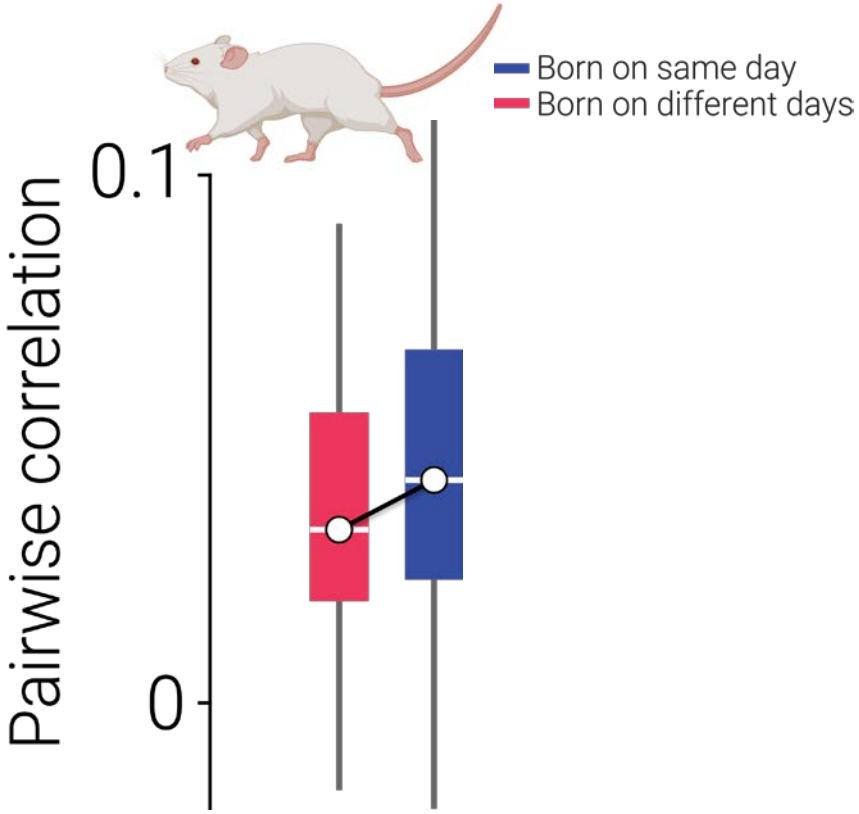
Neurons born on the same day



1) Converge onto same interneurons

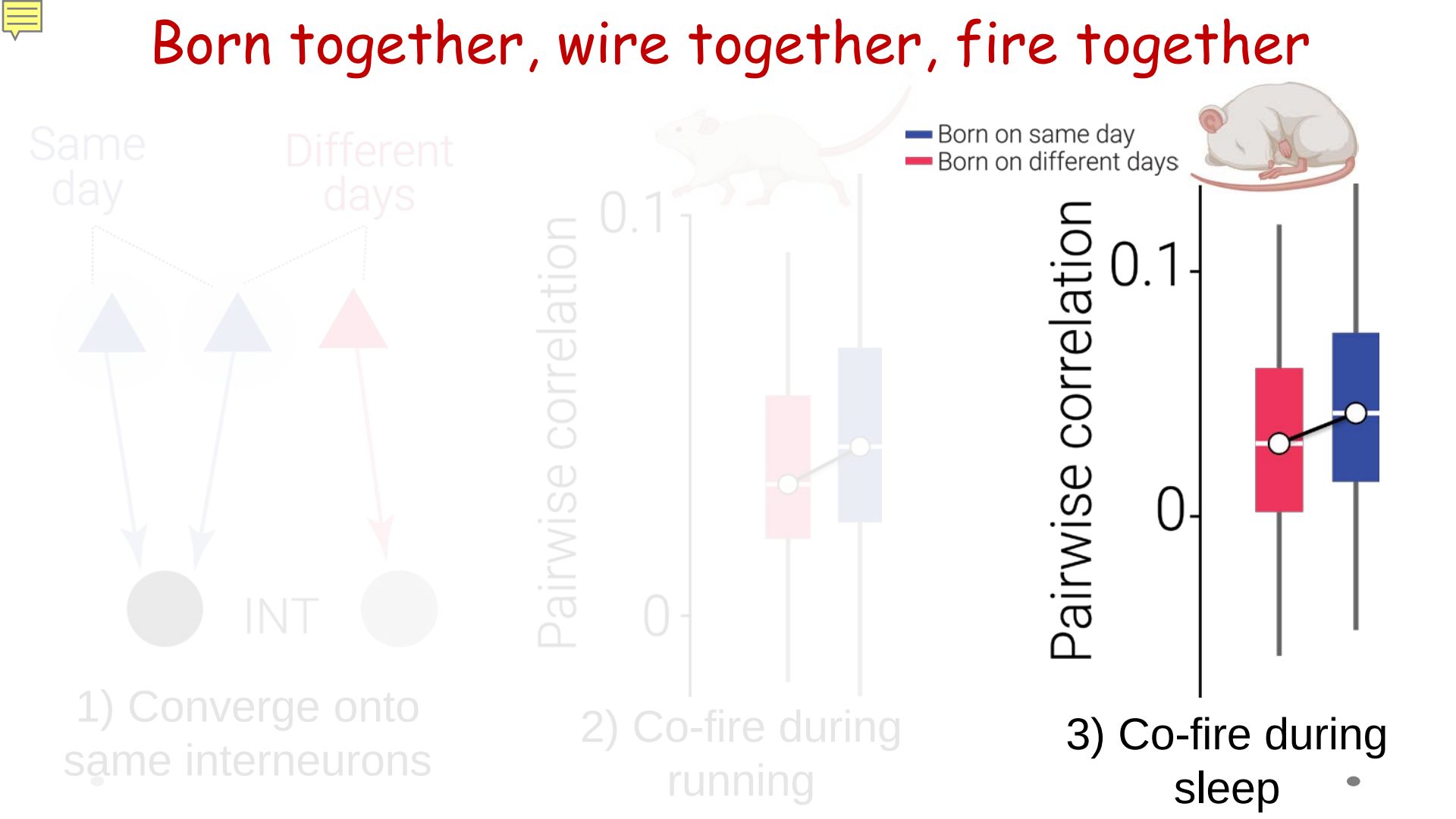
Neurons born on the same day

1) Converge onto same interneurons

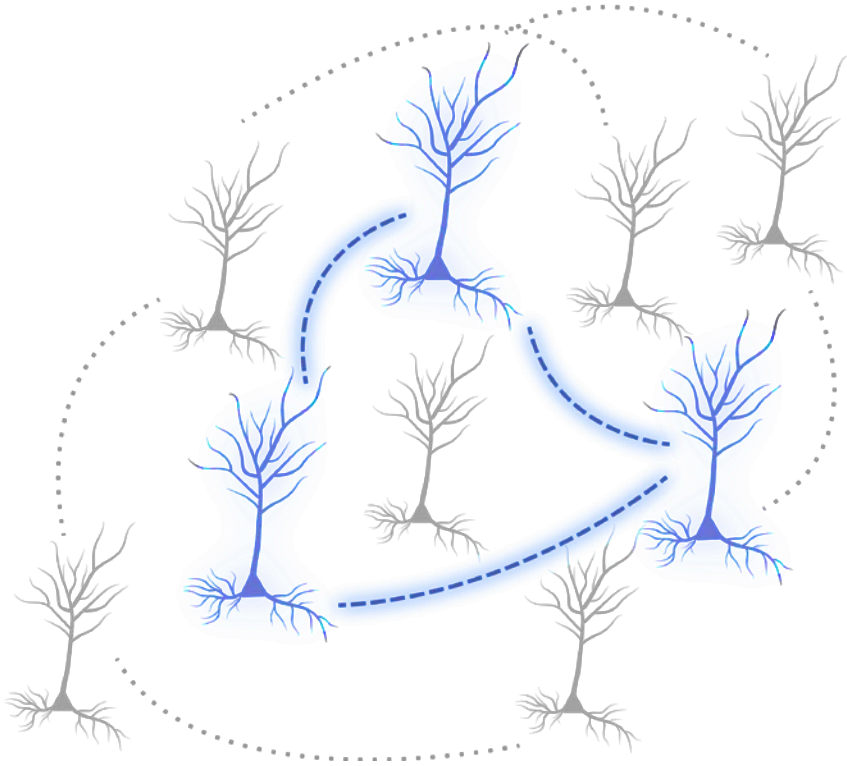


2) Co-fire during running

Born together, wire together, fire together



Developmentally specified circuit

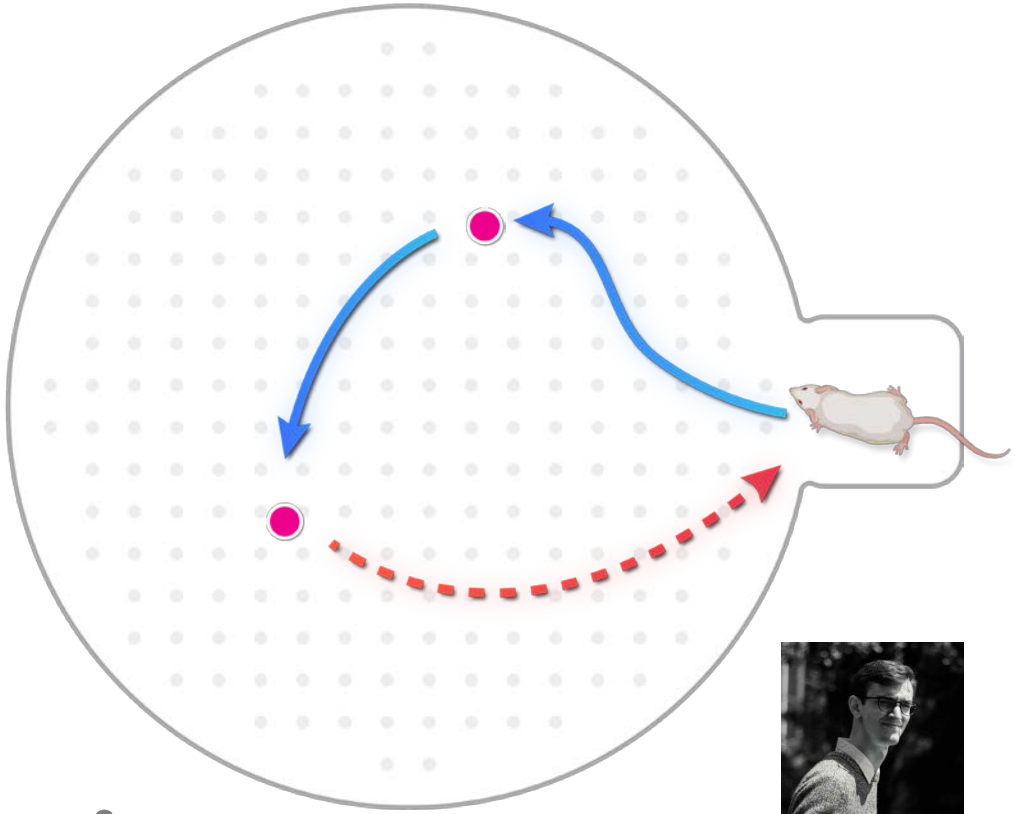


Is it just a connectivity constraint?

Or computationally relevant building blocks for learning?

Born together, Wire together, Fire together

Cheeseboard maze: spatial learning task

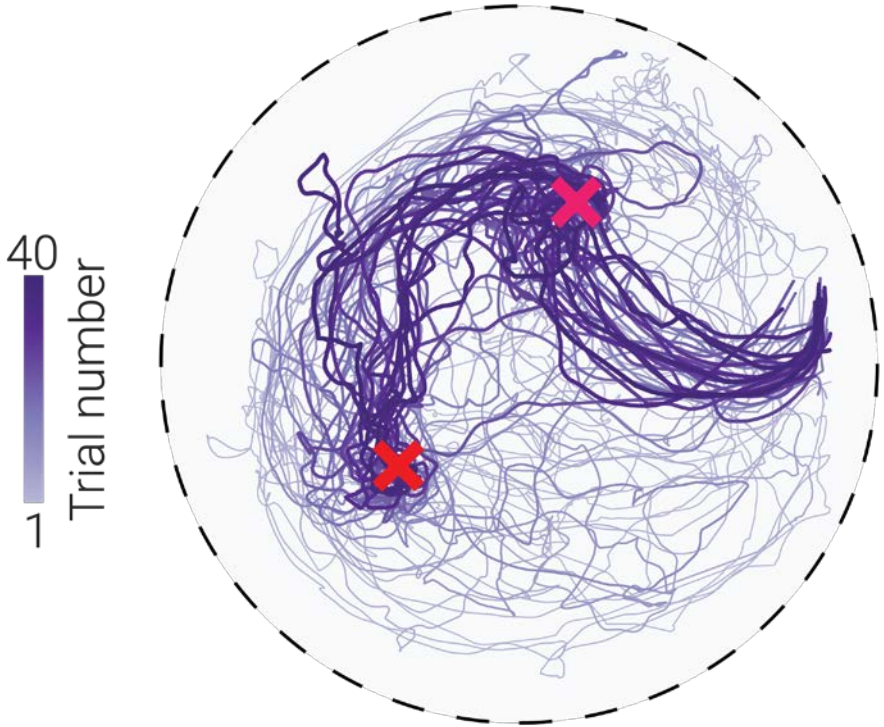


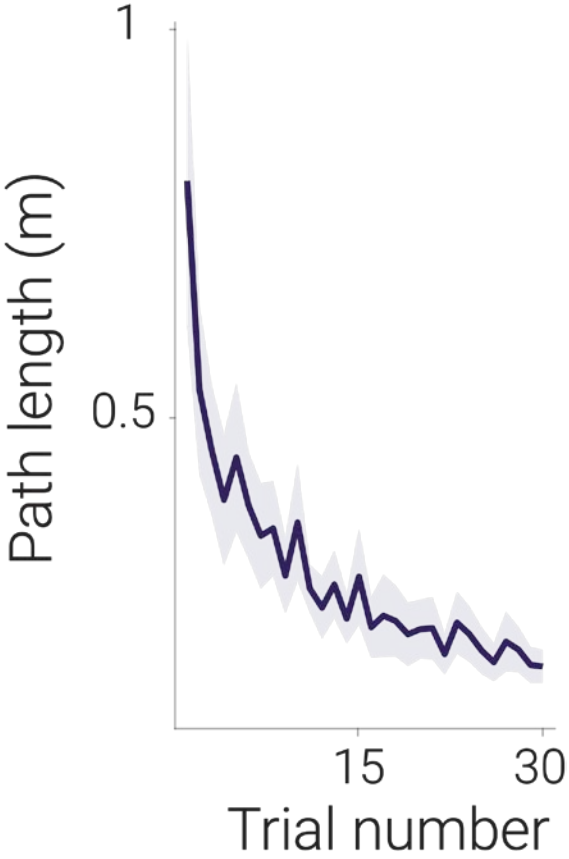
- Cheeseboard maze
- 2 water reward locations
- Task structure:
  - Collect rewards
  - Return to the waiting box

