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SPACE AND TIME:
THE HIPPOCAMPUS AS A SEQUENCE GENERATOR

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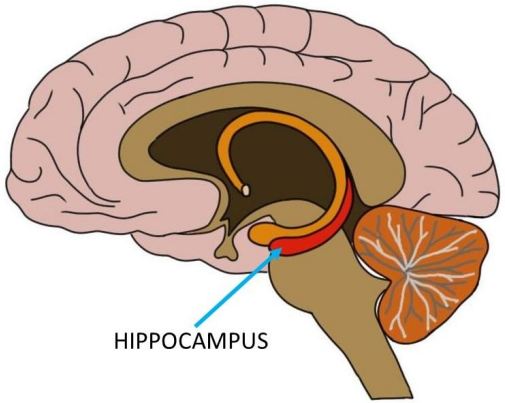
Cognitive Maps Seminar Jan 2023

Outline

- **Introduction**: The Hippocampal System
- The **Functional Anatomy** of Space and Time
- Cell Assembly **Sequences**
- **Place** Cells and **Time** cells
- From Hippocampus to **Action**
- **Conclusions**

The Hippocampal System



Spatial description of environment

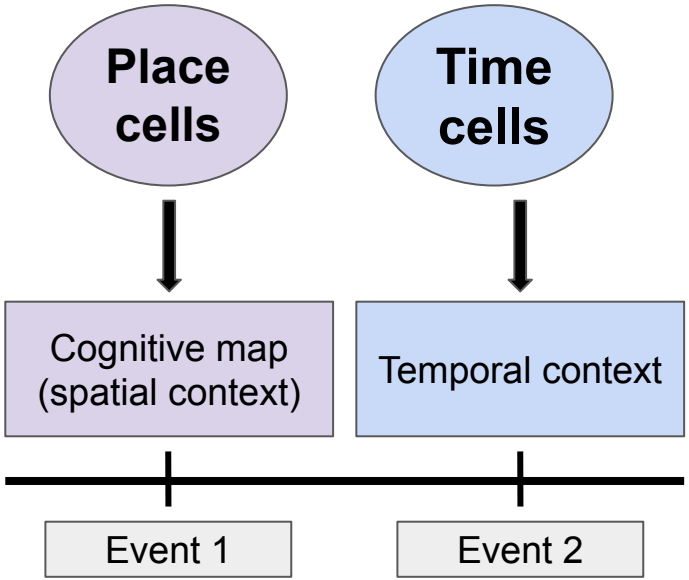
Cognitive map

Episodic memory

What, where and when

- Encoding of every specific combination
- Separation of memory components

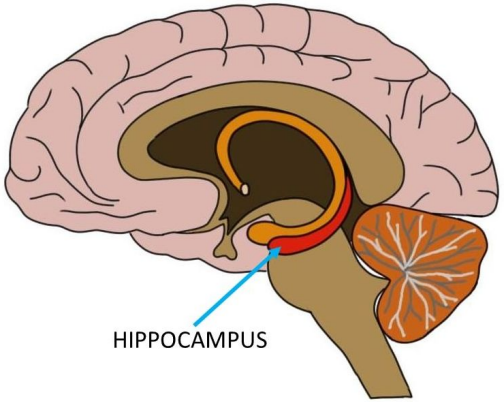
Separation of Memory Components



Organizing coordinates

“time cells may play a role in episodic memory by tagging when events occur in time, just as place cells map where events occur in space.”

The Hippocampal System



Spatial description of environment

Cognitive map

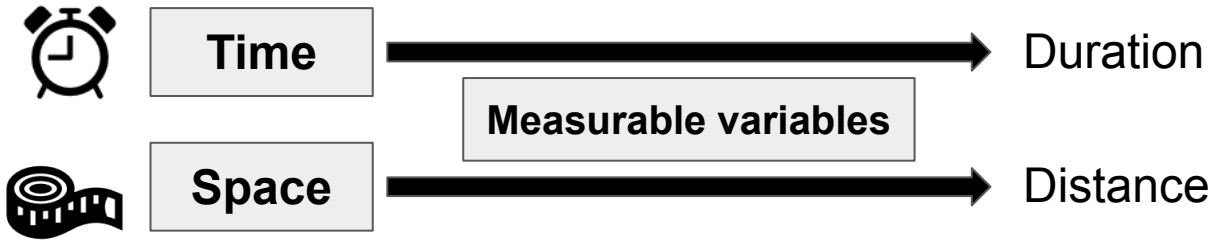
Episodic memory

What, where and when

Spacetime

Input modality blindness

Space and Time Coordinates vs Spacetime



Are space and time independent?

Space and Time Misconceptions

Temporal sequence of representations ≠ **Representation of temporal sequences**

Spatial and temporal properties of the **process** of representing an event

Representations of space and time themselves

"The experimenter interprets both the meaning of the neuronal responses, as measured against instruments, and the meaning of the units measured by those instruments without independent grounding."

The Functional Anatomy of Space and Time

Outline

Goal :

Explain how the brain might **represent sequences of events without** the need for encoding external **space and time** (distance & duration)

Strategy :

- **Episodic memory** and its requirements
- Hippocampal **anatomy** and connectivity
- Hippocampal **firing** and **theta oscillations**
- **Equivalence** of distance and duration

Episodic Memory

"... is the name given to the *capacity* to consciously remember personally experienced events and situations."

Episodic Memory

Event/Representation/Memory:
Lunch with a friend at the Colosseum

Visual:
Friend
Colosseum
pizza

Auditory:
Speech

Tactile:
Wind breeze

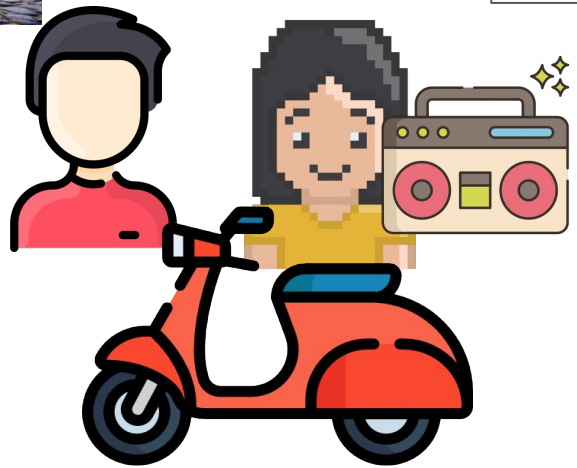
Gustatory & Olfactory:
Pizza

Requirement 1 :
Combine information from *multiple sensory modalities* into a single neuronal representation

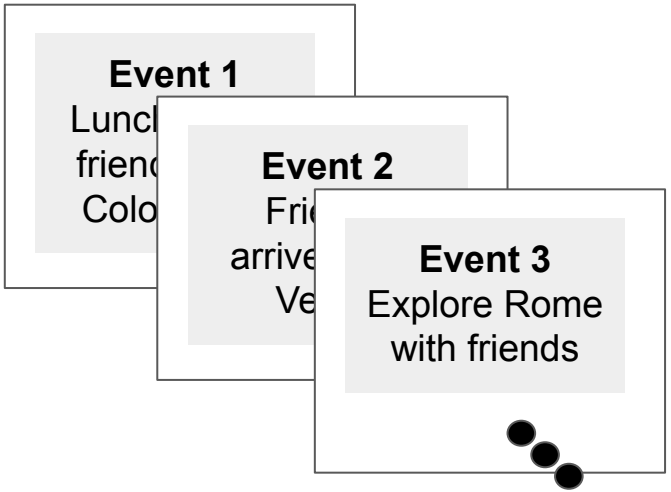
Episodic Memory

Event 1
Lunch
friend
Colo

Event 2
Friends arrives on a Vespa

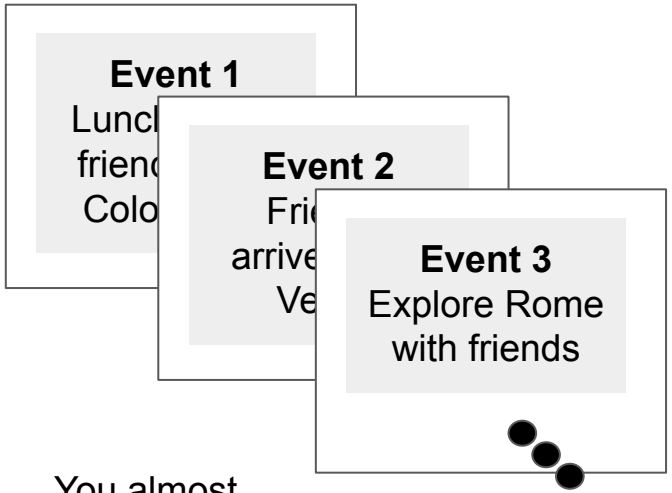


Episodic Memory



Episodic Memory

Requirement 2:
String together multiple events into a *sequential representation* that preserves their temporal order



Pizza arrives

Taste pizza

Friend makes a joke

You almost choke on the mozzarella

. . .

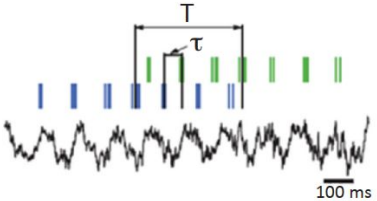
Requirements for Episodic Memory

Requirement 1 :
Combine information from *multiple sensory modalities* into a single neuronal representation

→ **Hippocampal network**

Requirement 2:
String together multiple events into a *sequential representation* that preserves their temporal order

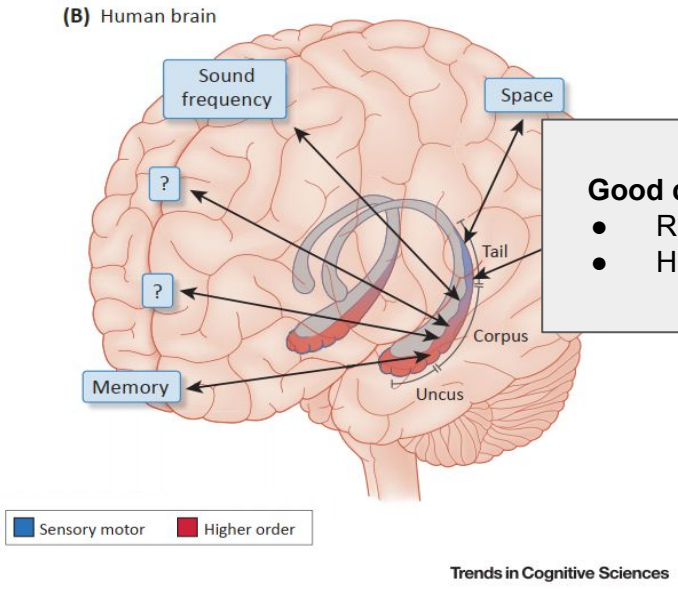
→ **Theta oscillations**



The Hippocampal Network

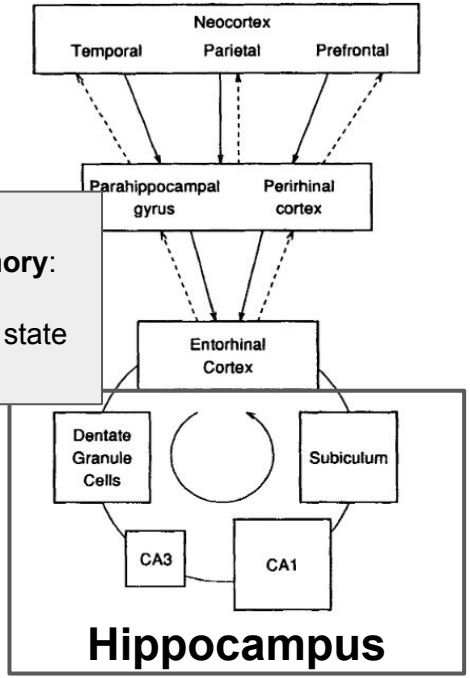
“Anatomy and Connectivity of the Hippocampus as a Substrate for Episodic Memory”

