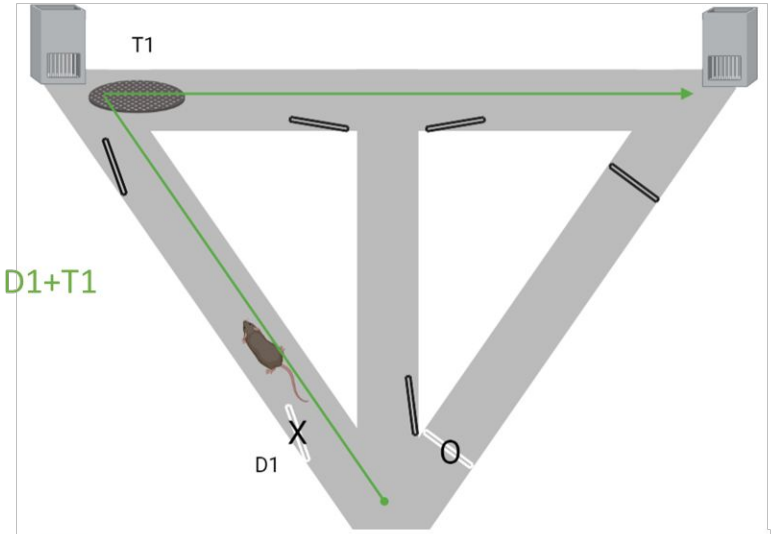
Bibliography

Follow-up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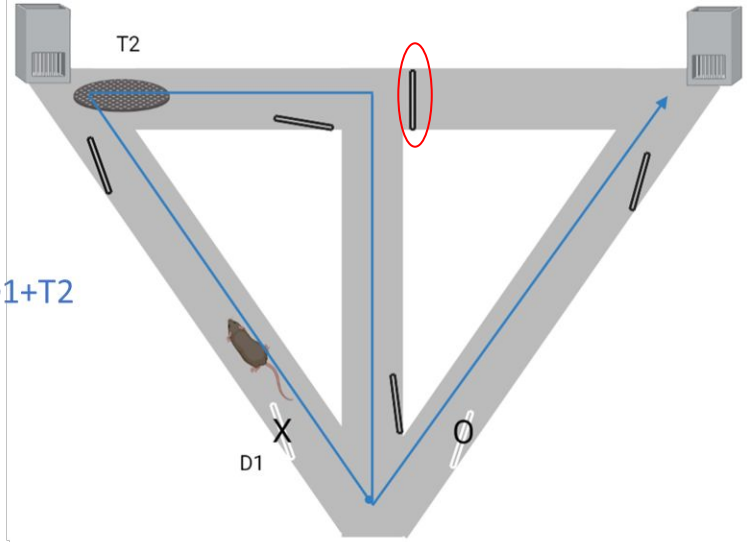
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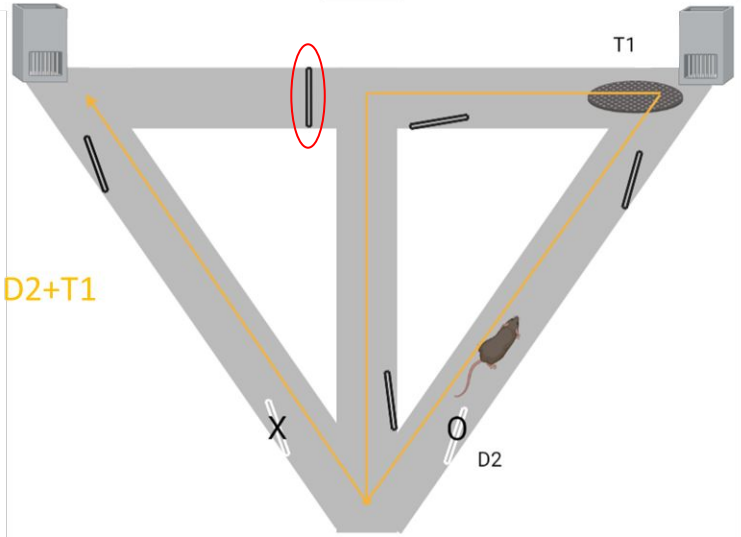
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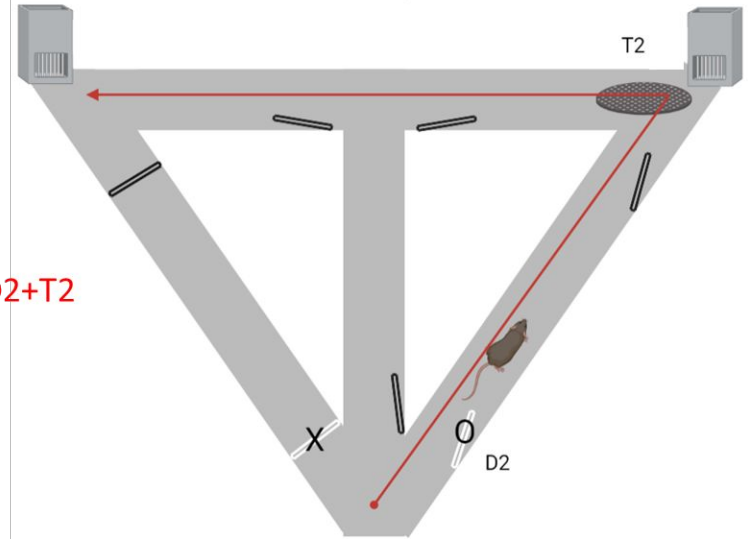
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1 - Episodic memory, PA, time cells, ISI