Roman Huszar

Artem Kirsakov

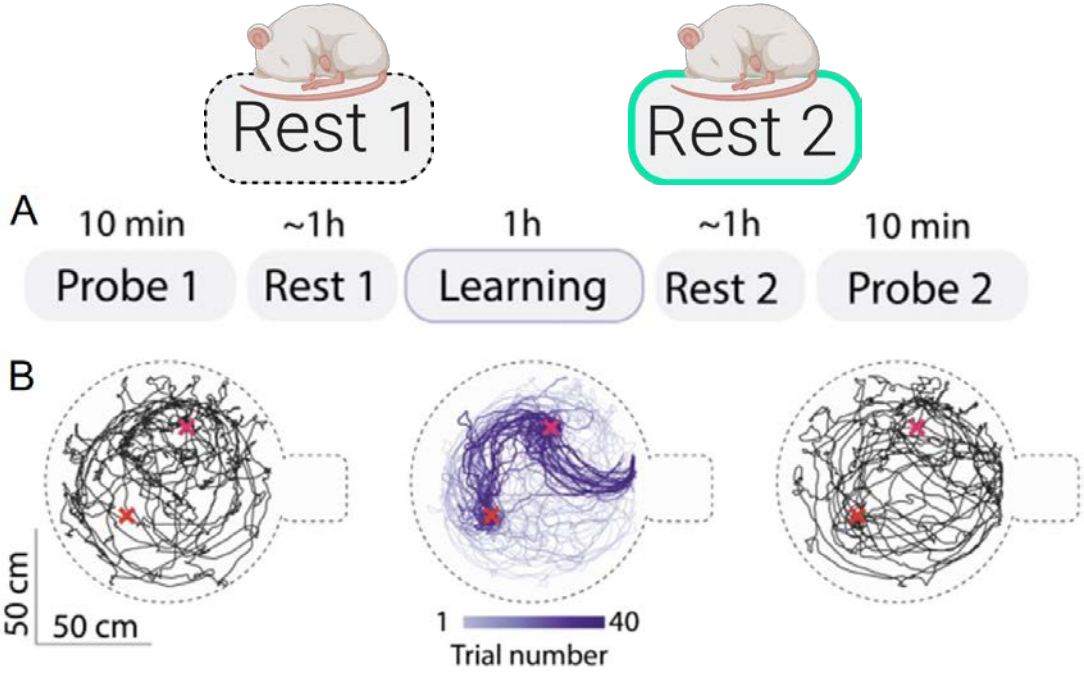
Cheeseboard maze: spatial learning task



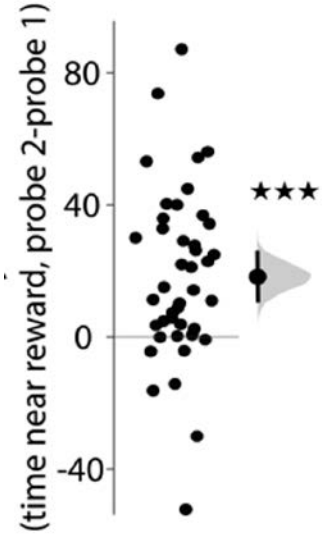


- Behavior becomes stereotyped

Cheeseboard maze: spatial learning task



memory retrieval



Cheeseboard maze: spatial learning task

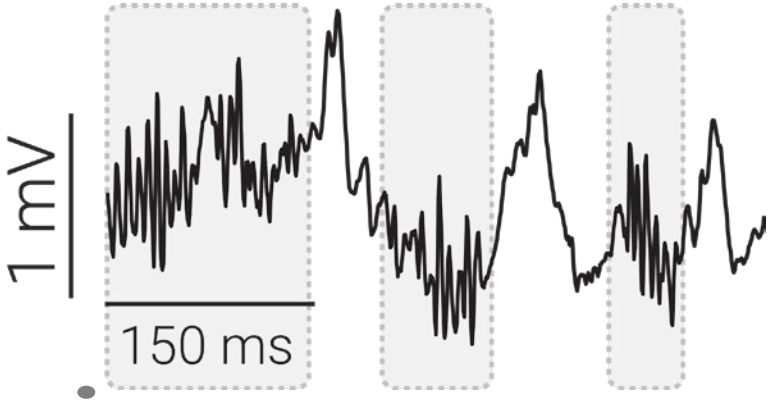
Rest 1

~1h

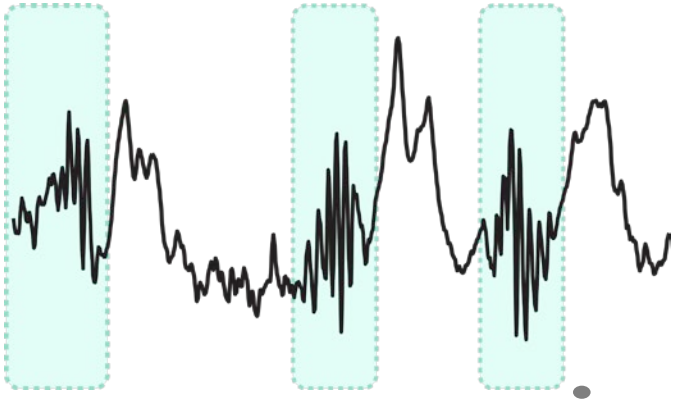
Learning

Rest 2

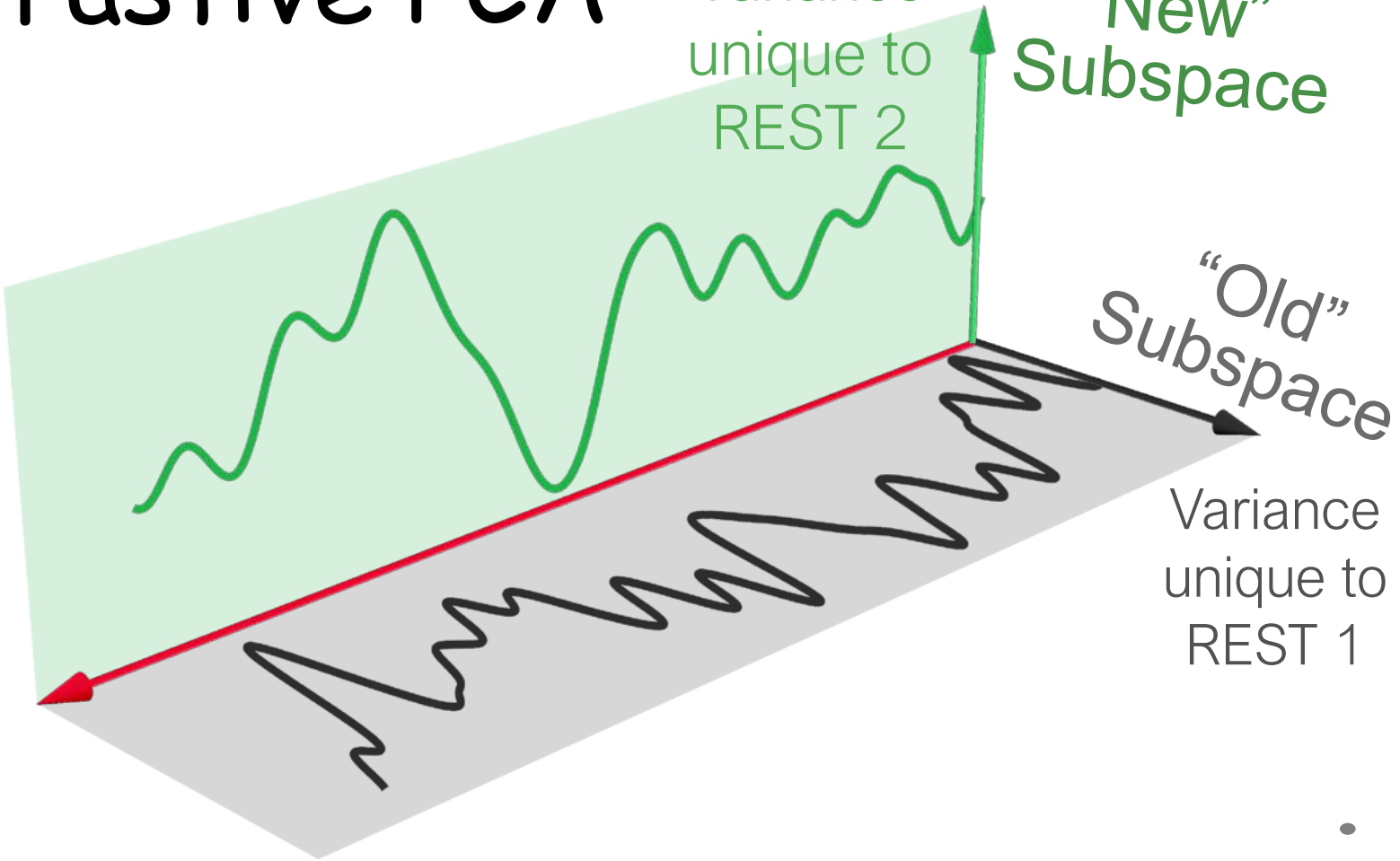
~1h



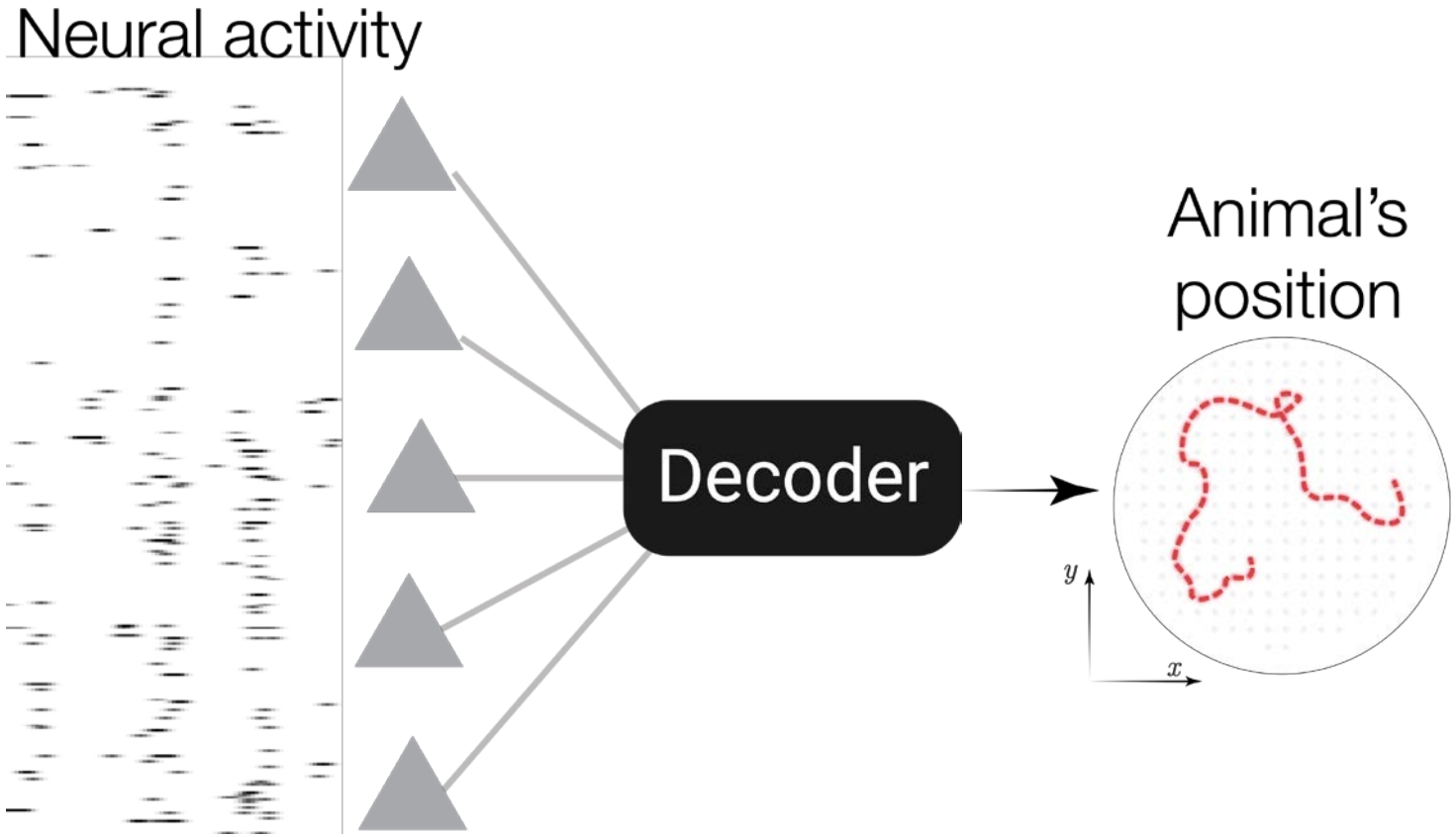
Offline replay activity (sharp wave-ripples)