The Hippocampal Network



Gradient of representations
from tail to head of hippocampus

Good candidate for episodic memory:
- Receives input from all cortex
- Has a 'snapshot' of the current state

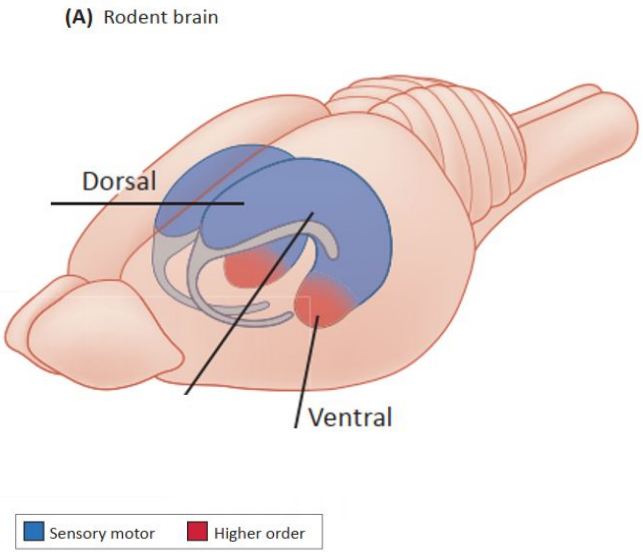


Topographically organized **bidirectional connectivity** with neocortex

Receives input from **all sensory & higher order modalities** through the entorhinal cortex

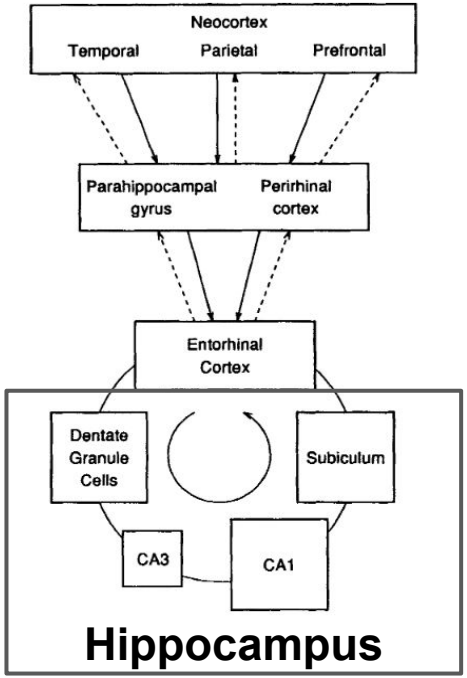
Treves & Rolls, *Hippocampus*, (1994)

The Hippocampal Network



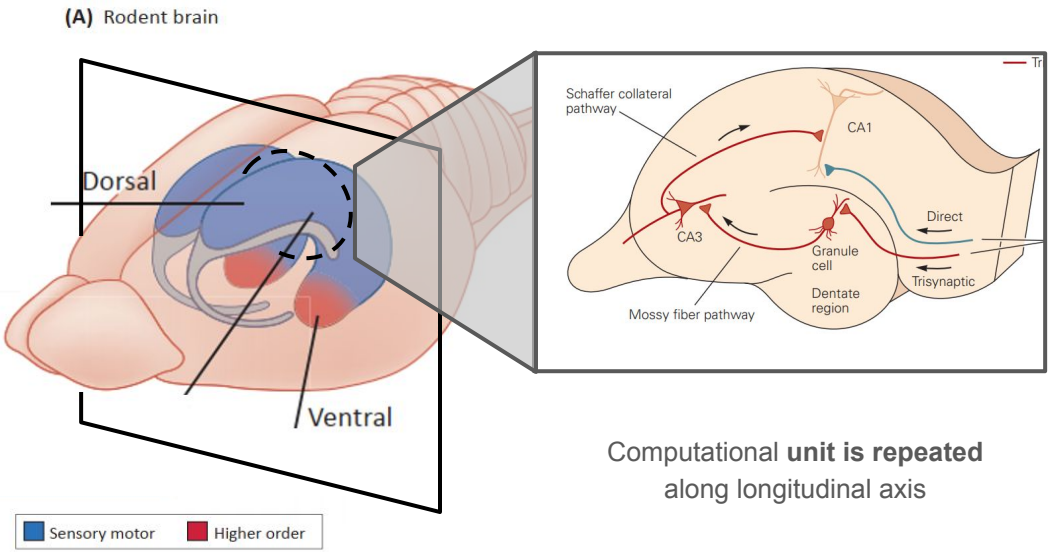
Gradient of representations
Distributed differently to reflect evolutionary needs

Hints at a **general hippocampal computation** applied to different cognitive processes

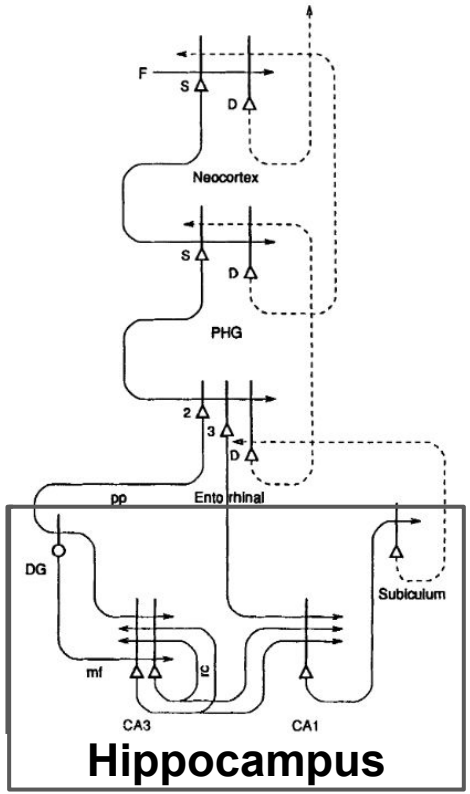


Treves & Rolls, *Hippocampus*, (1994)

The Hippocampal Network



Computational **unit is repeated** along longitudinal axis



Local circuit with **recurrent connections** forms a computational unit

Good candidate for episodic memory:

- Recurrent and longitudinal connectivity
- Facilitates combination and mixing of neuronal messages

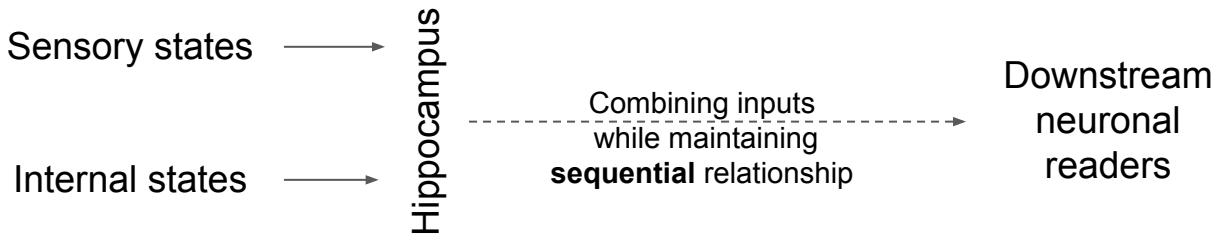
Yang et al., *PNAS*, 2014

Treves & Rolls, *Hippocampus*, (1994)

The Hippocampal Network

"... the **same general computation** is performed on all incoming signals to the hippocampus, largely **irrespective of the neocortical source.**"

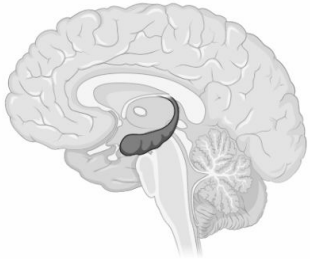
? " **Dimensionless relational computation** " ?



Requirements for Episodic Memory

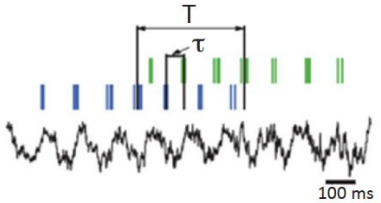
Requirement 1 :
Combine information from *multiple sensory modalities* into a single neuronal representation

→ **Hippocampal network**



Requirement 2:
String together multiple events into a *sequential representation* that preserves their temporal order

→ **Theta oscillations**

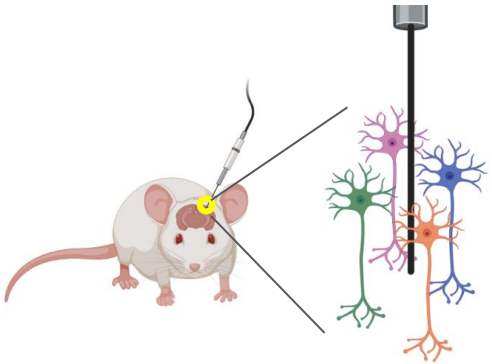


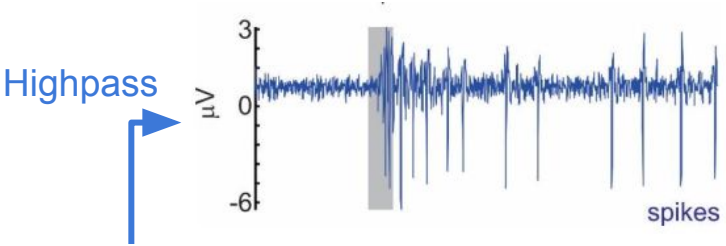
Hippocampal Neural Signals

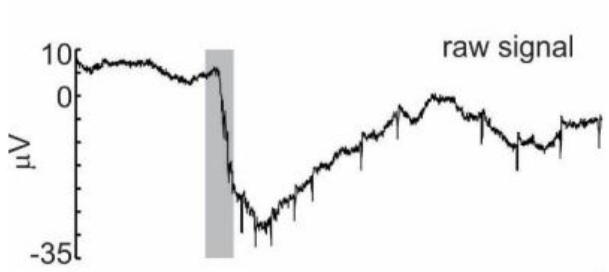
"Place Fields, Theta Oscillations,
and the Neural Equivalence Between Space and Time"