Episodic memory

Human episodic memory is the **conscious recollection** of **“what”, “where” and “when”** elements, which can eventually be **verbally communicated** (Dere, Tulving). Another specificity of episodic memories is that they **enclose a trace of the individual’s internal state (emotions, thoughts...)** during the encoding process (Dere et al. 2008, 2010).

As animals cannot communicate verbally on their past, nor can we prove when and if they do consciously recollect:

→ “Episodic-like” memory

Main critic of papers testing episodic-like memory

1. No explicit evidence that the animals **consciously recollected** their personal past experiences

2. Retrieval of info can occur when **encoding is incidental** (it is unknown if the info will be needed later on) and **memory assessment is unexpected**

   BUT majority of the papers use behavioral training, that likely gives rise to **well-learned expectations** about the sequences of events: animals may solve an “episodic-like memory” test by using **well-learned semantic rules** (without consciously recollecting the episode) *(Zhou et al., Rats answer an unexpected question after incidental encoding)*

Paired-associate learning

Classic memory paradigm that is used to understand **how people encode and retrieve newly formed associations** among stimuli.

Our interest: Understand how are PA handle between HPC and PFC.

2 papers:

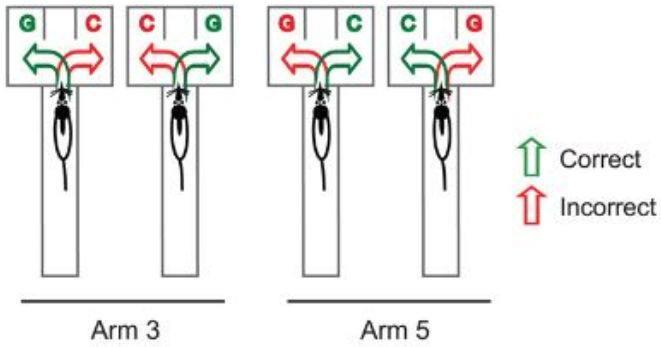
- Kim et al., 2011
- Kesner et al., 2003

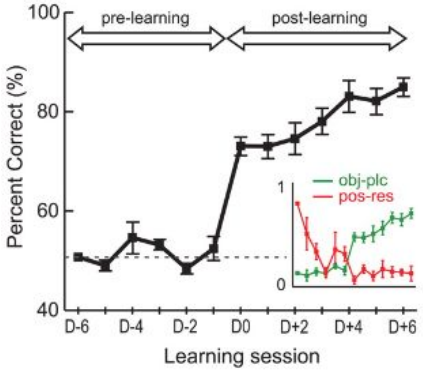
Kim et al., Neural Correlates of Object-in-Place Learning in Hippocampus and Prefrontal Cortex, JNeurosci. (2011)

The objective: observe the **neural activities in both mPFC and HPC simultaneously** in a OPPA.

The task: **Object-place paired-associate** (rats) in 2 arms of a radial maze. A trial started as the experimenter opened the guillotine door of the start box and **one arbitrary arm had already been opened by the experimenter before** releasing the rat from the start box. In the OPPA task, a particular object was always rewarded in association with a certain arm, and **whether the object occupied the left or right food well (i.e., object's position) in the choice platform did not matter**.
The timing of the experiment: Pre surgical training/habituation of 1-2 weeks. After, **64 trials** (intertrial interval, 20–30 s) were given **daily** (16*4 combinations). Rats learned in approx. 2 weeks and showed a sharp transition from chance performance (pre-learning stage) to a learned state (>75% correct; post-learning stage) from the **7th day of acquisition**.