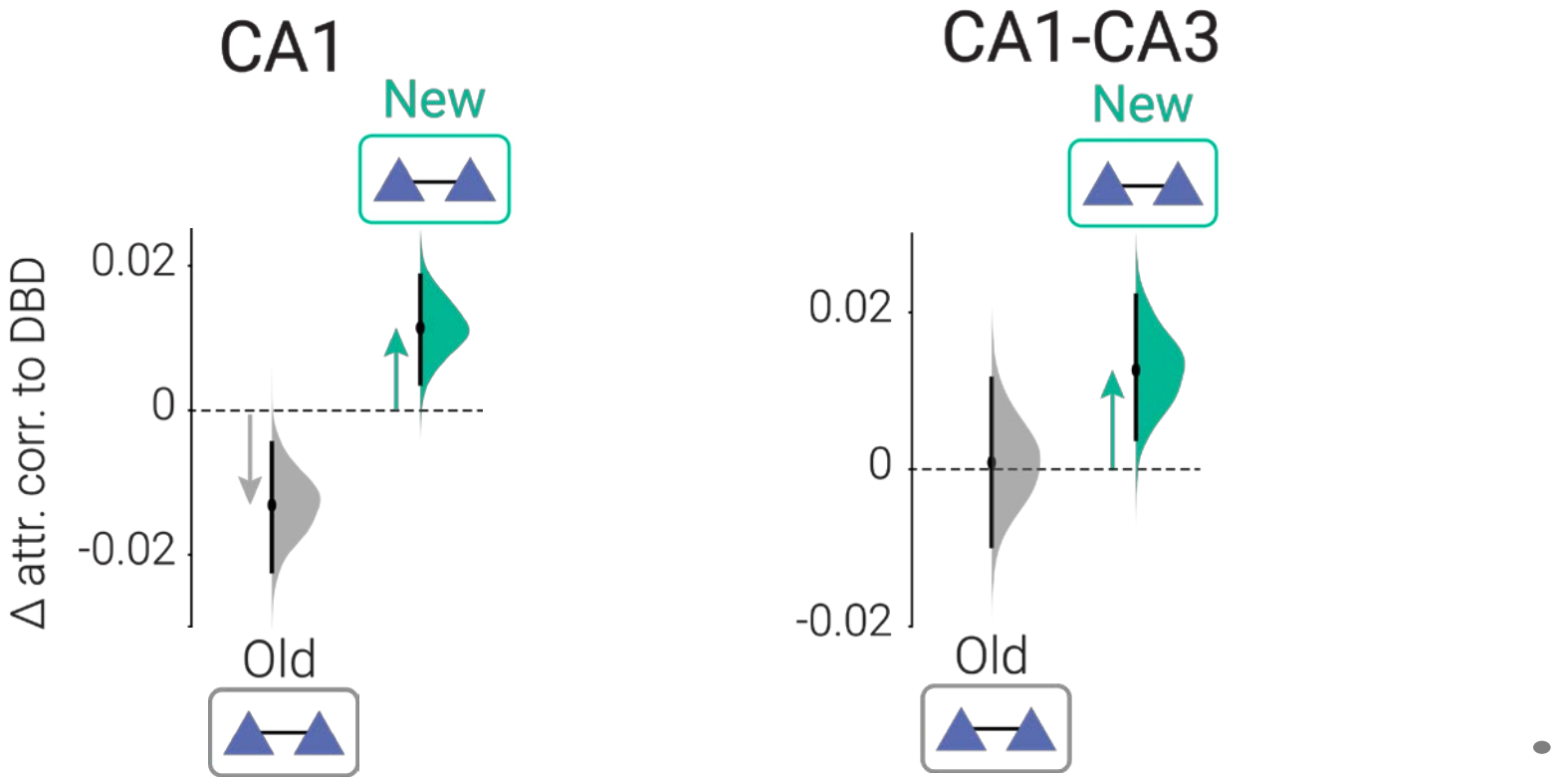
Contrastive PCA

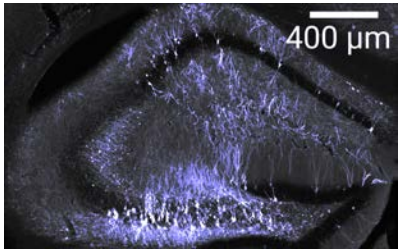


Decoding from subspaces (Rest 2 vs Rest 1)



Same-day born neurons encode similar positional information in NEW, but not OLD subspace

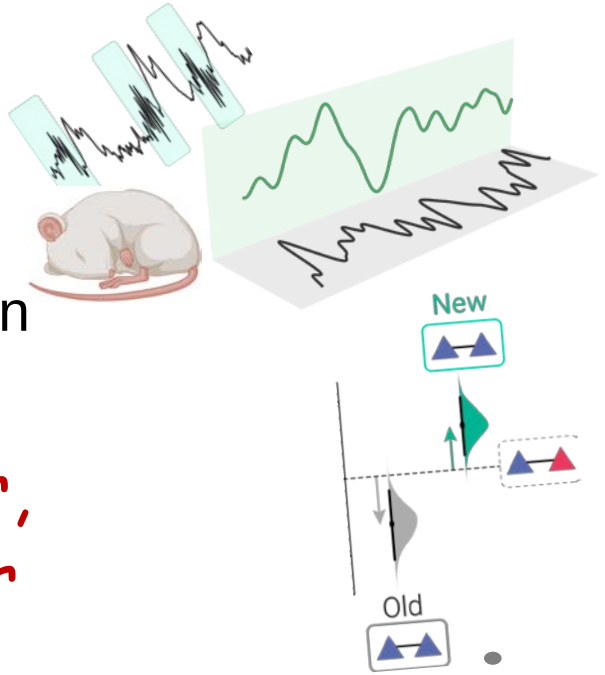




- Embryonic development results in microcircuits with constrained connectivity

- Correlated activity of these microcircuits is maintained during spatial learning, and reactivates during sleep, encoding rewards

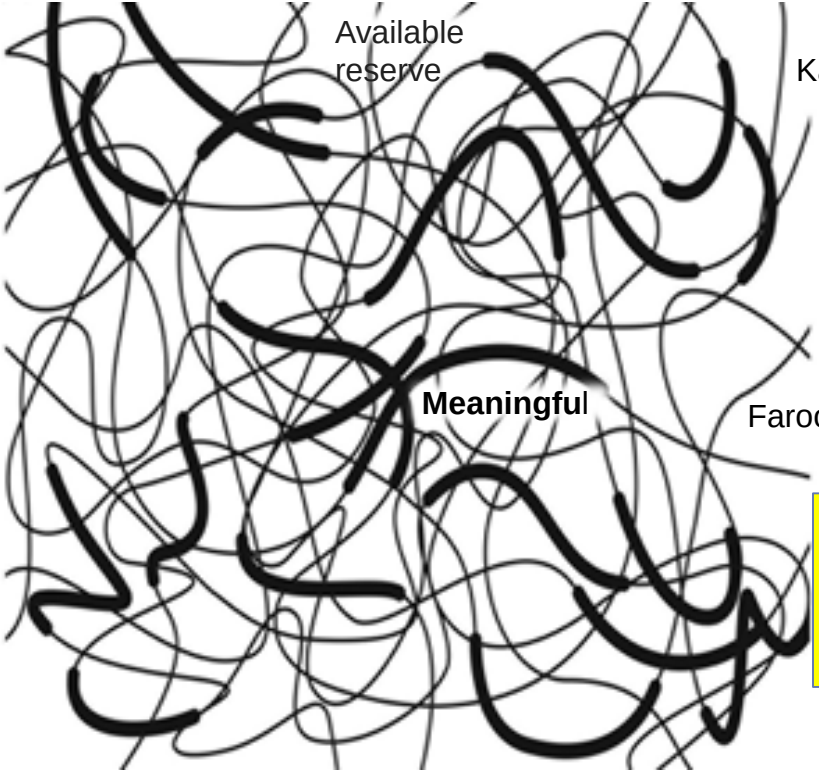
- Developmentally-defined microcircuits form preconfigured “modules” that play unique roles in memory encoding



Born together, wire together, fire together…learn together

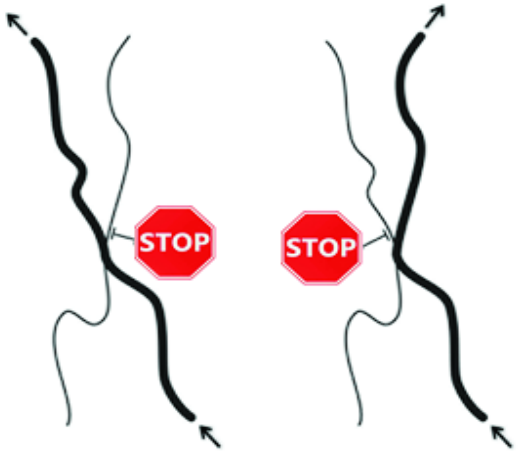

Blank
SLATE

Brains come with preconfigured connectivity and dynamic



Karmos, Martin, Czopf (1979)
Chomsky (1980)
Edelman (1987)
Kenet, Bibitchkov,Tsodyks,
Grinvald, Arieli (2003)
Buzsaki (2006; 2019)
Dragoi , Tonegawa (2013)
Sadtler… Batista (2014)
Golub…. Chace, Yu (2018)
Farooq, Sibille, Liu, Dragoi (2019)

Neurons that wire together fire together



Inhibition can reroute and link assembly sequences

Learning

Memory selection

Memory consolidation

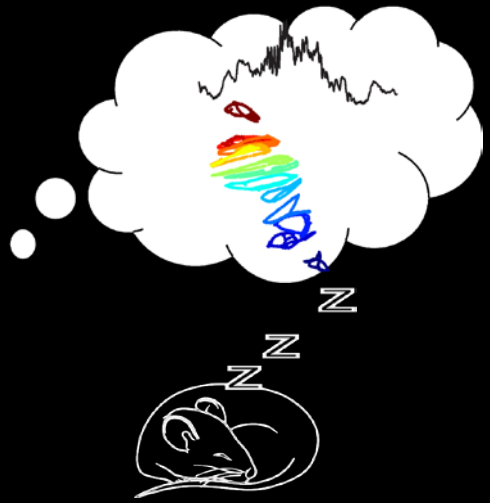
Buzsaki **Neuroscience** 1989

Theta

Winnie Yang

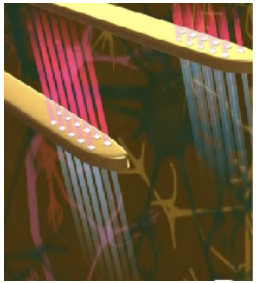
Roman Huszar

Chen Sun

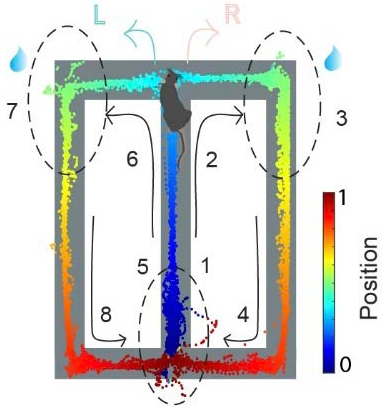


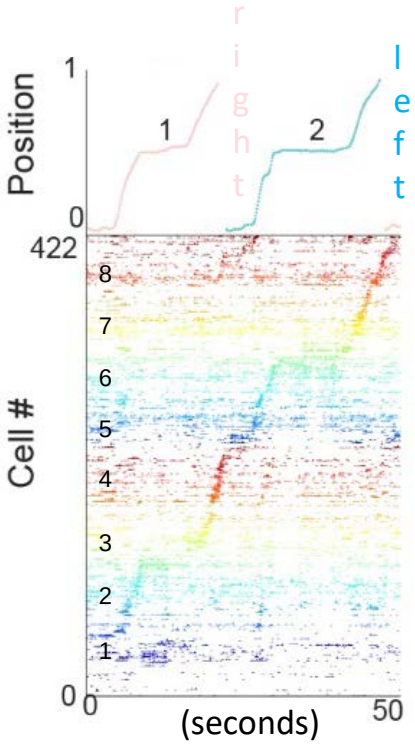
Sleep sharp wave-ripple (SPW-R)

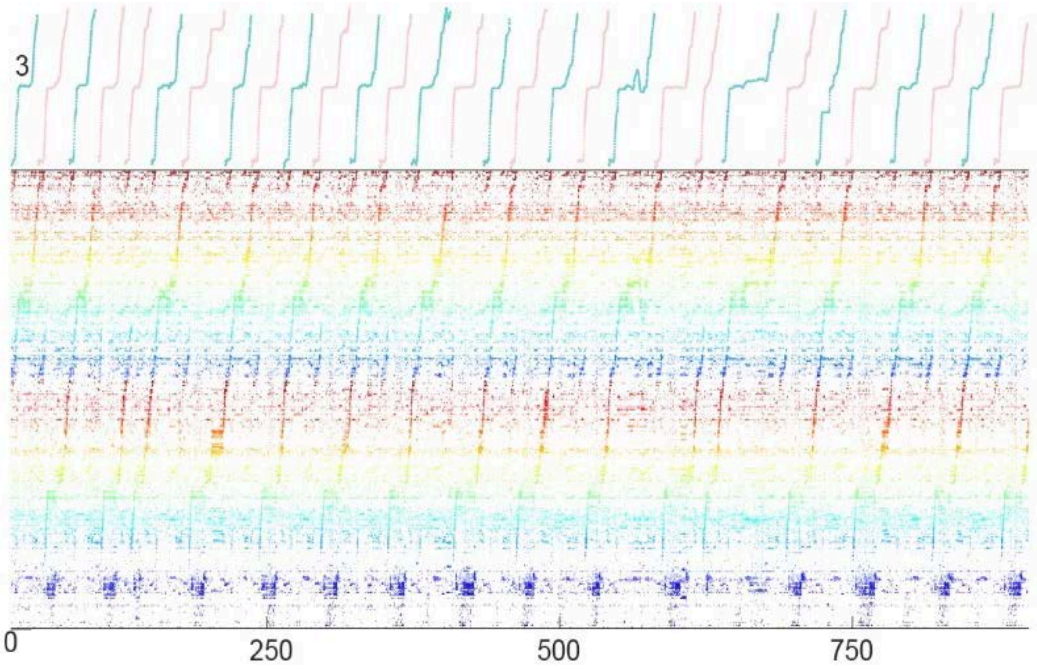
Spike sequences change perpetually even when environmental inputs remain constant