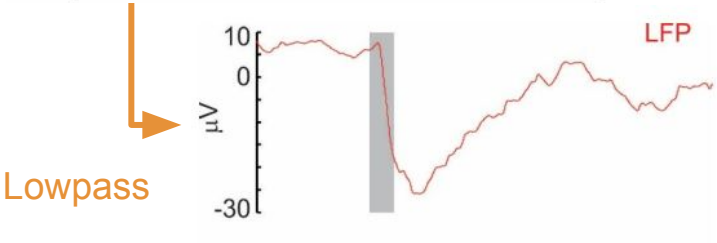
Extracellular Neuronal Signals

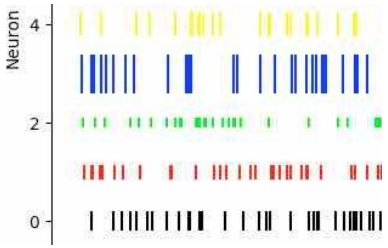
Action Potentials (Spikes) :
Discrete events of
single-neuron firing activity
Place Cells - Rate Coding





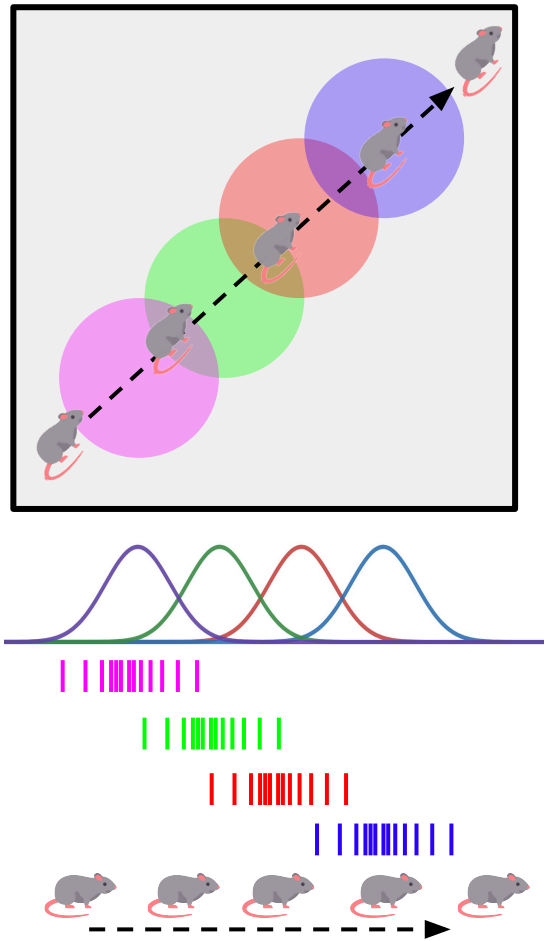




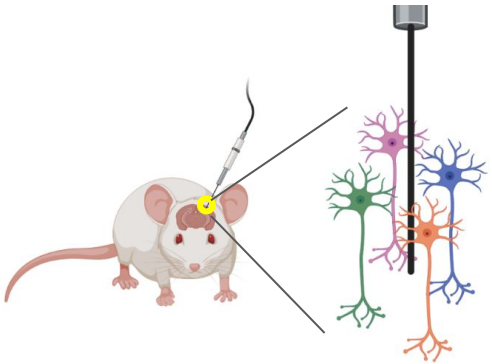


Place Cells in the Hippocampus

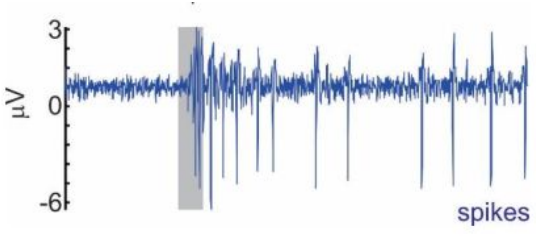
- Hippocampal (CA1 and Granule) cells
- Consistently active in specific locations of the environment
- Define a firing field
- **Firing rate** increases at the peak of the field => **rate coding**
- Firing fields overlap, such that multiple neurons are always active at a given position

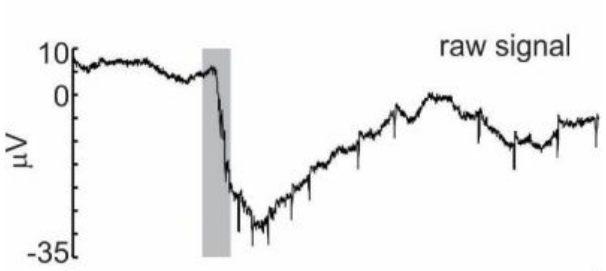


Extracellular Neuronal Signals



Highpass





Lowpass

Action Potentials (Spikes) :
Discrete events of
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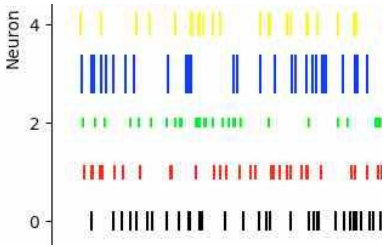
Place Cells - Rate Coding

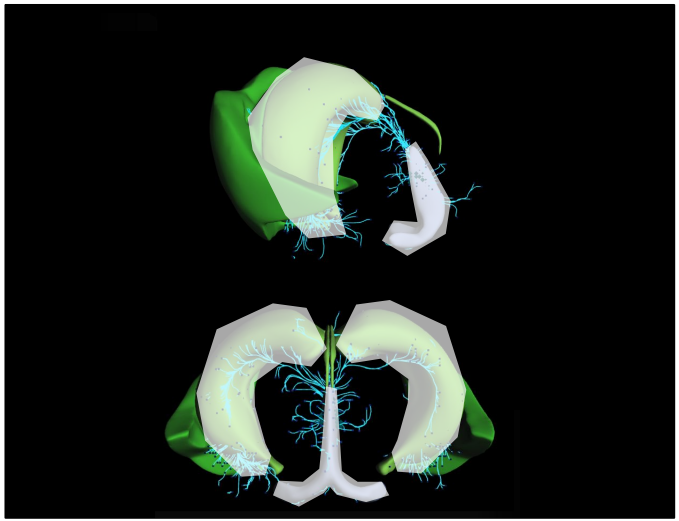


Oscillations (LFP):
Overall excitability state of the
local neuronal population
Theta precession - phase coding

(mostly synchronized
postsynaptic currents)

Theta Oscillations in the Hippocampus

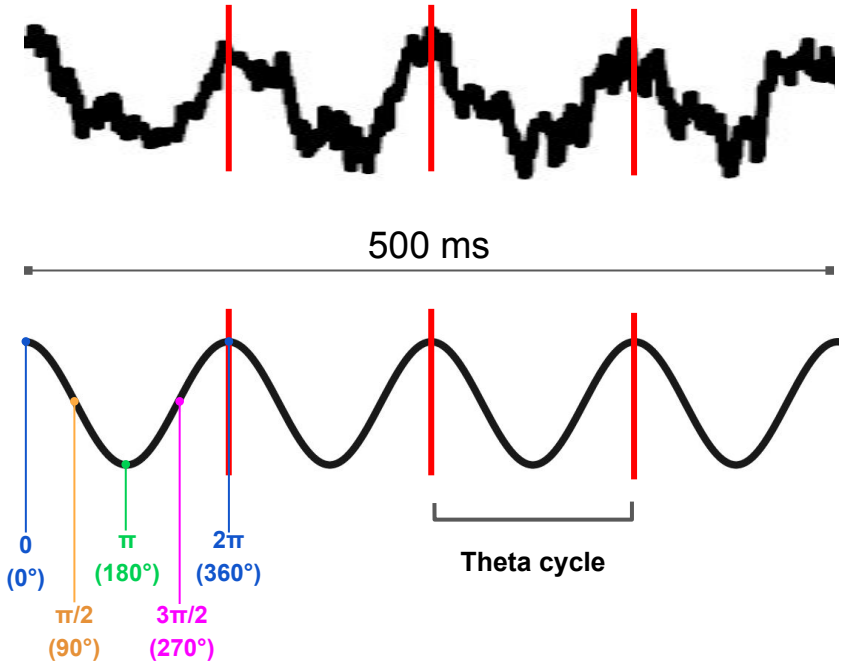
- **~8 Hz** oscillations
- Occur during **exploratory behavior** and locomotion
- Originates from a “master clock”: the **medial septum** (pacemaker)
- But they can also be generated **locally**



Data from: *Allen Mouse Brain* and *Connectivity* atlases

Theta Oscillations in the Hippocampus

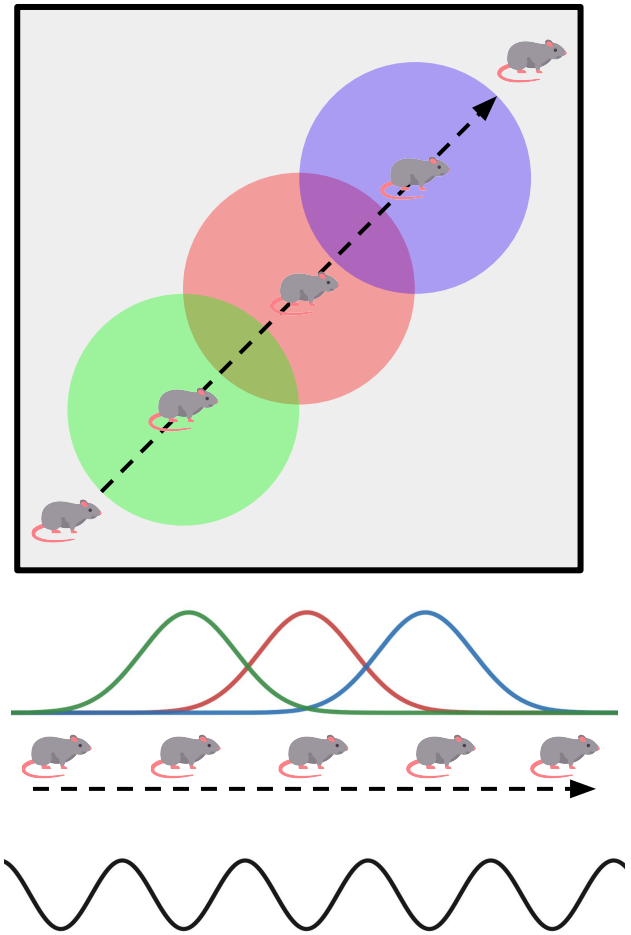
- Oscillation in the **excitability state** of hippocampal neuronal populations
- **Frequency :** ~8 cycles per second (8 Hz)
- **Theta-cycle :** one full period of the theta oscillation (~125 ms)
- **Theta-phase :** position along the theta cycle (in degrees/radians) at a given time



Theta Oscillations

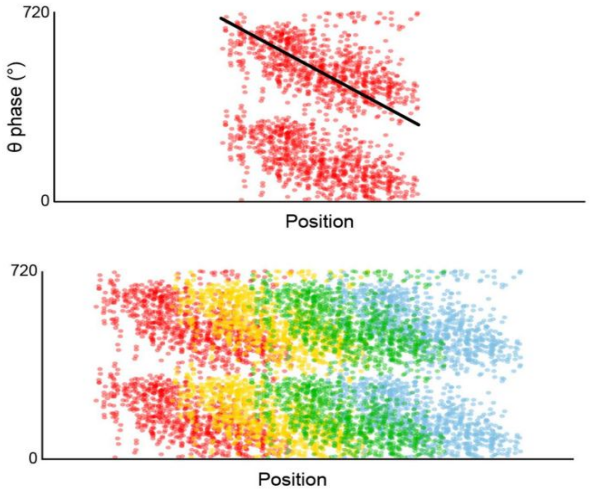
- As mouse runs in the environment across place fields