The output: recorded single units and LFP simultaneously from the CA1&mPFC.

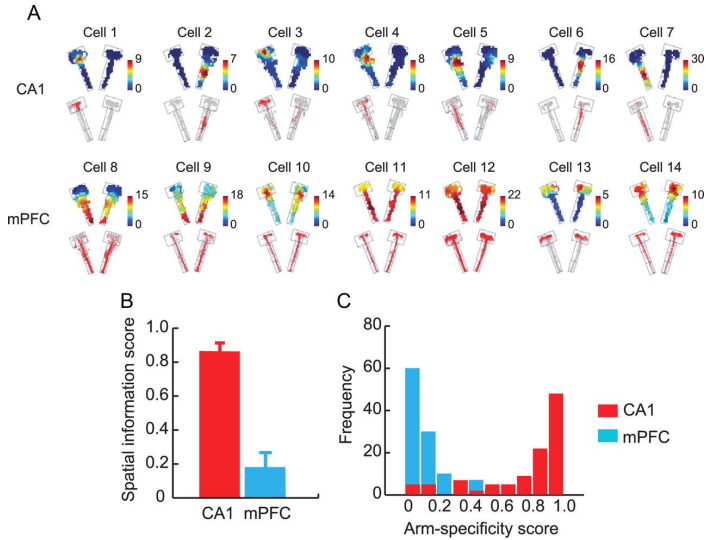




Kim et al., Neural Correlates of Object-in-Place Learning in Hippocampus and Prefrontal Cortex, JNeurosci. (2011)

The results:

- CA1 neurons showed well-isolated spatial firing fields (i.e., **place fields**) associated with a specific arm in the maze. Firing patterns of neurons from mPFC were not as localized in space but showed more **globally distributed firing patterns throughout the maze**. Some mPFC neurons fired locally in the maze, with localized firing occupied **similar locations in both arms** (e.g., near or within choice platform) as opposed to the single arm-specific firing of CA1 neurons.

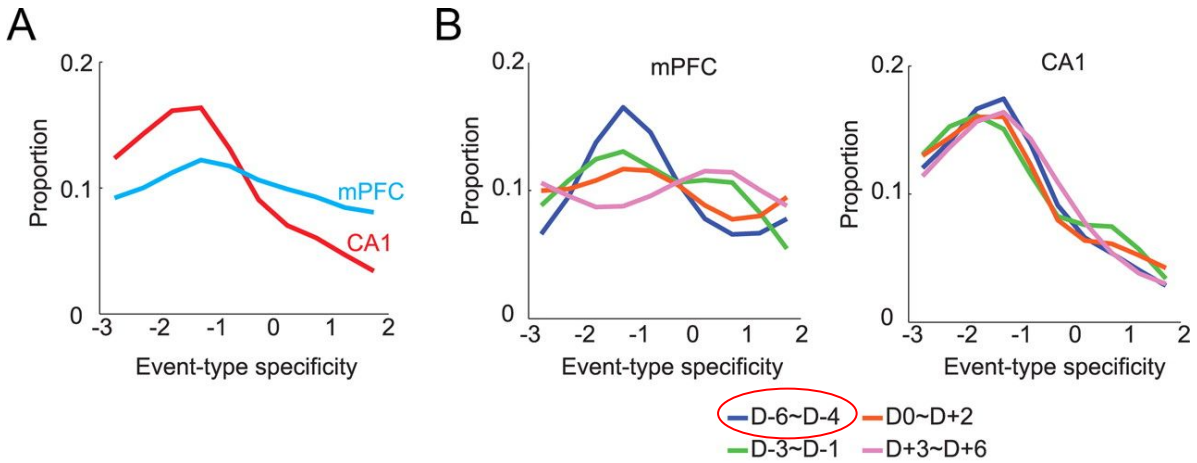


So mPCF firing patterns are not spatial specific but maybe event specific?

Kim et al., Neural Correlates of Object-in-Place Learning in Hippocampus and Prefrontal Cortex, JNeurosci. (2011)

The results:

- Examination of whether the neuronal activity was significantly modulated by the occurrences of the following three event types: Event 1, arm entrance; Event 2, choice-platform entrance; Event 3, object choice.
  Event-type specificity indicates **the degree to which neurons represent event types regardless of arms**. mPFC contained a significantly bigger proportion of neurons showing higher event-type specificity. The mPFC neuronal activity was more concerned with **representing a particular type (or types) of event** relatively independent of its associated spatial location, and such **coding for event-types gradually developed over time during learning**. In CA1, the proportional distributions **remained unchanged** throughout the acquisition period.