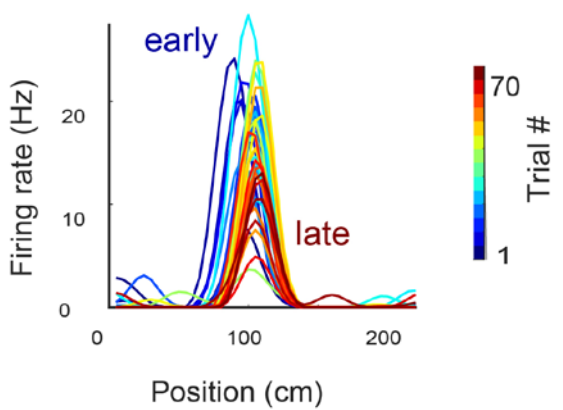
Dual-sided silicon probe

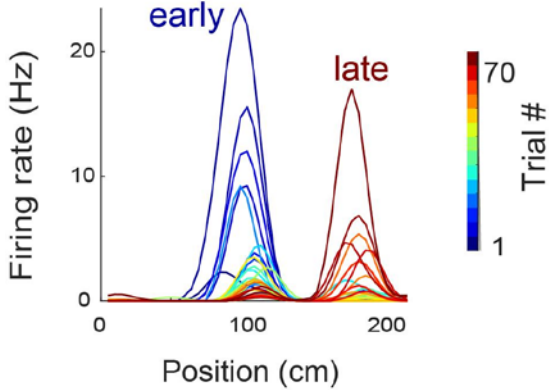


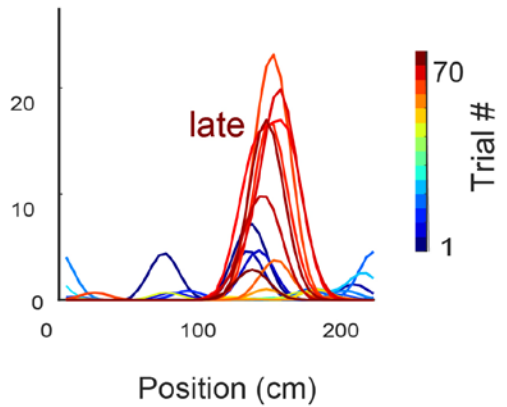


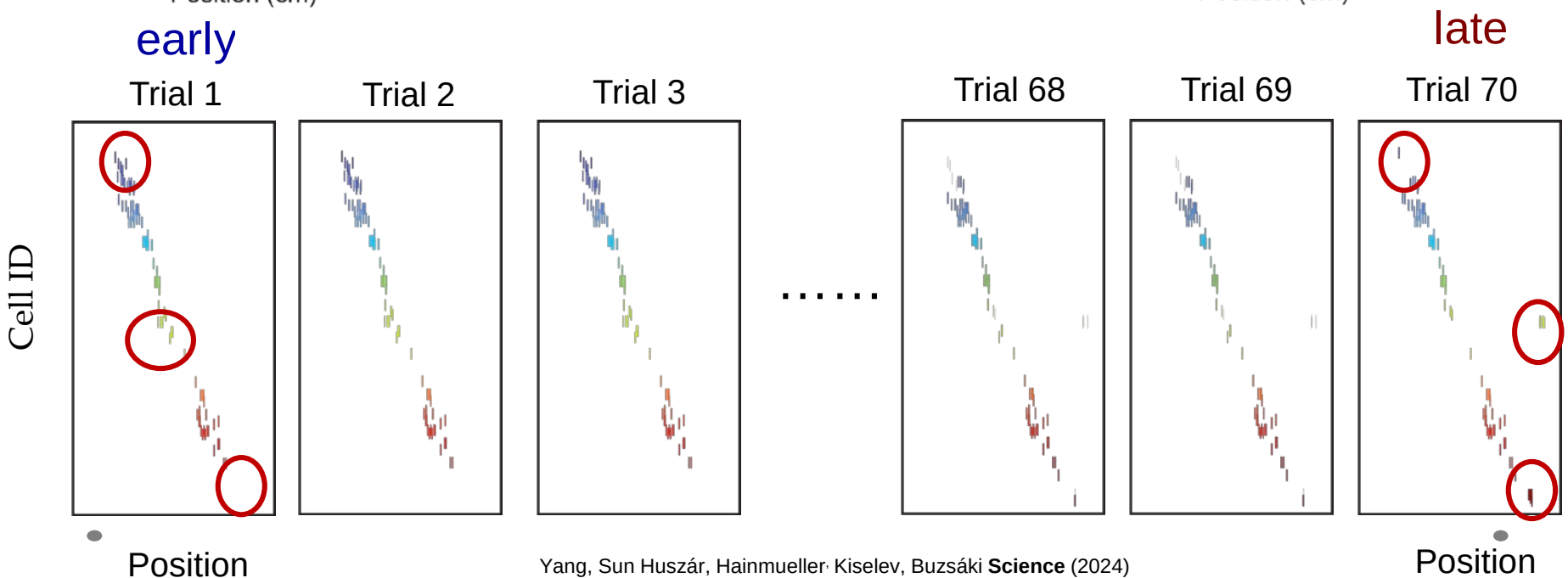


Yang, Sun Huszár, Hainmueller, Kiselev, Buzsáki **Science** (2024)





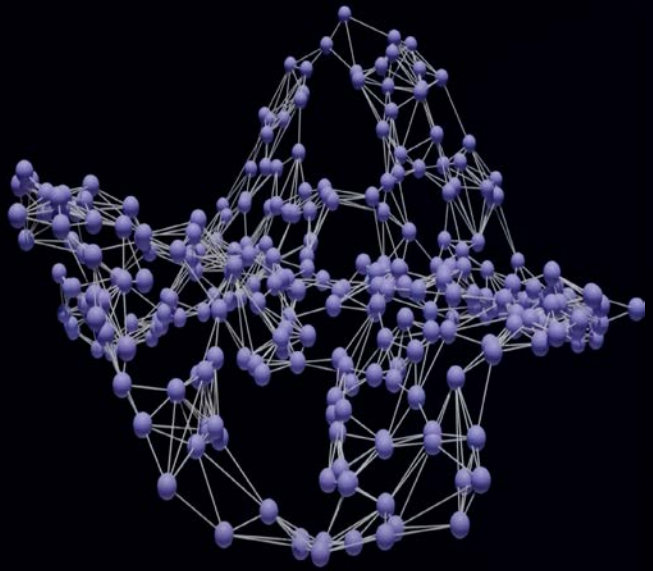


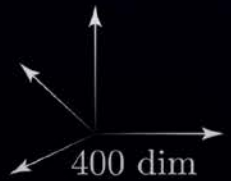


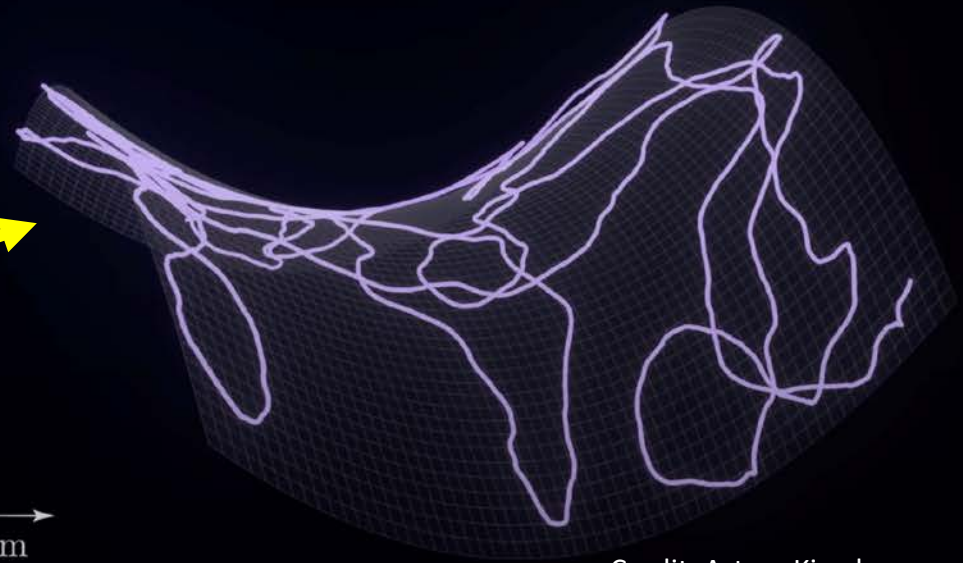
Yang, Sun Huszár, Hainmueller, Kiselev, Buzsáki **Science** (2024)

Manifold

Region in the neural state space,
which brain activity is confined to
due to interactions between neurons







Credit: Artem Kirsakov

Dimensionality reduction: readout of position and event sequence (trial #)

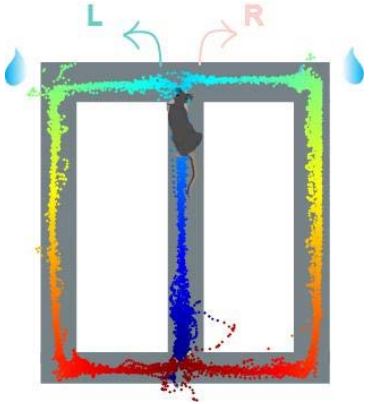
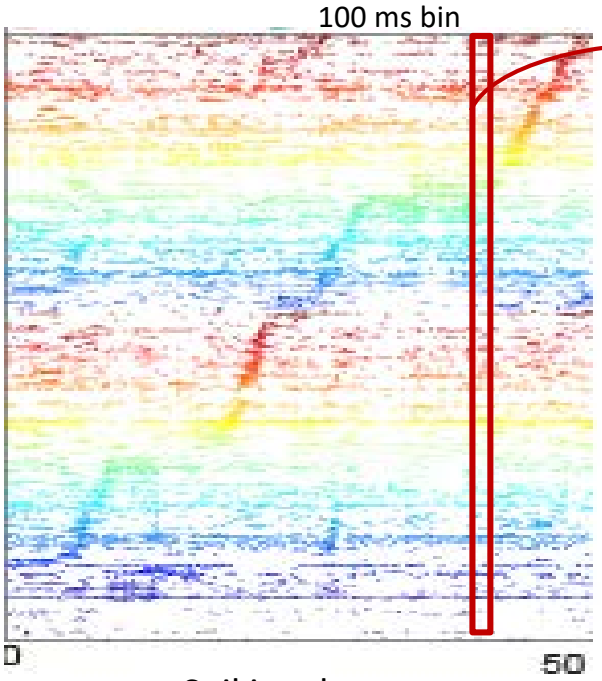


Figure 8 maze

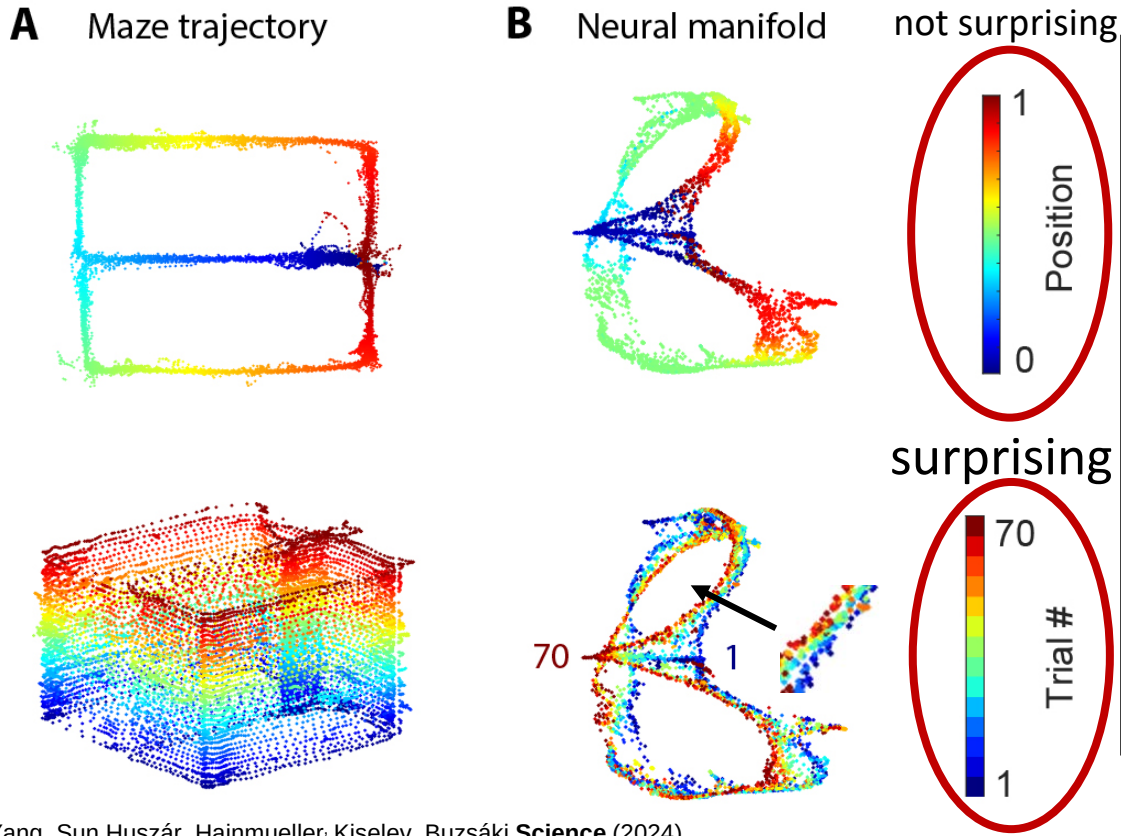


Spiking data

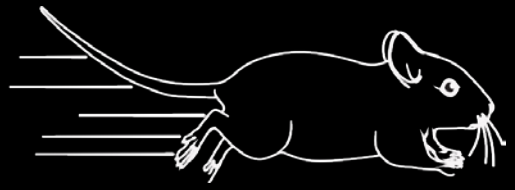
~500 neurons ➔
500 dimensional space!