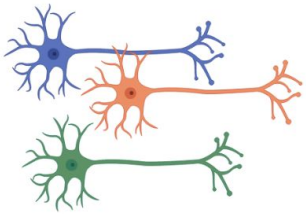
- Theta wave is occurring in the background

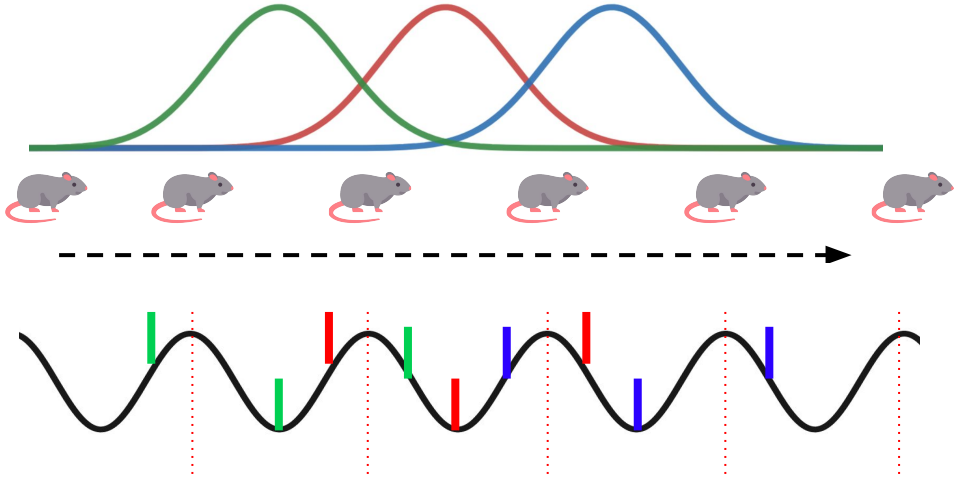


Theta Phase Precession

- **Interaction** between **theta** oscillations and **place cells**' firing



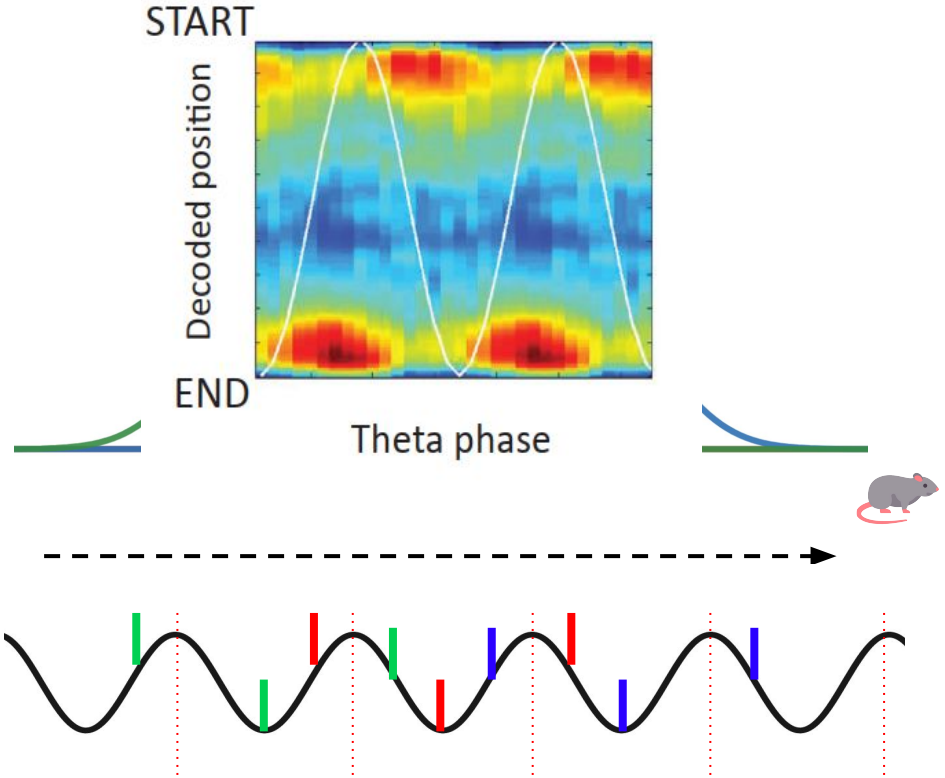




Drieu & Zugaro, *Front. Cell. Neurosci*. (2019)

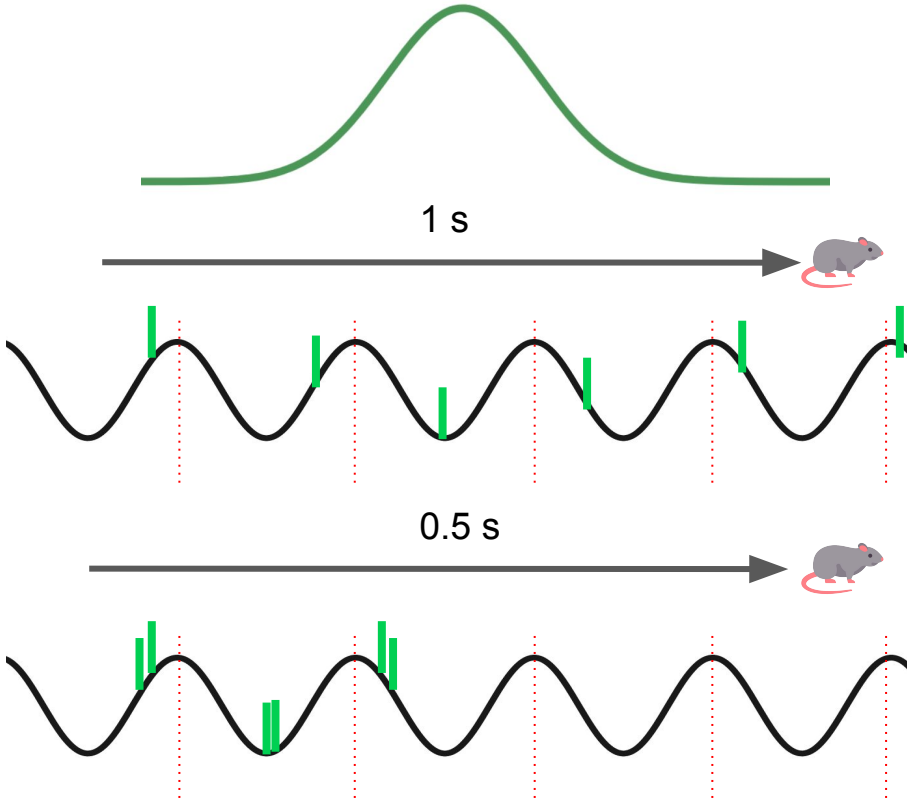
Theta Phase Precession

- For each theta cycle:
- Sequence of spikes from different neurons (**theta sequence**)
- Contains information (snapshot) on
  - **Previous** location (memory)
  - **Current** location (state)
  - **Future** location (prediction)
- **Temporal order** of the sequence of events is **maintained**
- Can **decode start** (memory) and **end** (prediction) positions from early and late **theta phase**



Timing within Theta Sequences

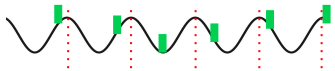
- Must be **kept constant across** running **speeds**
- Running-**speed modulates the time of firing** spikes across a field
- It **controls how many theta cycles** are occupied by a behavioral event
- Theta cycles can be used as a **timing mechanism** for sequences of events

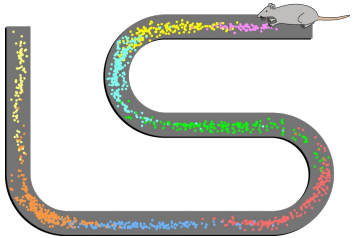


Running-speed, Duration, and Distance

Distance and duration are **equivalent**

Running **speed can modulate** the internal perception of **time and space**





Running-speed

Head direction

Velocity

x

Number of theta cycles

Duration

=

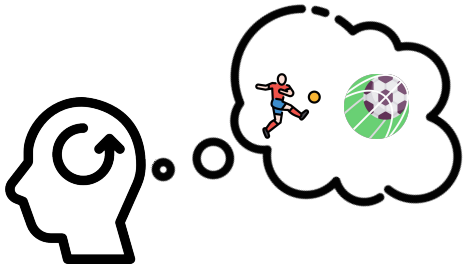
Distance travelled

Distance

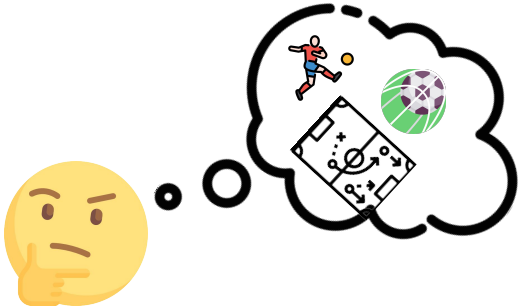
Modulation of Time Perception

- Internal ‘perceived’ time **not equal** external ‘clock’ time
- Other **internal processes** such as attention **might also modulate time computation** such that it diverges from external clock time

Event
(clock time)



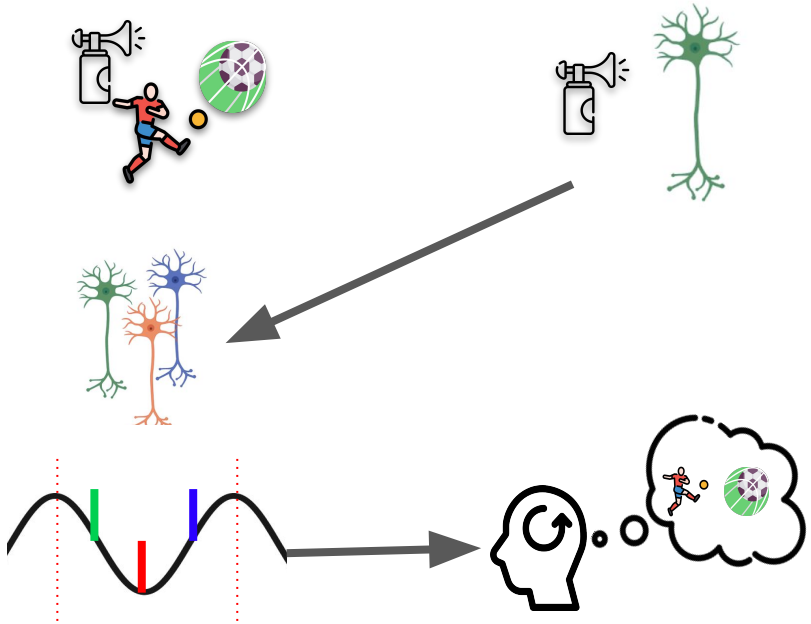
Recollection
(internal time)
Faster



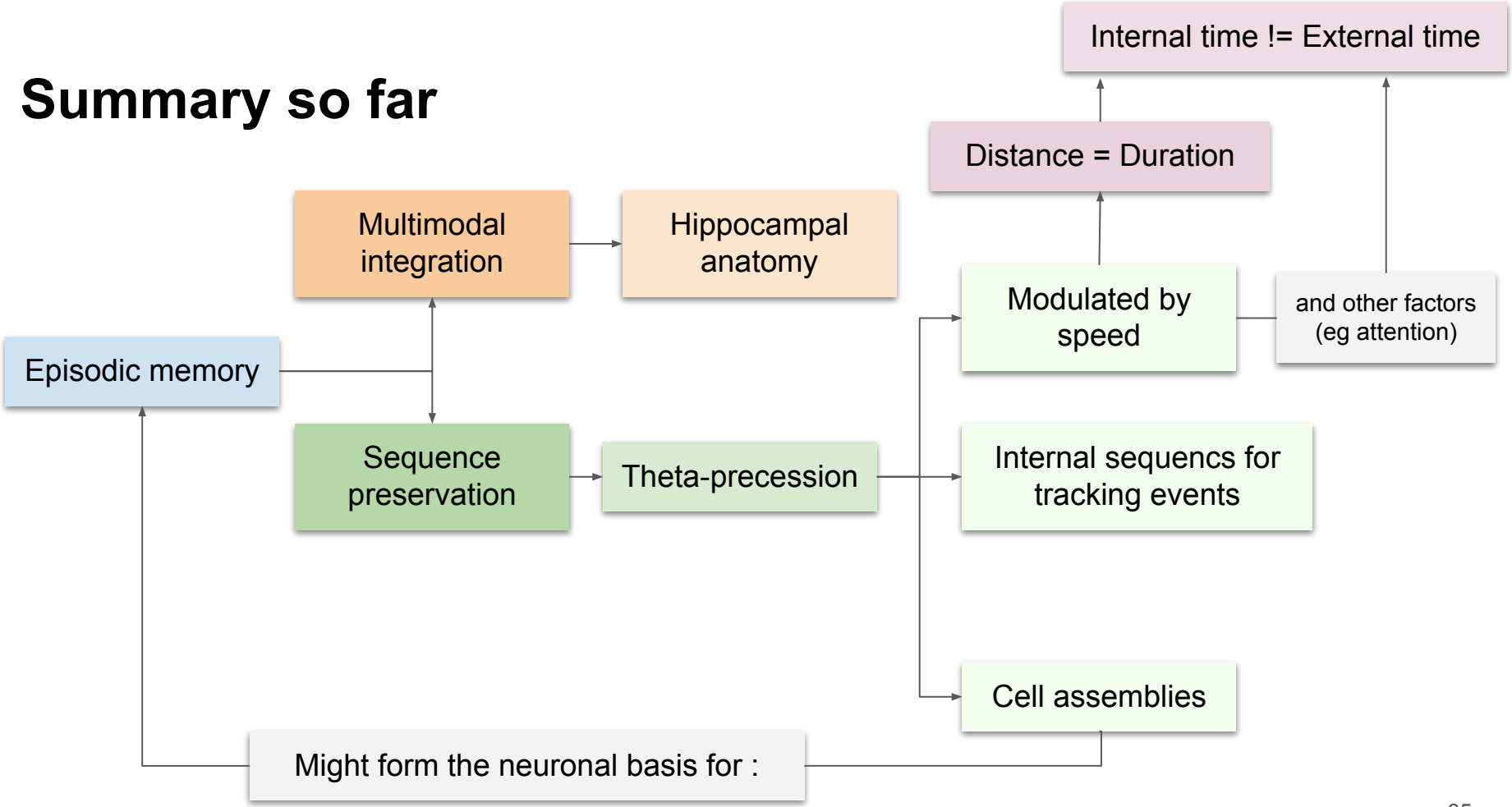
Recollection for analysis
(internal time)
Slower

Formation of Cell Assemblies for Memory

- Neurons firing in theta-cycle are paired via **synaptic plasticity** mechanisms
- **Cell assemblies** group together temporally coordinated neuronal events into sequential representation
- **Partial activation** will lead to **reactivation** of the entire cell assembly
- Mechanism for **memory recollection** by auto-associative recurrent neural network



Summary so far



Any questions so far?

5 min break

Outline

Hypothesis :

hippocampus can generate **perpetually changing sequences**,

Questions :

- **Cell assembly sequences** in hippocampus
  - - are only externally imposed? or also internally generated?
  - - can be referenced by **theta oscillation**?

- **Place** cells and **time** cells?

Outline

Hypothesis :

hippocampus can generate **perpetually changing sequences**, without the need to refer to the concepts of space or time

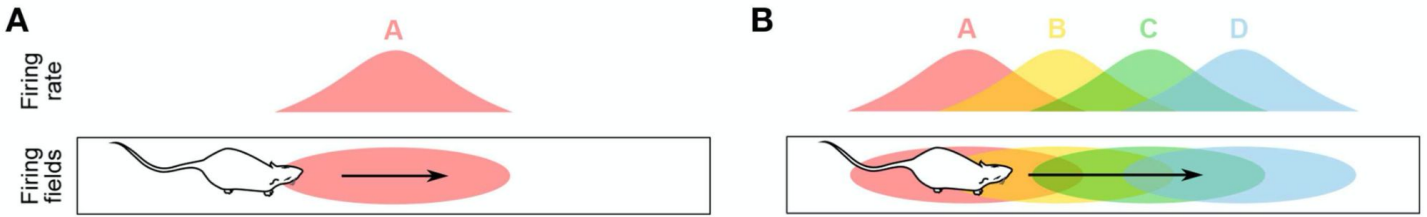
Questions :

- **Sequential activity** in hippocampus
  - - externally imposed or **internally** generated?
  - - referenced by **theta oscillation**?
- **Place** cells and **time** cells?

Cell Assemly Sequences

- found in a wide range of neural systems and behavioral contexts
- critical in temporal information coding
- encode spatial nagivation

Cell Assemly Sequences



Drieu & Zugaro (2019)

sequential firing of place cells is imposed by the **external environment**

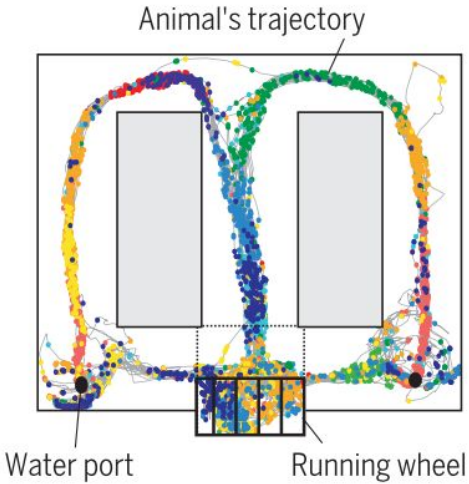
Cell Assemly Sequences: environment-dependent

only **place cells** encode current location **fire continuously** while **other** neurons would remain **silent**

(Omer et al. 2018)
(Danjo et al. 2018)

Cell Assemly Sequences

delayed-alternation memory task

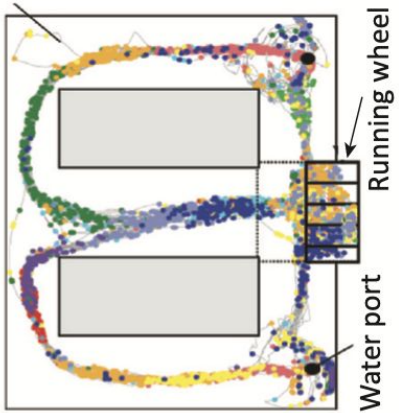


same position

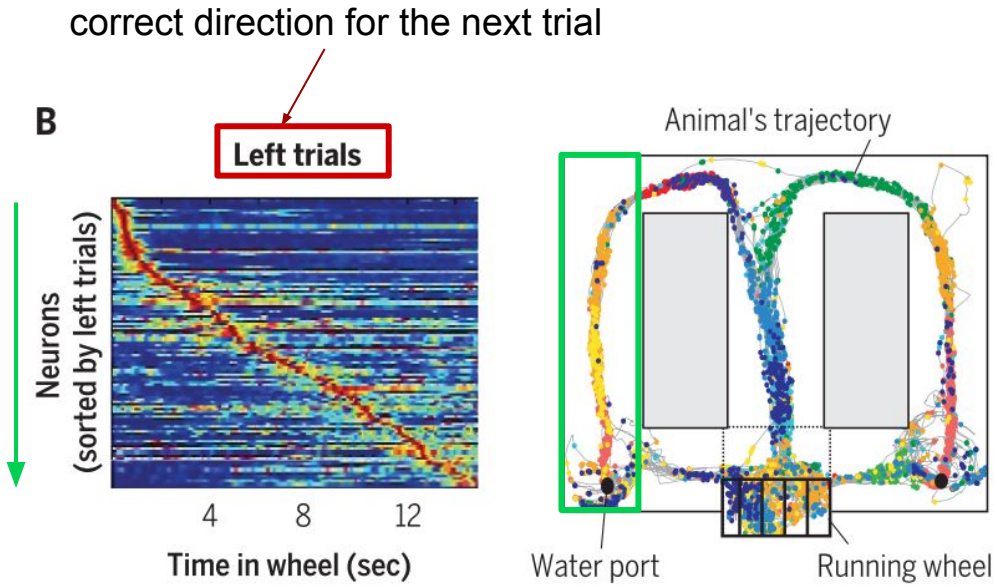
Cell Assemly Sequences

Right

Left



Cell Assemly Sequences



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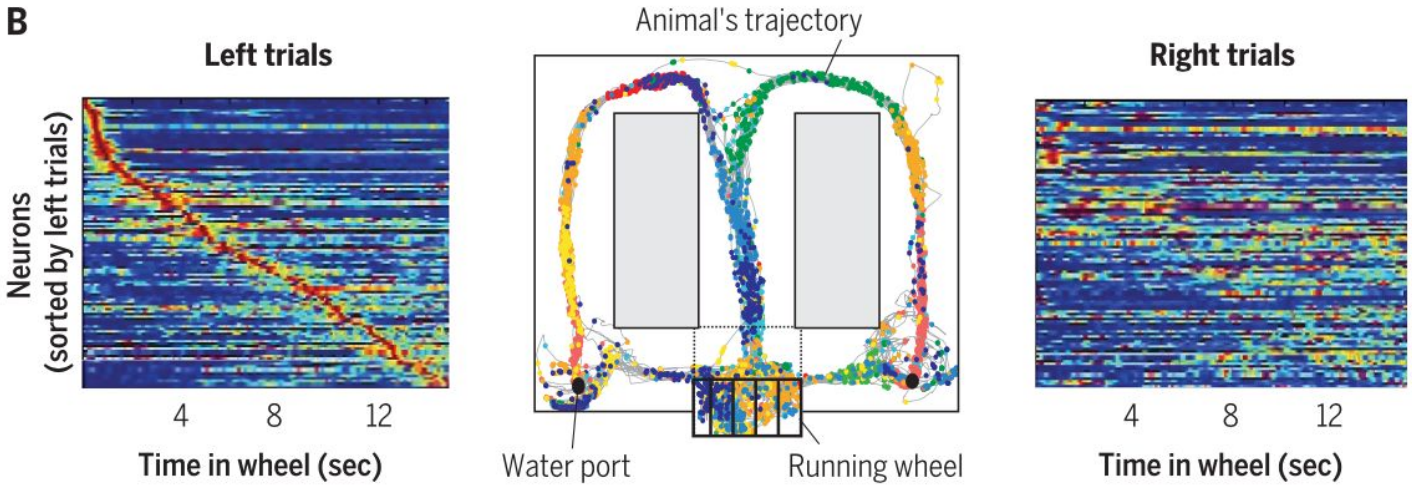