Uniform Manifold Approximation and Projection (**UMAP**)

Dimensionality reduction: readout of position and event sequence (trial #)

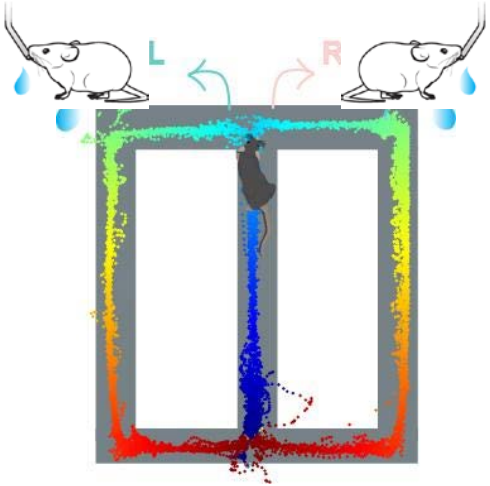


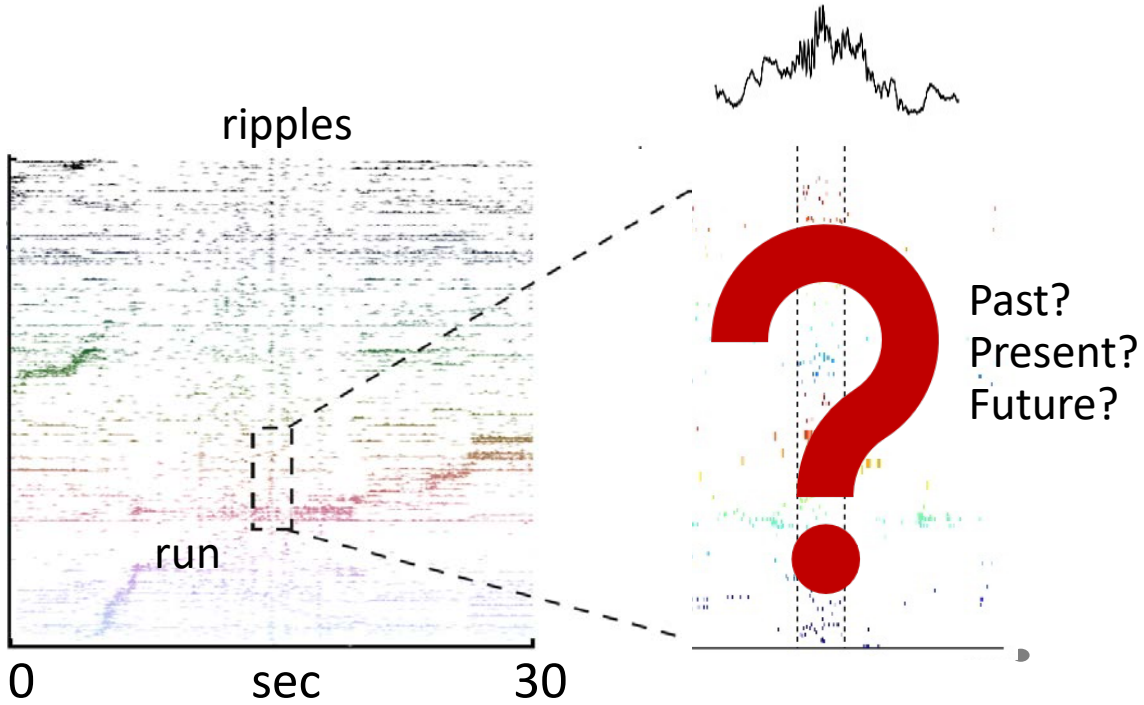
Yang, Sun Huszár, Hainmueller, Kiselev, Buzsáki **Science** (2024)

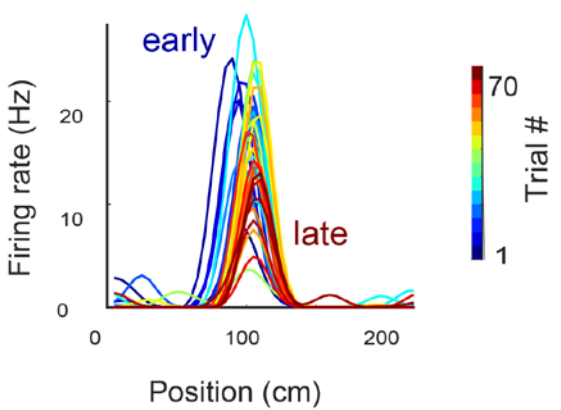


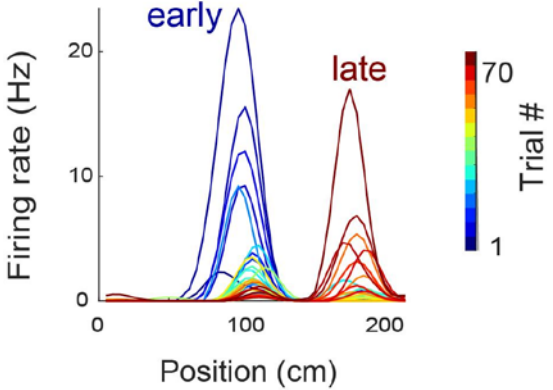
Both the animal's position and trial number (event) can be identified from population activity of hippocampal neurons during running

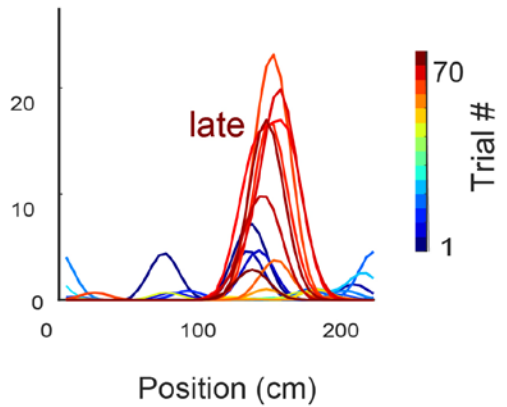
Reward affords brain state change → SPW-Rs and replay

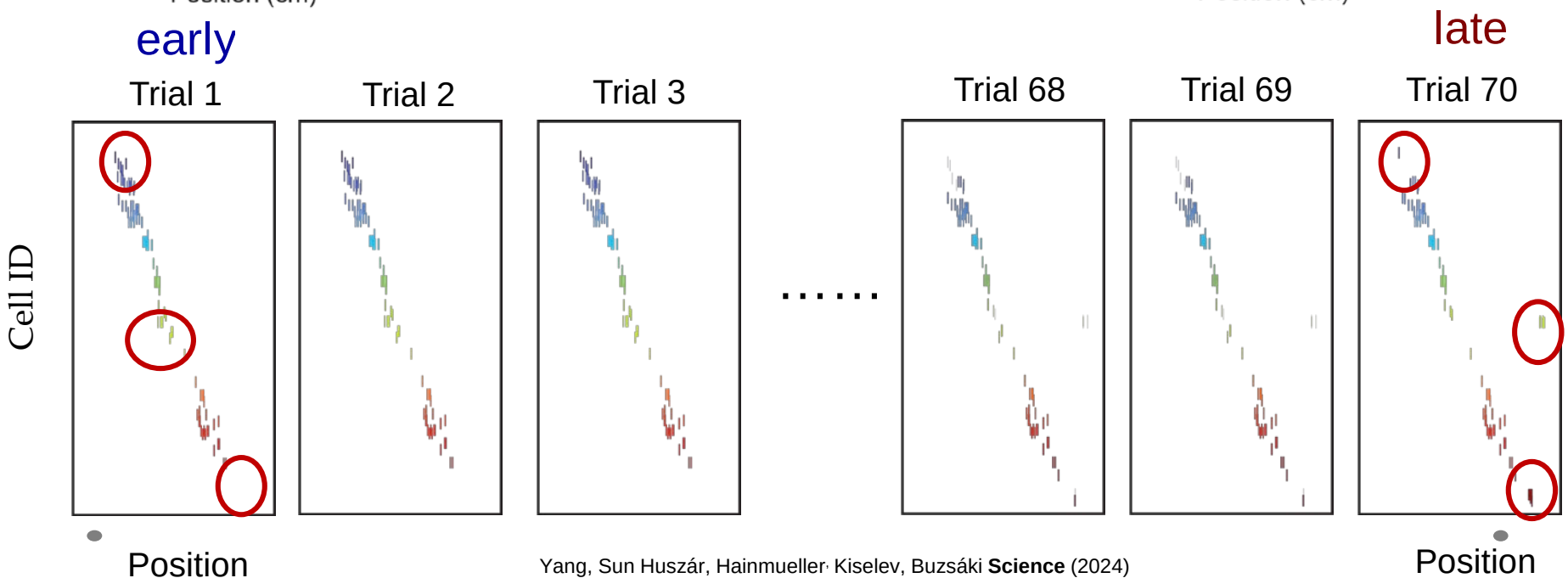








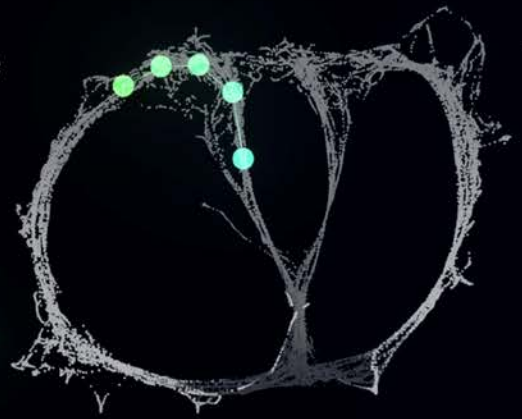




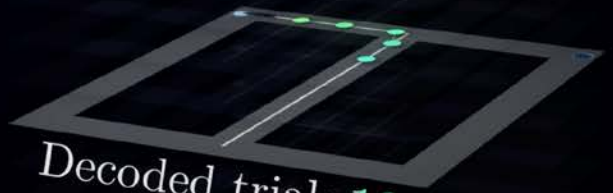
Yang, Sun Huszár, Hainmueller, Kiselev, Buzsáki **Science** (2024)