Outline

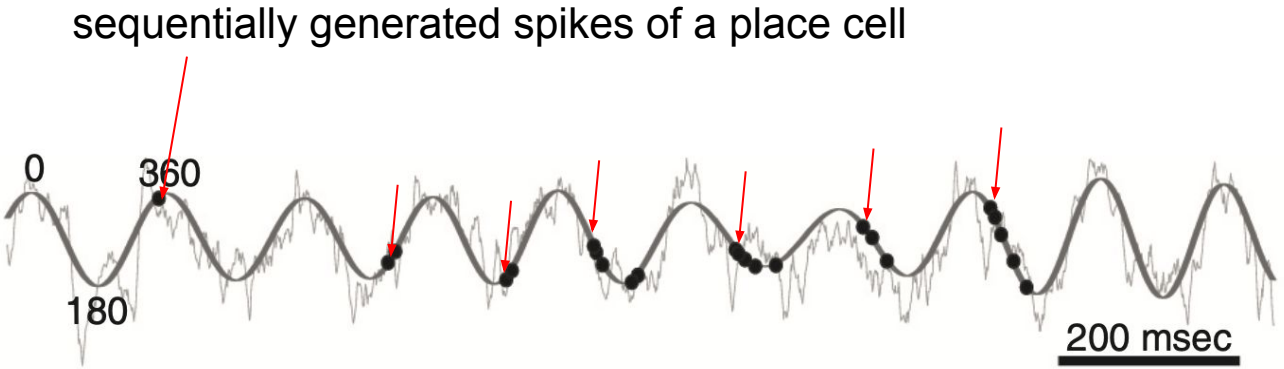
Hypothesis :

hippocampus can generate **perpetually changing sequences**, without the need to refer to the concepts of space or time

Questions :

- **Sequential activity** in hippocampus
  - - externally imposed or **internally** generated?
  - - referenced by **theta oscillation**?
- **Place** cells and **time** cells?

Self-organized sequences display **theta precession**



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Place cells vs. Time cells

- Same neural data can be related to distance or time

- The **interpretation** of neurophysiological data is **determined by** the **unit** of measuring **instruments**

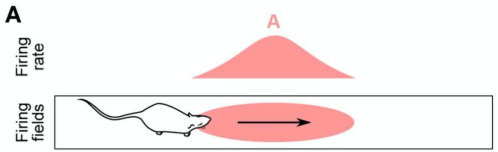
Clock time-independence of neuronal sequences

neural dynamics are **flexible** and **adaptive**

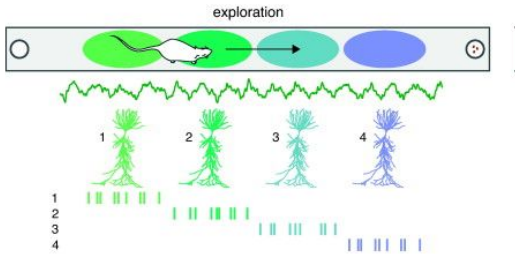
behavioral sequences
1-2 second

theta sequences
100-200 ms

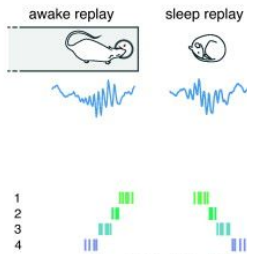
ripple sequences
10-20 ms



Drieu & Zugaro (2019)



Girardeau et al. (2011)



In summary

- **Sequetial neural activity**:
    - can be **internally organized**
    - is referenced to **theta oscillation**

- **Place cells and Time cells**
    - the reference and interpretation are determined by measurement unit

„There are no pure time/space cells“

- Neuronal assemblies always turn out to compute **something else as well**.

  Examples:

  - **“Time cells”**: Some parietal cortex neurons (not hippocampus) show **time representation**.
  - At the same time, their firing patterns **correlate to other observations**:
    actions, objects, routes.
  - **“Place cells”**: Action potential timing (theta wave) correlates with distance and duration, but number of neurons and strengths of their correlations do not.

-> Time/space for the brain **= combination of those other arbitrary signals**?

What could be the exact role of those cells then?

„The hippocampus generates sequences“

Sequencing!

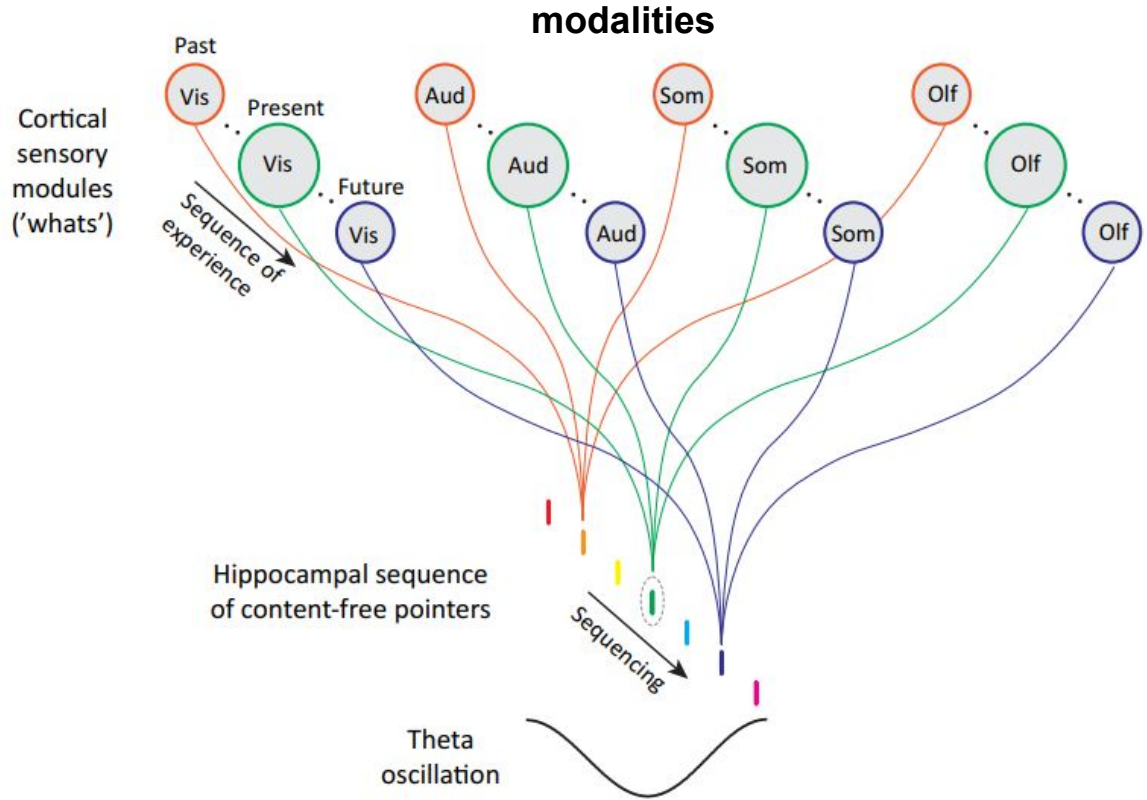
Hypothesis:

The hippocampus is a **general-purpose sequence generator** that carries **content-limited ordinal** structure.

- Experience is a **succession of events.** Our life and our world consist of sequences.
- The hippocampus produces content-limited cell assembly sequences **without details**.
- Benefits of sequences: **Predictions, order**

„The hippocampus generates sequences“

- Sequence cells **“general purpose”**
- What about the **“special, concrete purposes”?**
- **Proposition:** Sequences in hippocampus **point to items in neocortex** (visual, auditive, somatic, olfactoric etc.) in the **same order as they were experienced**
- **“Librarian”** Knows where the books are, but not their content (in detail)



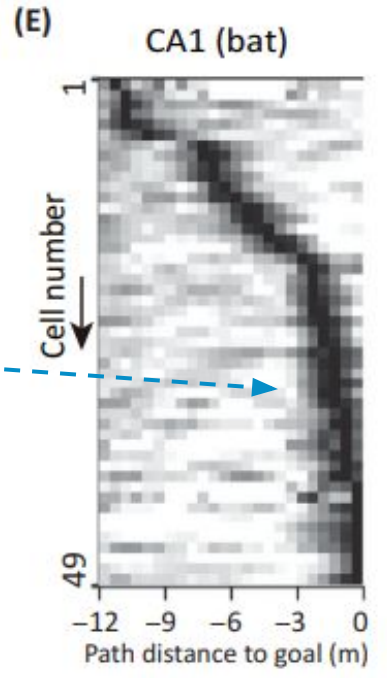
„The hippocampus generates sequences“

Support for sequences: “inaccuracy”:

Sequence cells **can represent** distance or duration in to a certain degree, but **do not have to do it “accurately”**

- **warping**
- **scaling (recall)**

-> flexible representation of the world



„The hippocampus generates sequences“

Support for sequences: Order is an important concept

- Eichenbaum‘s **transitive inference:**
- Experiment:
  - Rats and overlapping odors
  - Rats learn that odors **A, B** and odors **B, C** are related because they overlap
  - They can **infer** that odors **A, C** are related

„The hippocampus generates sequences“

Support from human studies

- Hippocampus-damaged amnesic patients had **problems with recalling the sequential order** of distances and durations they experience, but **less problems with estimating and recalling them**
- Lesioned rats could **recognize** odors but **not remember their order**
- **Remembering: different scales** of time and space, **similar** ippocampal activation patterns (because order counts?)

„Dissociation of order and quality/quantity”

„The hippocampus generates sequences“

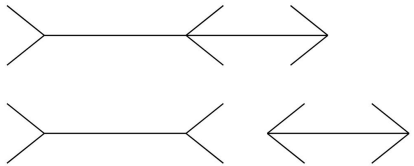
Support from human studies

- Neural patterns in hippocampus **scaled both with space and time proximity** -> **common coding mechanisms** for both

- Information is **represented differently**
  - if in the **same context (1)**
  - if **separated (2)**,
  - although real distance (time, space) is **equal**
  - (1) appear more closely together
  - (1) memory more accurate
  - (1) neural pattern more similar

„Contradiction to previous finding? Order and quality/quantity together?”

„Inaccuracy”



Optical illusions: inaccuracy is common!

„The hippocampus generates sequences“

Conclusion

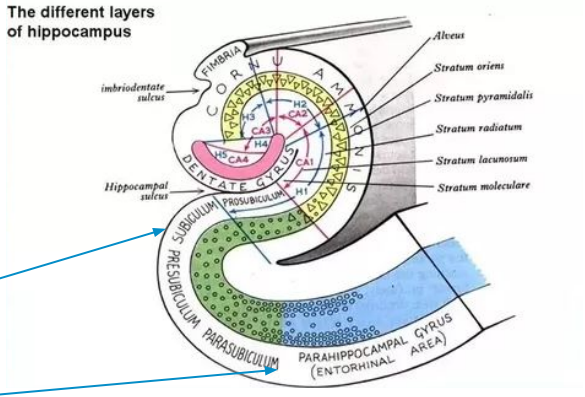
Classification of hippocampal neurons as **place cells, time cells etc. are irrelevant** for the brain.

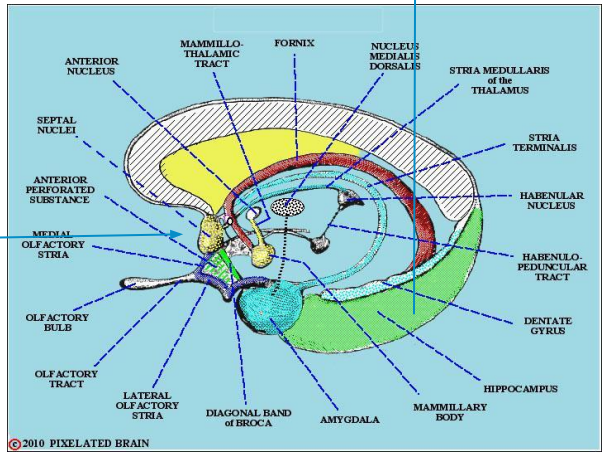
But **how exactly** is **abstract** representation in hippocampus **linked** to the **more concrete** representations in **other brain regions**?

From Hippocampus to Action

- Hippocampal neurons do **not project directly** to muscles

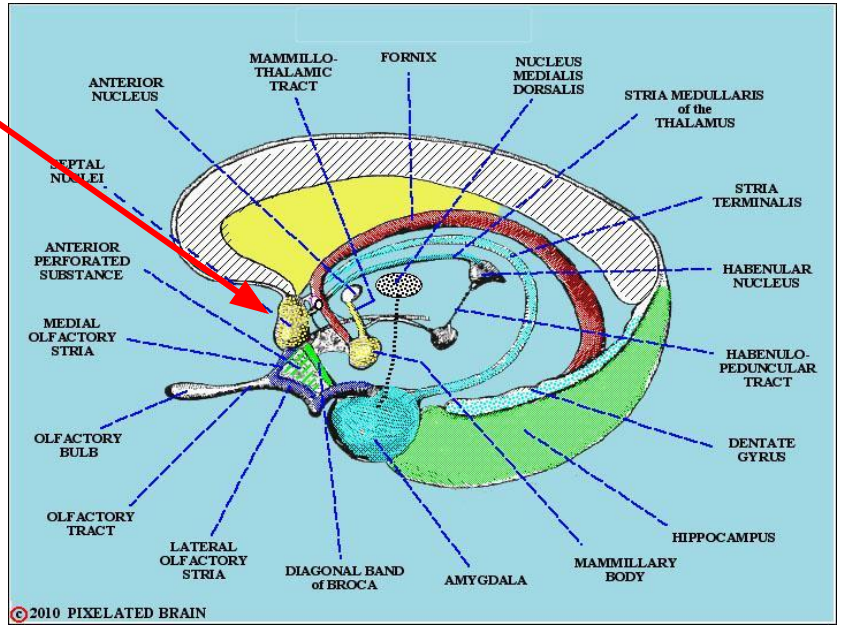
- instead **output structures** (candidates):
  - Entorhinal cortex
  - Subiculum
  - Retrosplenial cortex
  - Prefrontal cortex
  - Septal nuclei





From Hippocampus to Action

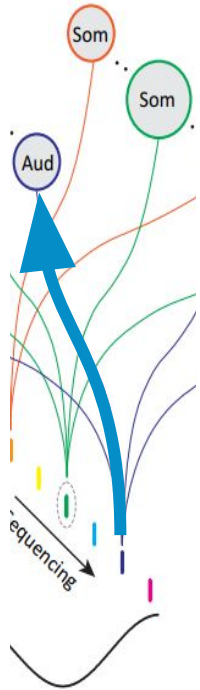
- **Lateral septum most likely**, since it receives the **densest** hippocampal projections: CA1 and CA3 inputs
- Lateral septum **projects directly** to
  - Motivational centers of hypothalamus
  - Midline thalamus
  - Brainstem
- Potentially allowing selection of **action programs: Planning based on the sequences?**



From Hippocampus to Action

Information flow from hippocampus to lateral septum

- Information in **lateral septum** should **build up on** information from **hippocampus**
  -> Difference in activity patterns?



Video (min. 2-3):
https://www.sciencedirect.com/science/article/pii/S0896627318303362?via%3Dihub

From Hippocampus to Action

Article

Neuron

Transformation of a Spatial Map across the Hippocampal-Lateral Septal Circuit

Highlights

- LS neurons carry a rate-independent phase code for position
- The LS spatial phase code is as reliable as the hippocampal rate or phase codes
- LS phase code is a transformation of the distributed CA1/CA3 cognitive map
- The Hippocampus-LS circuit may be the conduit for translating representation to action

Authors

David Tingley, György Buzsáki

Correspondence

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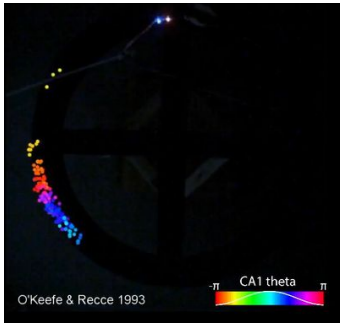
In Brief

How abstract representations are translated into action is unknown. Tingley and Buzsáki describe how the hippocampal cognitive map is "read out" by a target region. The transformation relies on population coordination referenced to theta oscillations rather than the tuning of individual neurons.

From Hippocampus to Action

Neural activity different in hippocampus than in lateral septum



Hippocampus (place cell) neuron

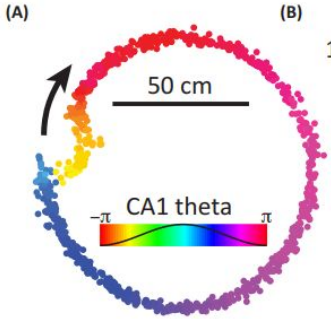
- **Theta phase** (action potential) of lateral septal neuron **correlates with position and distance <u>in place field</u>**

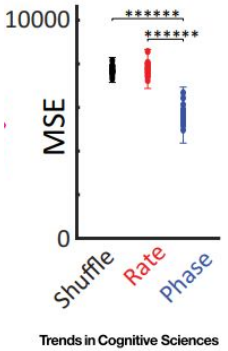
- **Firing rate correlates <u>with place field</u>**

Lateral septum neuron

- **Theta phase** (action potential) of lateral septal neuron **correlates with <u>global</u> position and distance**

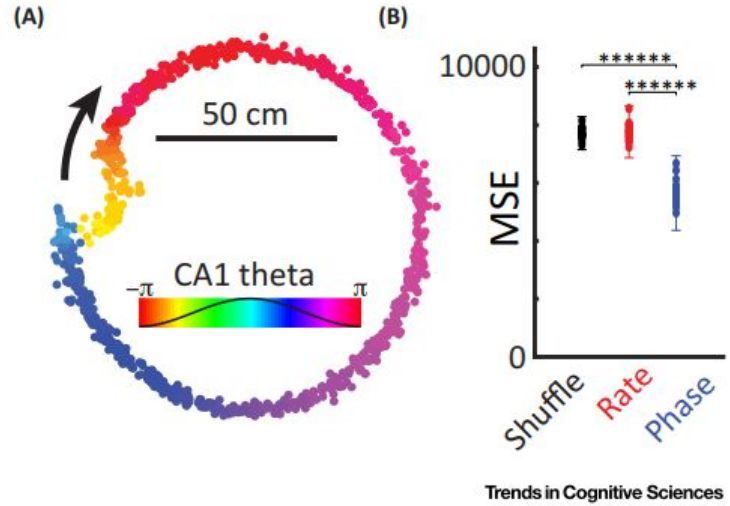
- **Firing <u>rate does not correlate</u> (stays "the same")**





From Hippocampus to Action

- Theta phase correlation **does not come** from phase or rate of **individual hippocampal place cells**
- But from **“changing relationship between CA1 and CA3 place cell assemblies”**
- Then **“action selector”** quickly **identifies source** of information and **mediates action** from a higher-order map



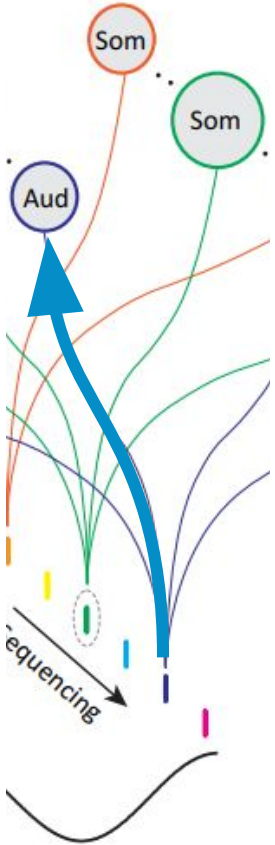
?

From Hippocampus to Action

Information flow from hippocampus to lateral septum

- **Theta sequence** in hippocampus - relevant for space - relevant for planning
  -> the **lateral septum** should **be able to read** it
- However, studies found **only degraded spatial information** in firing rates of lateral septal neurons.

?



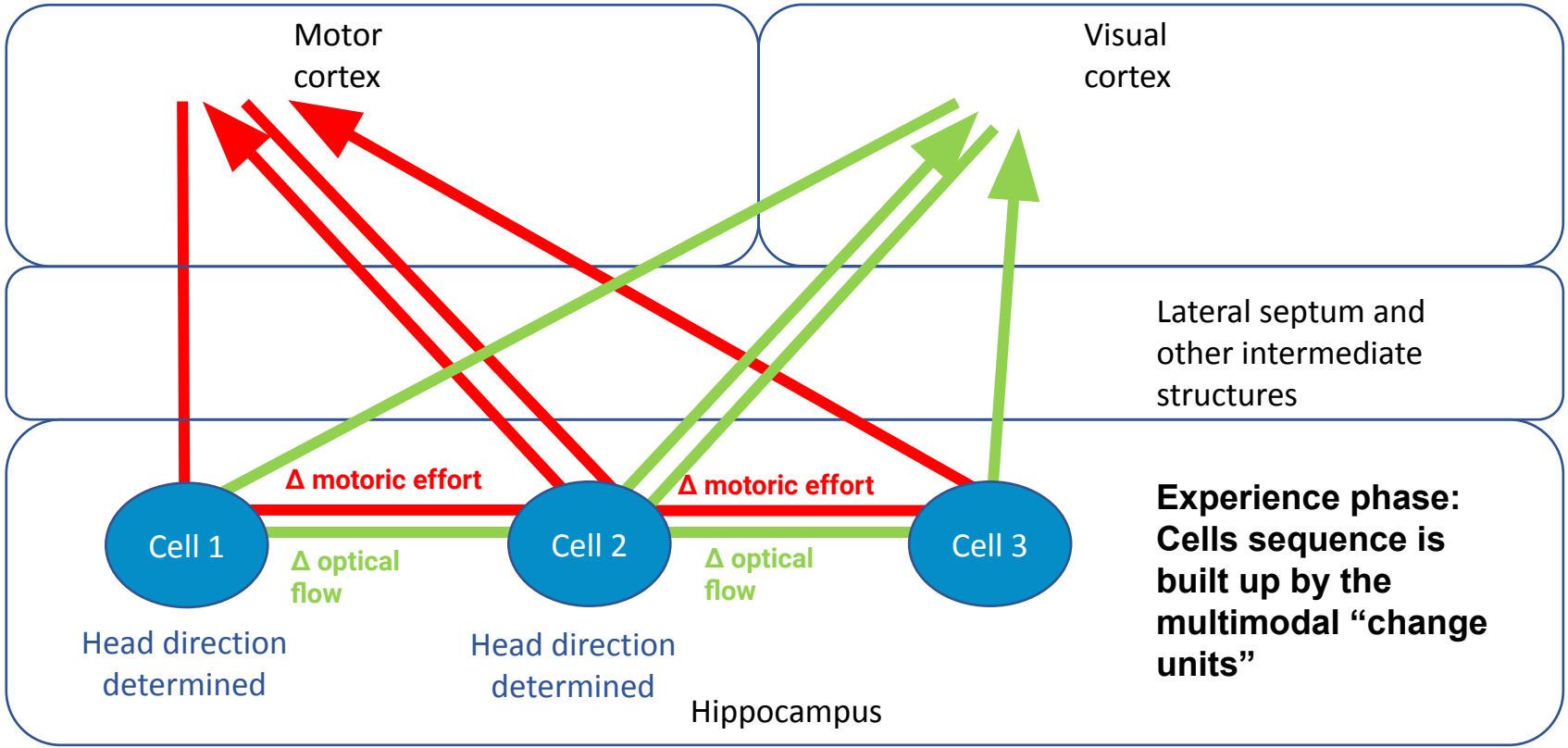
Several things unclear!