Awake replays capture recent paths to the reward

Awake ripple projected onto the manifold



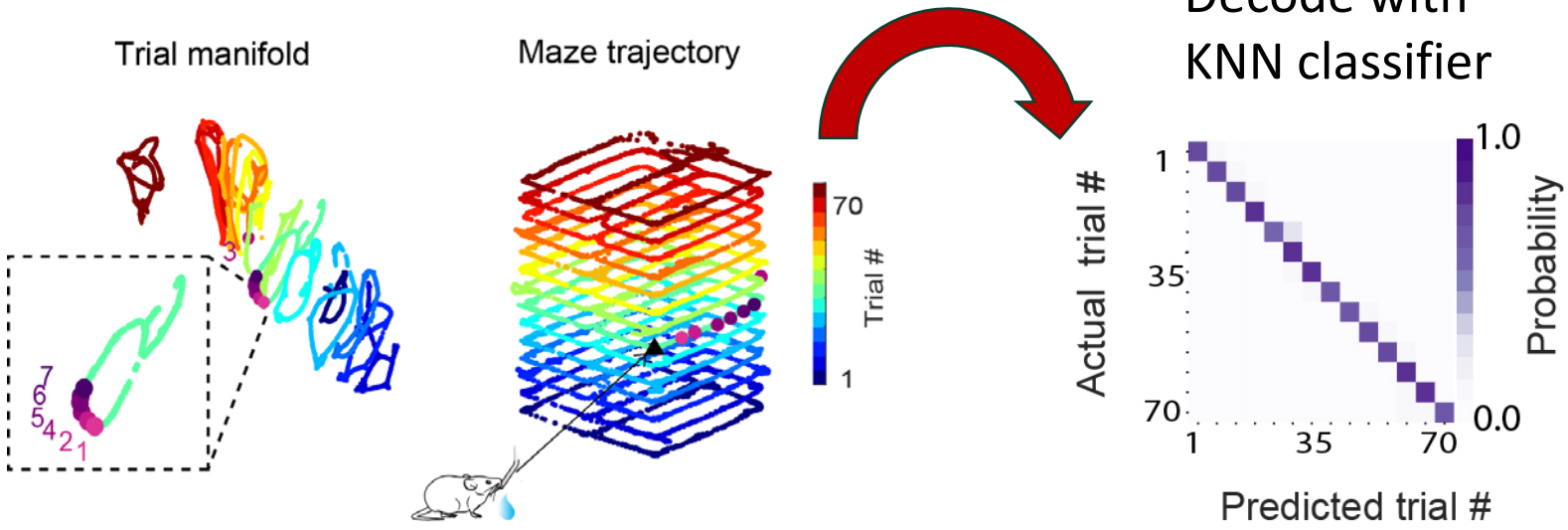
Decode position and trial number



Decoded trial: **10**

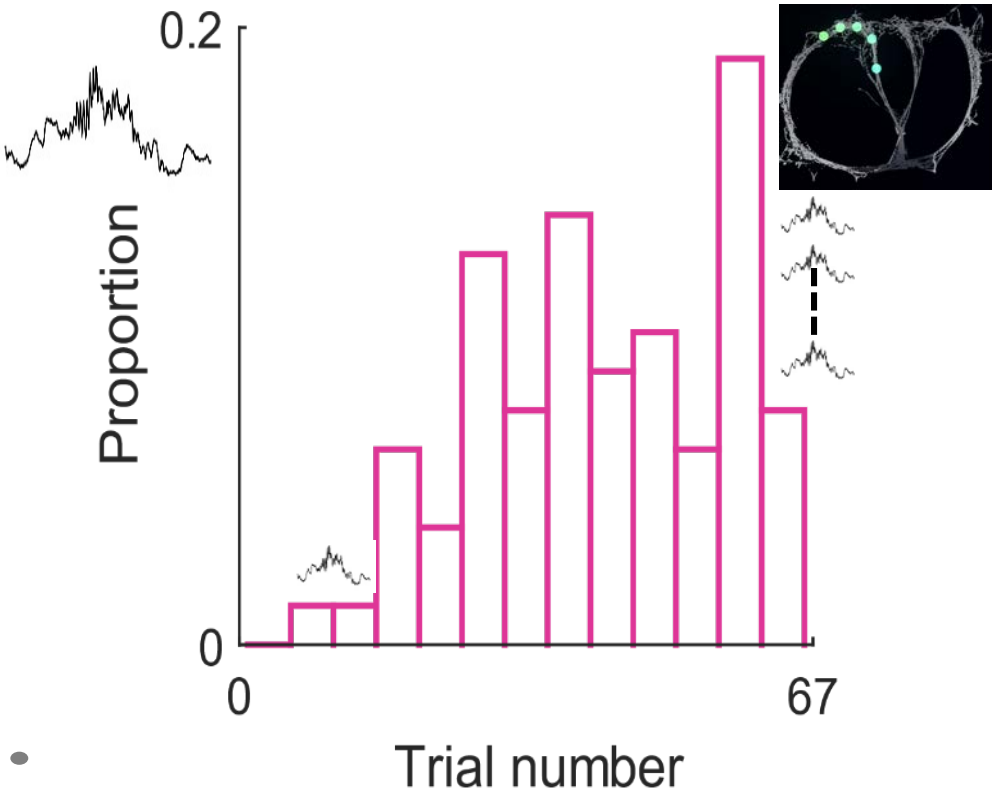
Reward consumption on trial **10**

Events that surround waking SPW-Rs are replayed



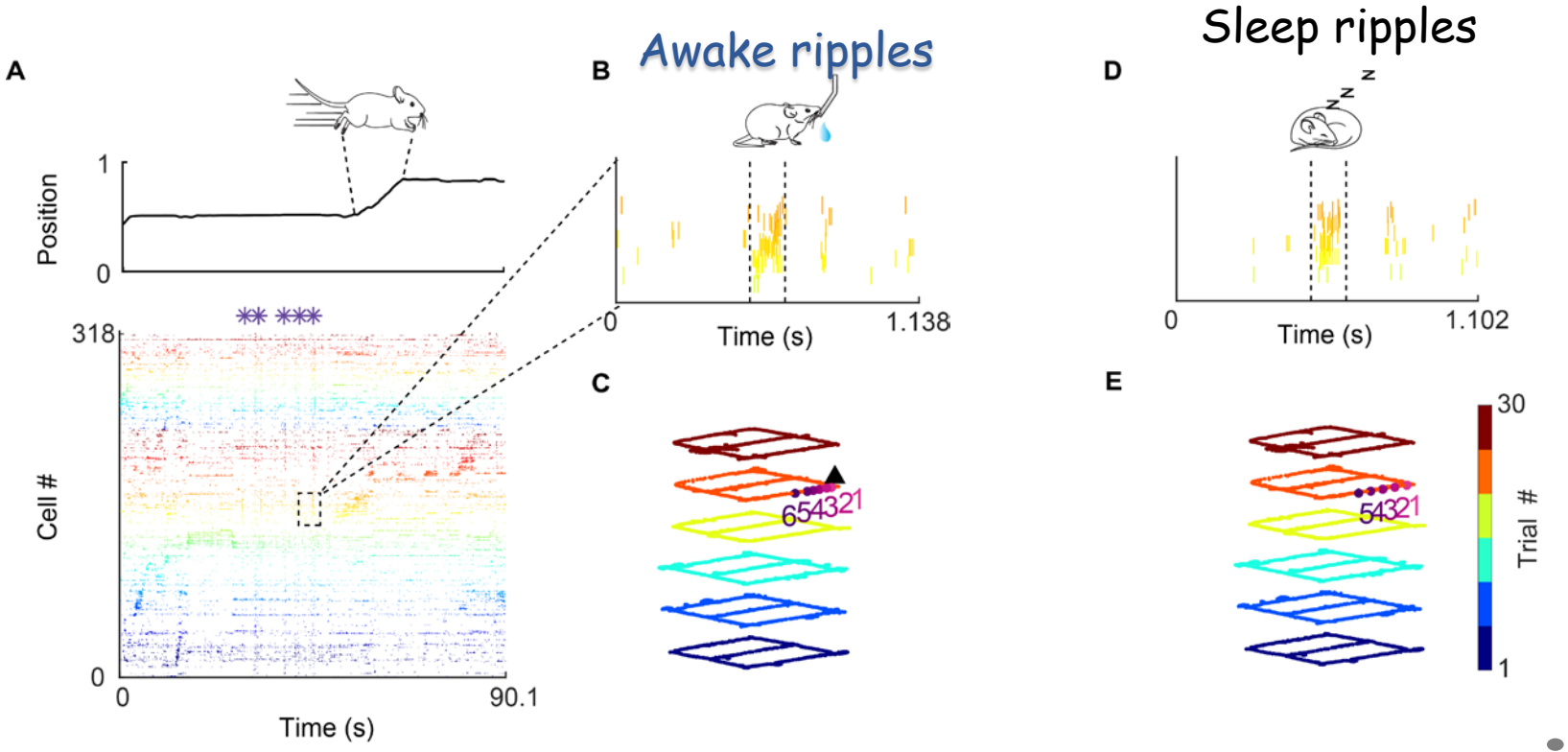
Yang, Sun Huszár, Hainmueller, Kiselev, Buzsáki **Science** (2024)

Weighing the "importance" of particular events by waking SPW-Rs



Different trials are followed by different probability of ripples. These ripples replay mainly the spike content of the current trial

How do waking replays affect SPW-Rs during sleep?



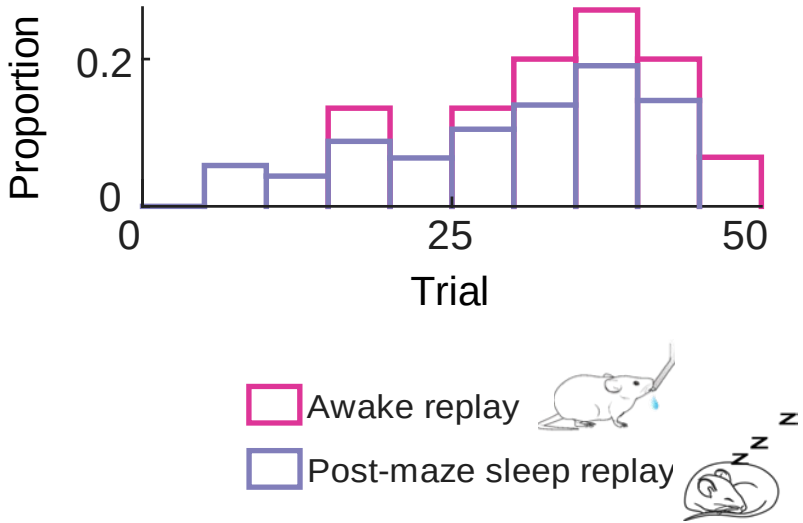
Ripples during subsequent sleep replay similar content, as awake ones

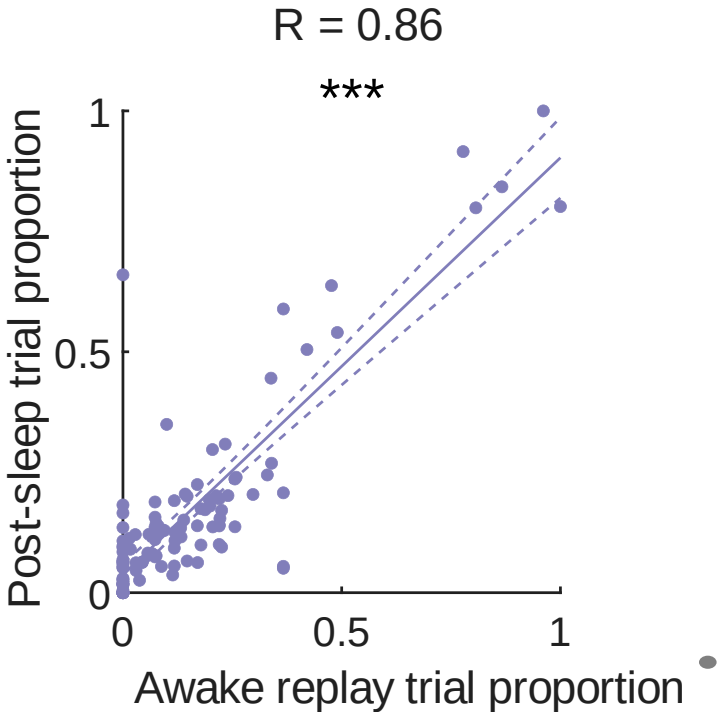
Post-learning **sleep ripple**

Awake ripple

Sleep SPW-Rs replay the tagged events during waking

Spike content of wake and sleep replays are correlated





Learning

Memory selection (tagging)

Memory consolidation

Theta

Awake ripple

Sleep ripple

Credit assignment is brought about by awake hippocampal sharp wave ripples

or

selection

garbage

Yang, Sun Huszár, Hainmueller, Kiselev, Buzsáki **Science** (2024)

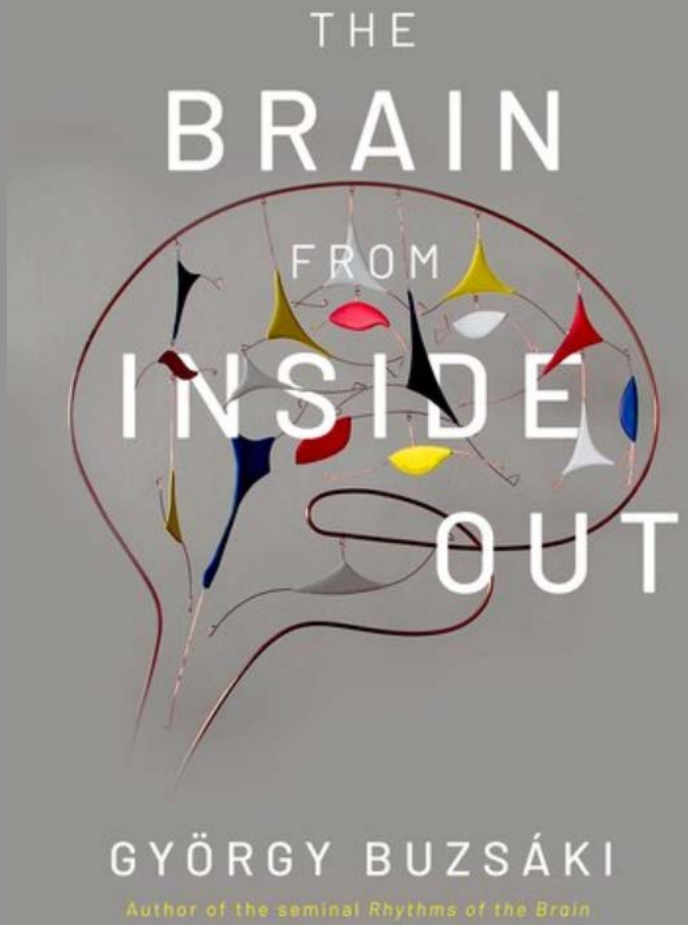
- The place cells may reflect planned and executed trajectories rather than space and time
- This trajectory may be in physical or abstract space, such as thought and intention
- The machinery that evolved to support navigation through space was exapted into a much bigger role
- Navigation in physical and mental space is based on the same neuronal algorithm
- Mechanisms for tracking space and time are general-purpose algorithms for tracking sequences of events and mapping the relationship between them

Buzsaki **OUP** (2019)

- Different species have their versions of reality
- Brains divide (partition) the outside world into objects and construct "space" into which to place these objects
- We arrange the world into what, where and when by our internally organized sequential brain activity

OVERALL SUMMARY

- Brain networks are preconfigured 'dictionaries' filled initially with nonsense patterns
- Learning is a *matching* process between preconfigured patterns and experience
- Meaning is acquired by adding utility to some of the preexisting patterns by experience



Prose Award Winner in Biomedicine and Neuroscience (2020)

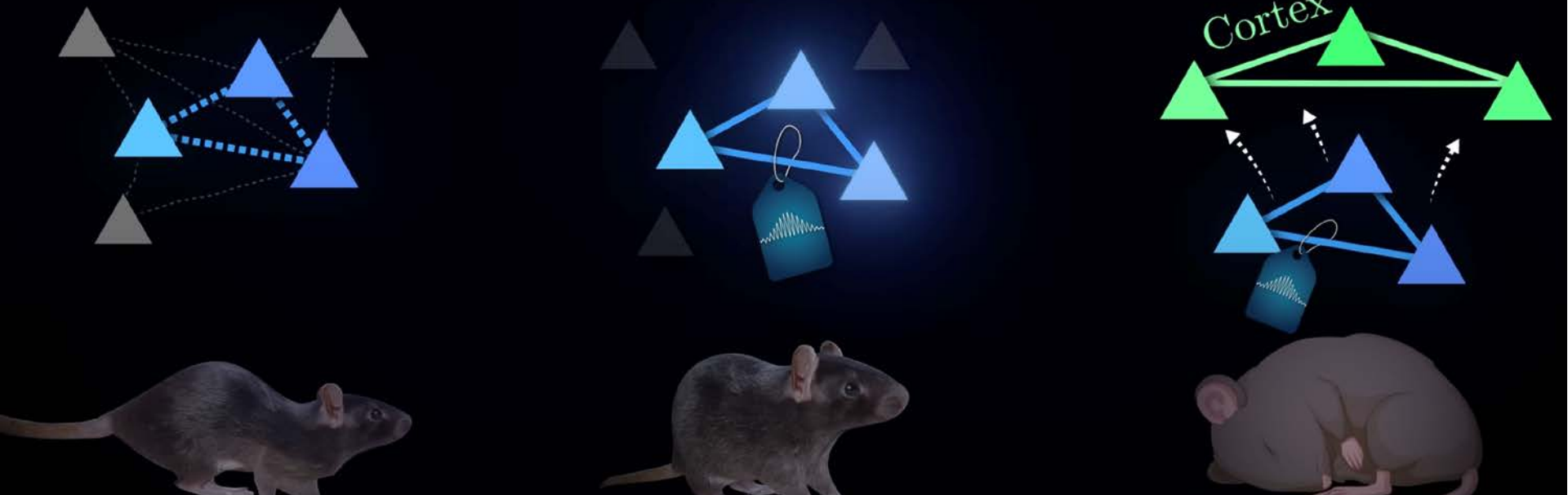
Oxford University Press (2019)

Awake replays tag memories for consolidation

Experience

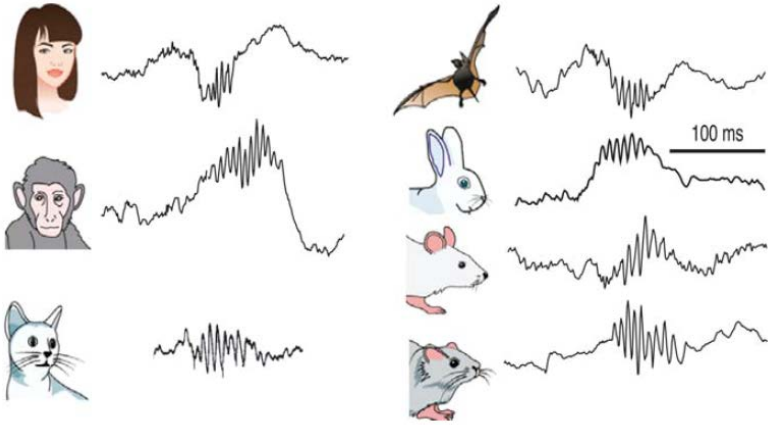
Awake replay
(tagging)

Sleep replay
(consolidation)



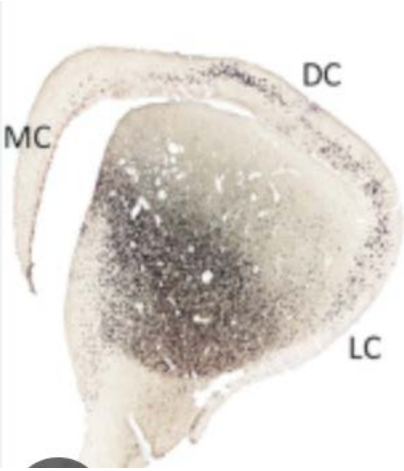
2024

SPW-Rs are conserved during evolution

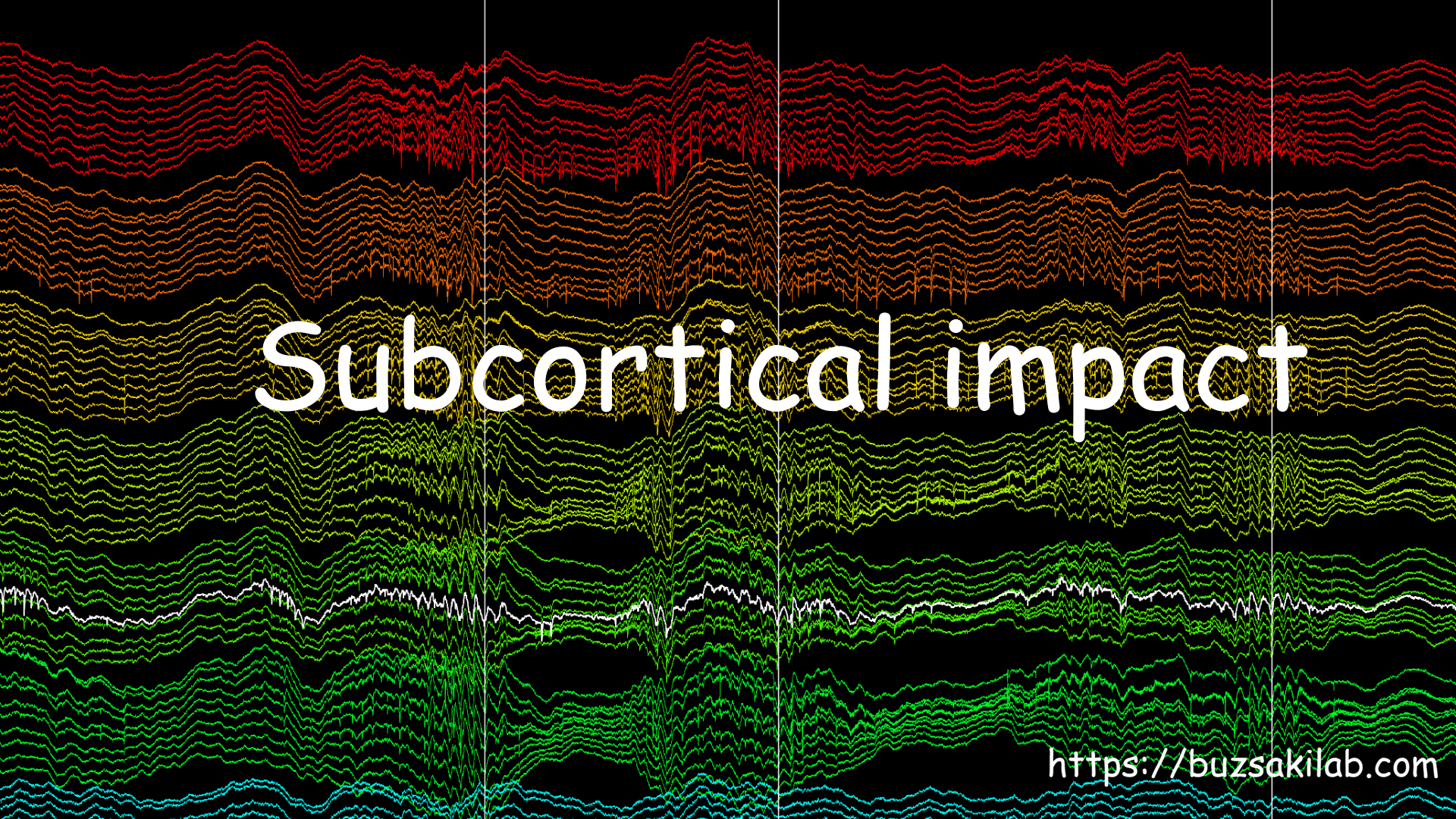


Buzsáki, Logothetis , Singer **Neuron** 2013

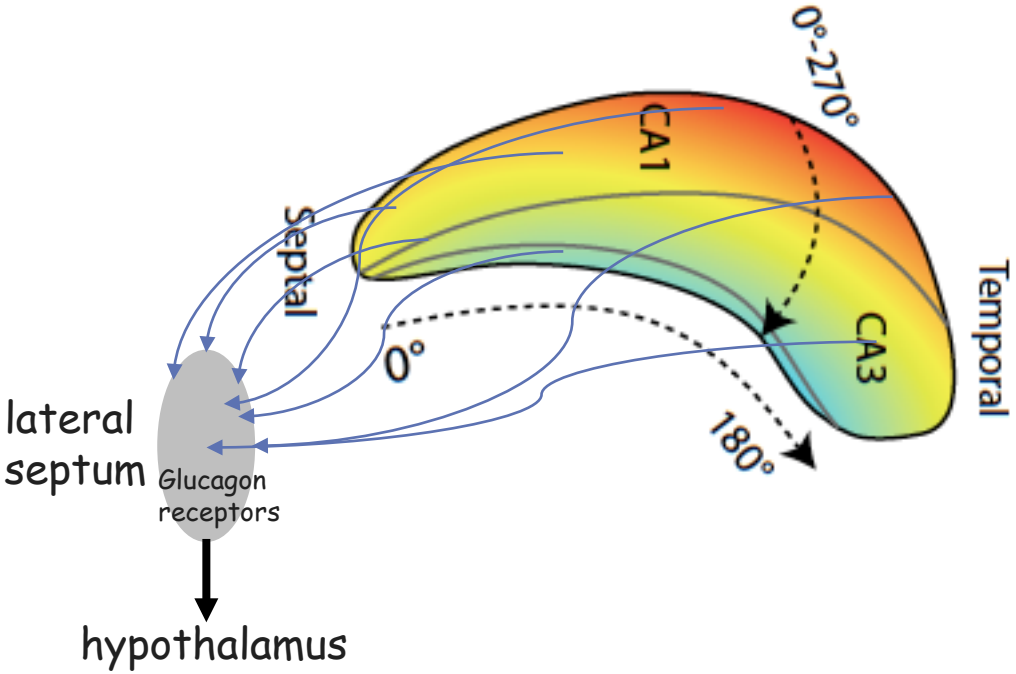
Shein-Idelson et al., **Science** 2016

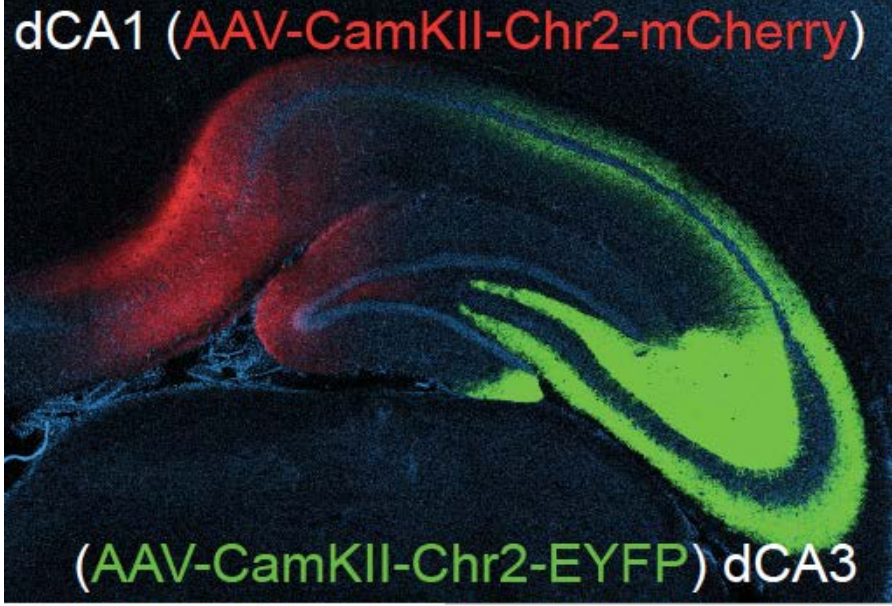


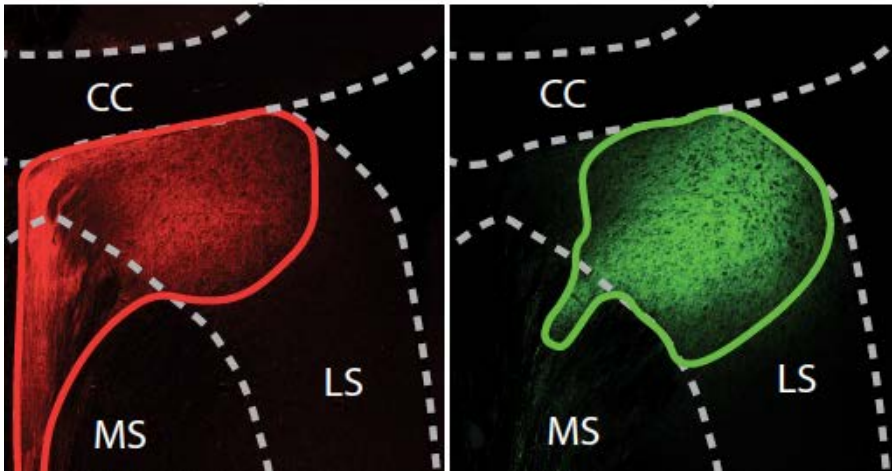
Buzsaki **Hippocampus** 2015


Subcortical impact
https://buzsakilab.com

Convergence = firing rate readout

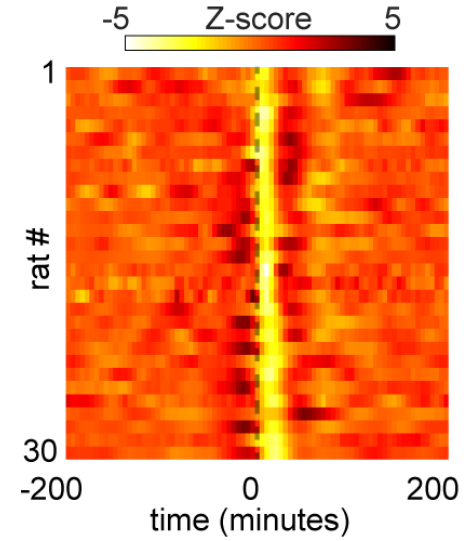


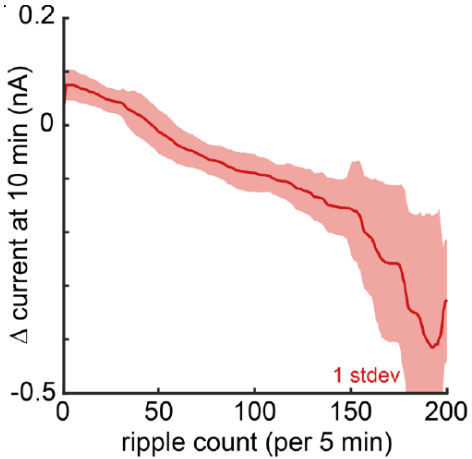




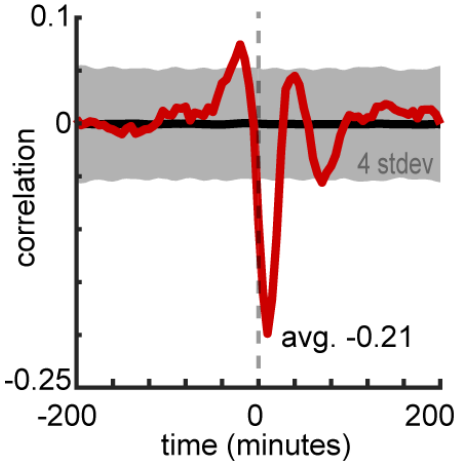
Tingley, Buzsaki **Neuron** 2020

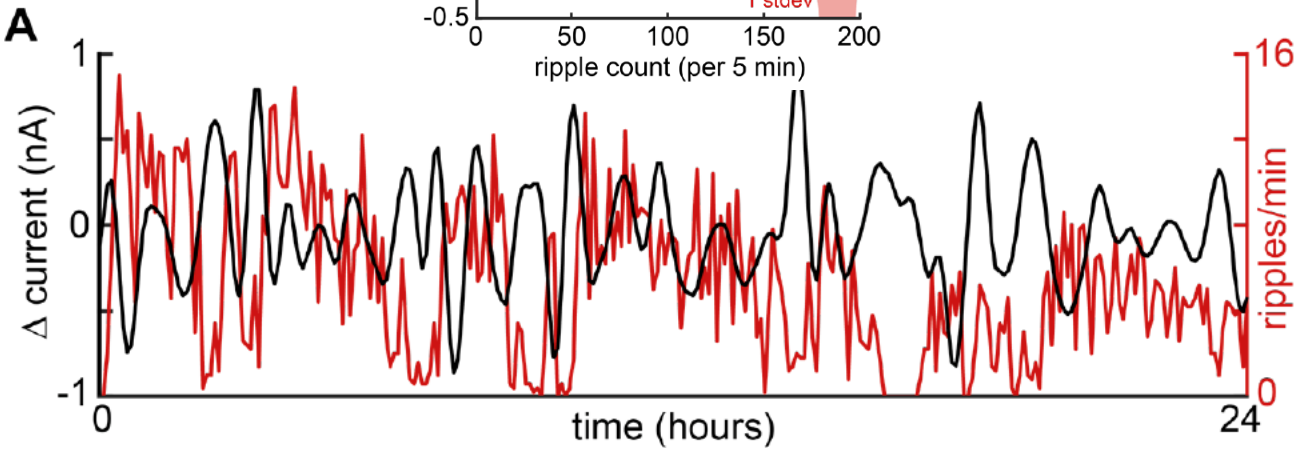
Inverse correlation between glucose levels and SPW-Rs