- Lateral septum still gets and shows all information, really **qualitative difference** to hippocampus neurons?
- How does information get **INTO** hippocampus?
- How is the **transition** between two hippocampus sequence neurons triggered?

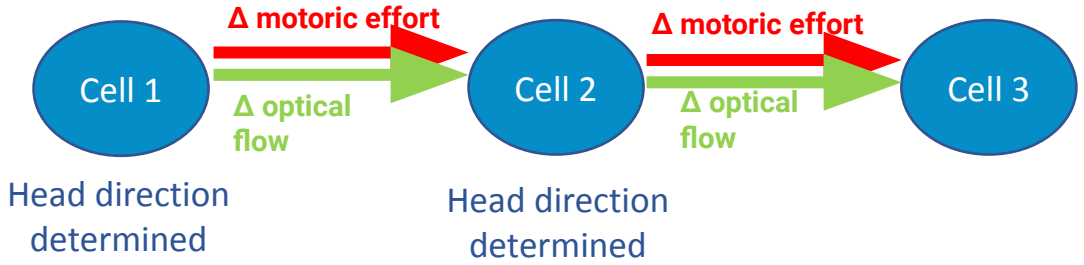
Own hypothesis:

Place cells, time cells etc. -> “Change cells”

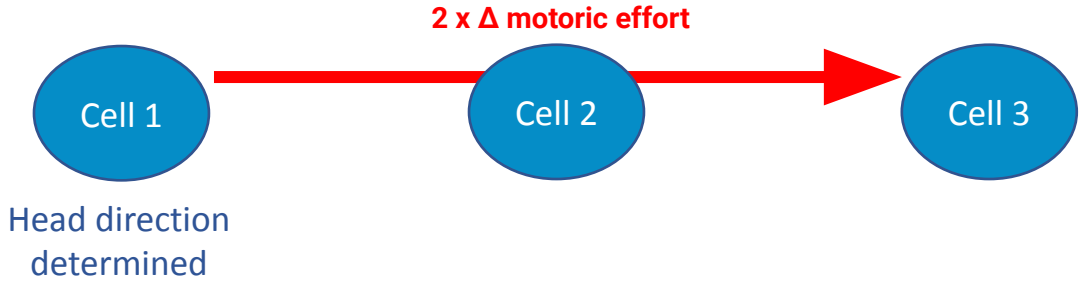
„Change cells“



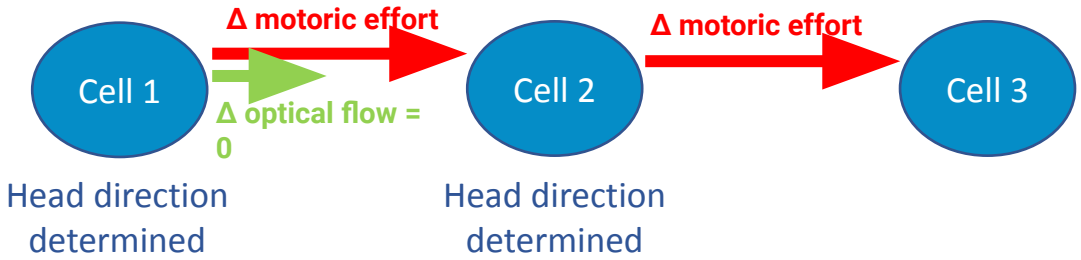
Evaluation phase: Multimodal “change units” trigger traversing of cell sequence



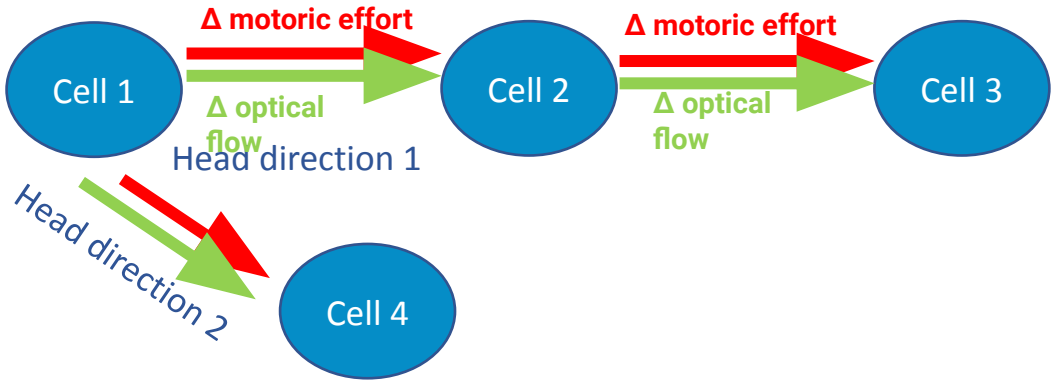
Double speed



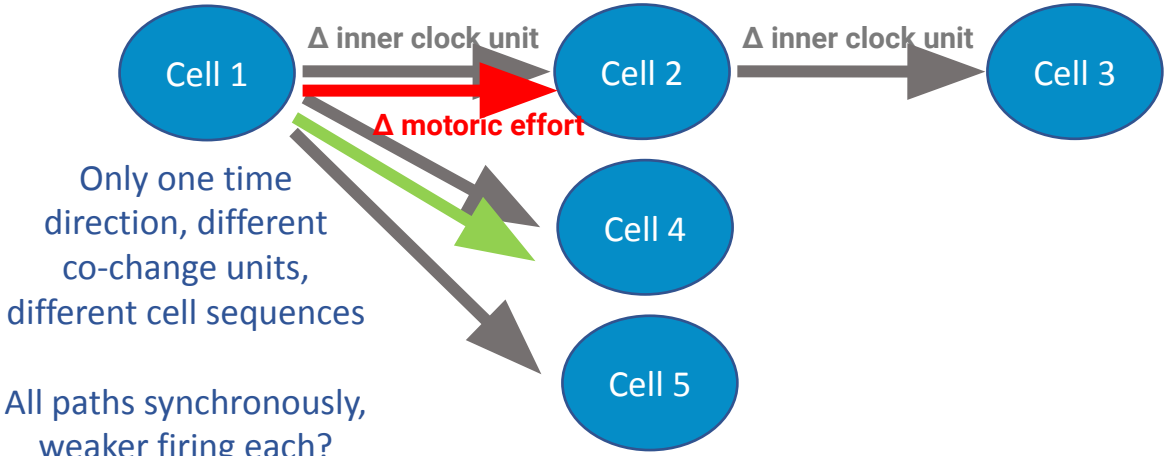
Wheel running,
But **with** visible optical landmarks
-> contradiction, re-interpretation of situation



Different head directions
at beginning



Relatively precise time measurement:
„Inner clock unit“ can be **theta wave** or something else



CONCLUSIONS

- The hippocampus is potentially **blind to the modality of its inputs**
- Activity in the HPC (and beyond) should be **interpreted in terms of neuronal readers** and not in reference to external measurements
- Sequential neural activity can be **self-organized** and referenced to the **theta oscillation**
- The hippocampus generates reference **sequences** over which sensory experiences are organized and stored across the cortex
- Neural dynamics **across brain regions** can be understood without specifying the roles of space and time

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Thank you for your attention!

Any questions?

Your Questions

- How far can our meta-thinking about concepts like space and time or the concept of a concept itself go, when our meta-thinking itself is constrained by our mental concepts?

- Grid map vs Euclidian map: what do you think are the advantages and disadvantages of this point of view? How could we design an experiment to explore more the equality and differences of considering time and space?

- But, there must be space and time in the brain, it is so inherent to the human experience! Where does it come from?

- The authors offer an alternative to the dominant view of memory consolidation (see outstanding questions). Can you think of an explanation how could this model could work?

Your Questions

- The authors criticises classical research approaches where a meassure wich is defined by humans (like seconds for time or meter for distance), and the look for that measure in the brain actualy sets a wrong focus of research because those meassures are also constructed and do not have to represent what happens in the brain. Could this argument/critic also be true for other research domains in neuroscience (e.g. the visual system, psychophysics) , and how could research in those domains that overcomes this issue?

- Very interesting, and very controversial paper! Many questions… I think one can fundamentally disagree with the some of their arguments. For one thing, just because HC seems to encode sequences, why does that mean it also does not estimate time? It seems strange that they profess that the HC does not have a mechanism to encode or compute time, when the unifying theta oscillations they often mention would be a good candidate for just this. The fact that this is evidently not clock-faithful (as they also often mention) seems trivial, and can be explained as an approximate solution to a difficult, uncertain problem. Or even if it does not encode time directly, is not a sequence a representation of just that? If humans implicitly measure time as “time taken to walk to the train station” or “time taken to blink”, and not in the time taken by caesium atoms to jump between energy levels, this, as mentioned, seems trivial. Organisms are dynamic systems, with the internal conditions constantly in flux. It seems reasonable that it is difficult to produce a consistent base unit of time from this system. Whether it occurs in the HC or not, self-evidently we do estimate time, to varying levels of accuracy. On the subject of encoding space, the authors seemed to be stuck on the notion of space as distance, rather than location nodes separated by uncertain estimates of distance. It seems true that humans are even worse at measuring distance than we are at measuring time, and that time and space are often combined when talking or thinking about the two. However, this is nothing surprising. The two are after all related, as the authors mention, and modalities are usually combined in the brain to provide a better prediction in the face of uncertainty. Finally, the authors completely neglect to address how sequences might be used to enable novel shortcuts between different points on different sequences, or why place cell are insensitive to the direction of approach.