David Tingley
Nemko Prize 2021

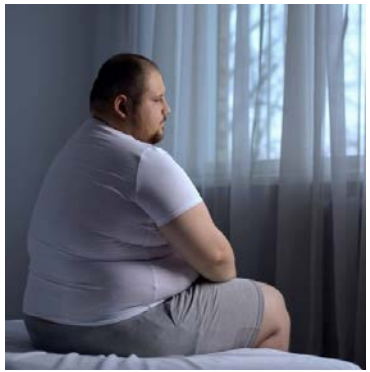


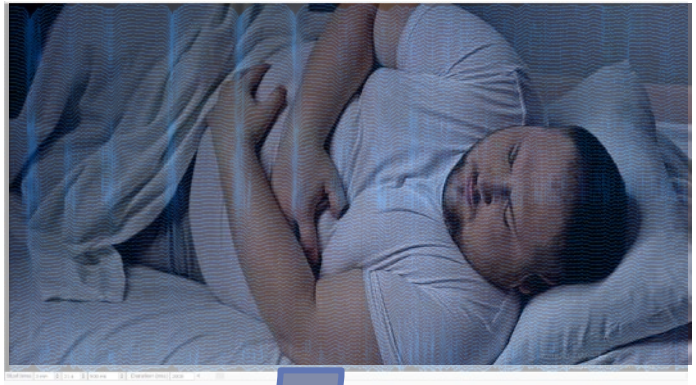


Tingley, Kaya, McClain, Carpenter, Buzsaki **Nature** (2021)

Hippocampal regulation of glucose levels via lateral septum-hypothalamus-pancreas pathway

Indirectly weight dependent:
hyperglycemia, hyperinsulinemia,
leptin resistance





Sleep: brain
reorganization

sleep fragmentation
sleep apnea
sleep hypoxia

obesity
type 2 diabetes
sleep complaints
depression

Buzsaki, Tingley **Ann Rev Neurosci** 2023

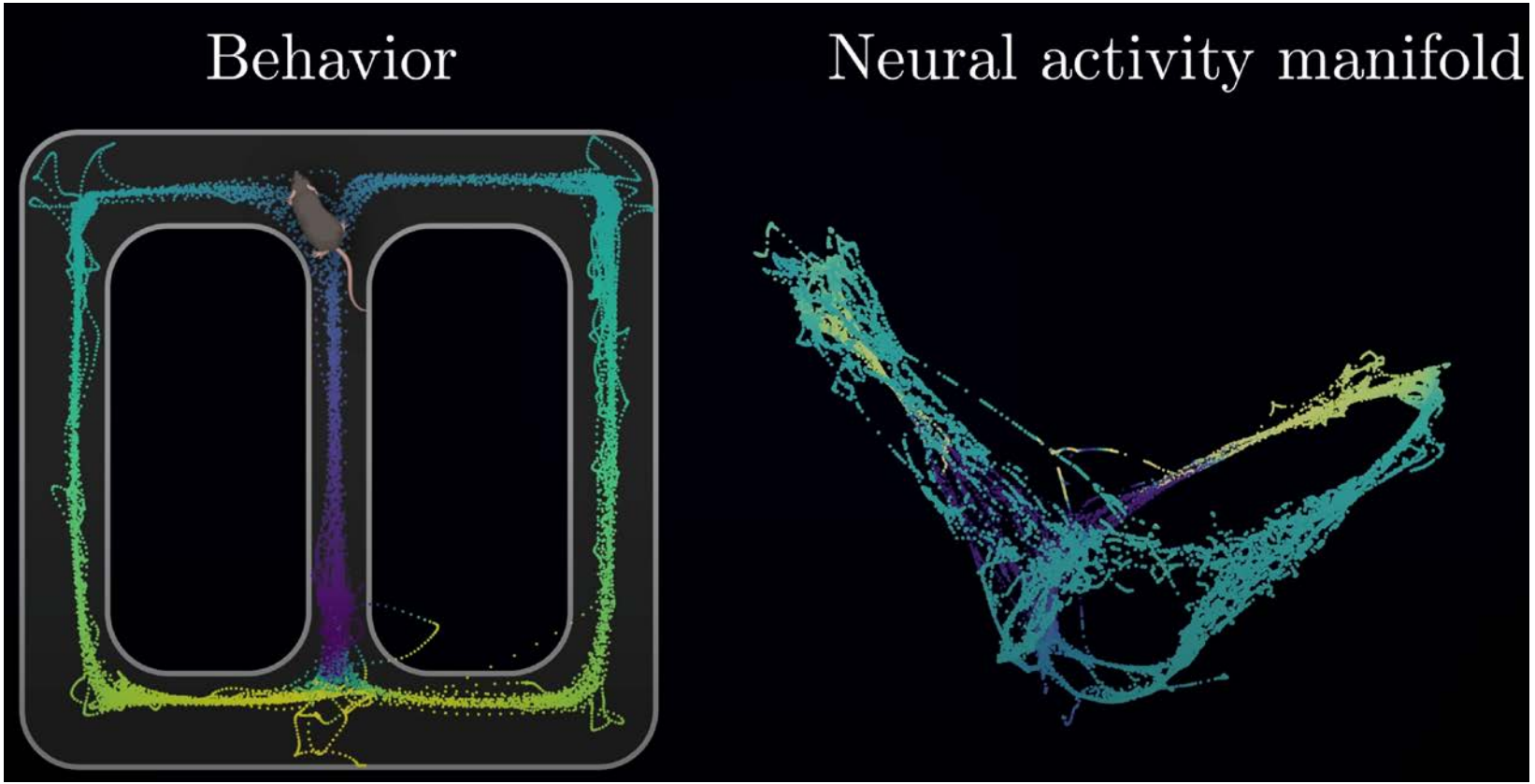
- SPW-Rs emerged to serve body function
- Exapted as memory transfer and consolidation mechanisms

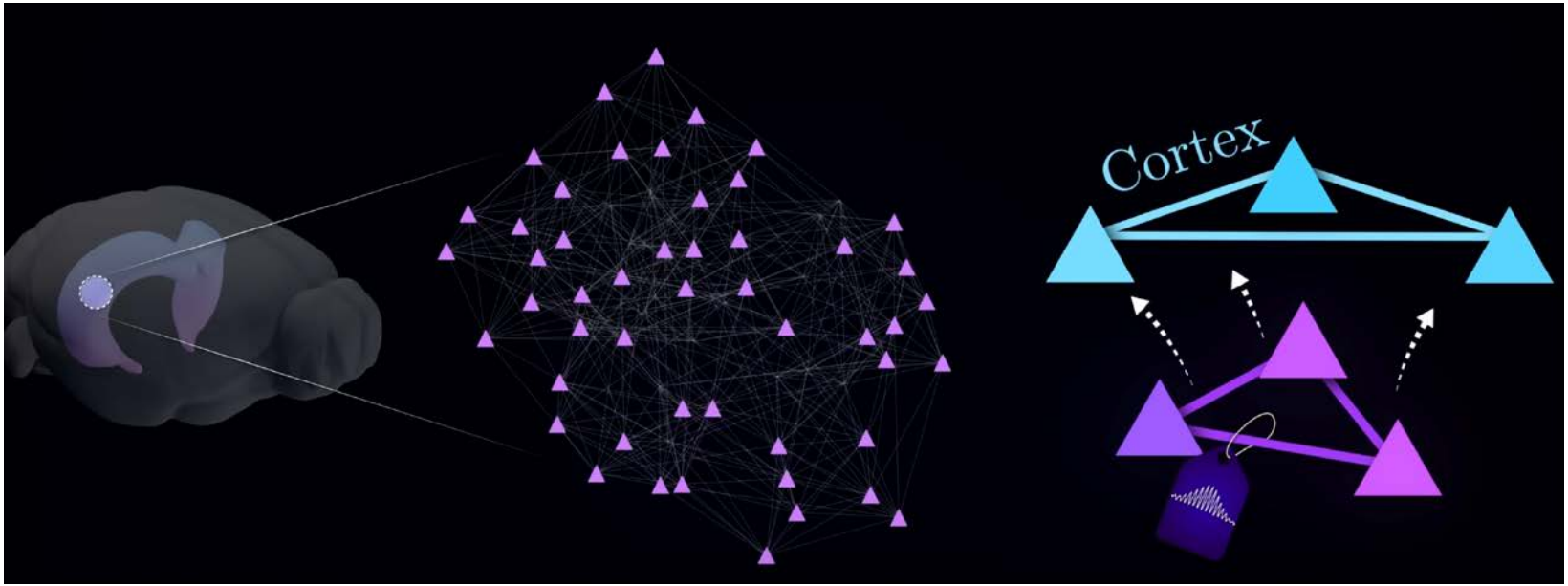
Selection of episodic experience is performed by hippocampal SPW-R

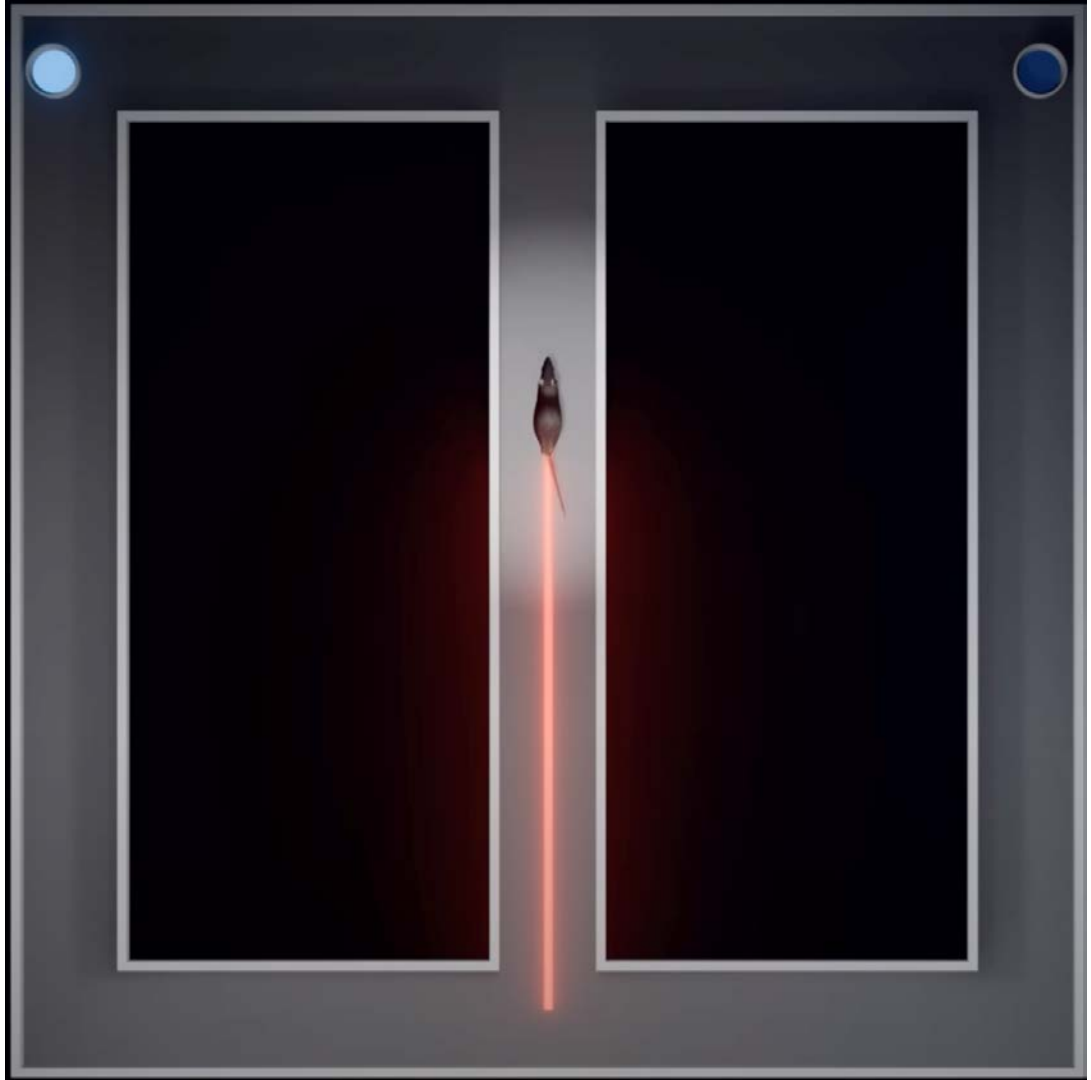
The NEW subspace patterns satisfy criteria that qualify them as 'learned activity':

- they emerge with learning near the rewarded locations
- they are reactivated in rest2 SPW-Rs
- they predict subsequent memory retrieval

How to interpret collective activity of hundreds of cells?


Behavior
Neural activity manifold


Cortex



Dimensionality reduction: supervised readout of position and event sequence (trial #)

Dimensionality reduction: unsupervised readout of position and event sequence (trial #)