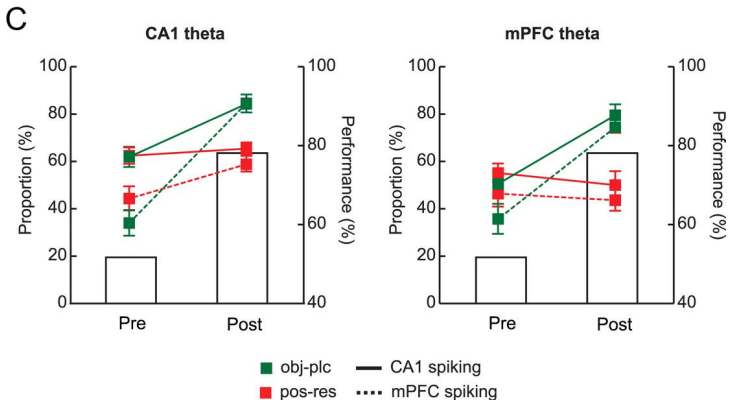
Kim et al., Neural Correlates of Object-in-Place Learning in Hippocampus and Prefrontal Cortex, JNeurosci. (2011)

The results:

Examination of whether spiking activities of CA1 neurons maintained a **significant phase relationship with CA1's own theta rhythm** and also **theta rhythm in mPFC** across learning.

- Spiking phases in relation to the theta rhythm during the period **between entering the choice platform and displacing an object** where compute in in order to capture functional interactions around the time of choosing the object. **Most neuronal spikes were phase locked to the troughs of theta.**
- **Bigger proportion of neurons in CA1 (44.9%) were phase locked** to theta rhythms than in mPFC (27.3%).
- An ANOVA with the spiking region (CA1 and mPFC) and theta region (CA1 and mPFC) as factors showed that there were significant main effects of both factors, and there was **a significant two-way interaction between the factors.**.
- **The above results strongly suggest a positive relationship between learning stage and the proportion of neurons whose spiking activities were significantly phase locked to theta oscillations across CA1 and mPFC.** Activity in the two regions became **more coordinated during the postylearning stage when object-in place strategy was used ONLY**.

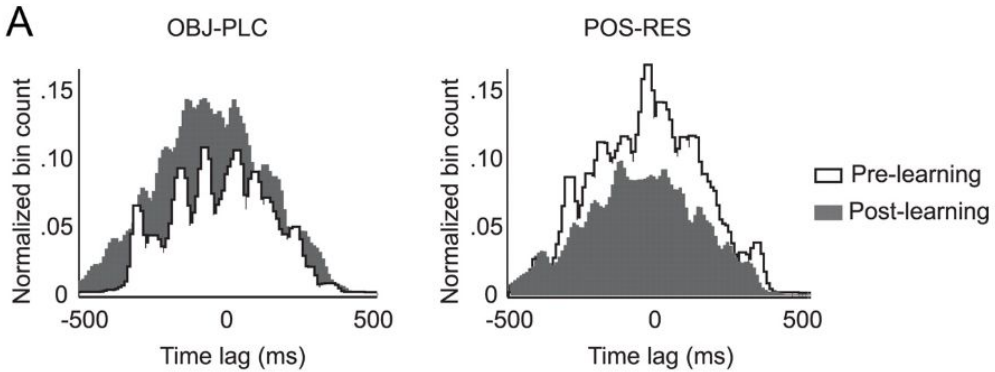
C



Kim et al., Neural Correlates of Object-in-Place Learning in Hippocampus and Prefrontal Cortex, JNeurosci. (2011)

The results:

- **CA1–mPFC coherence in spike timing** associated with different strategies **changes across learning stages:** Cross-correlograms (bin size, 10 ms) based on simultaneously recorded spike trains from CA1 and mPFC according to different learning stages.
- The correlation coefficient was lower in pre-learning but increased after learning in object-in-place trials, whereas the pattern reversed in position-response trials.

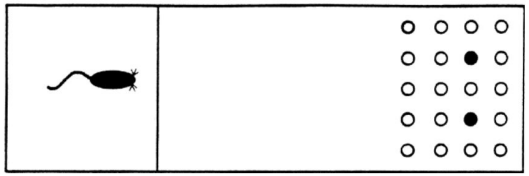


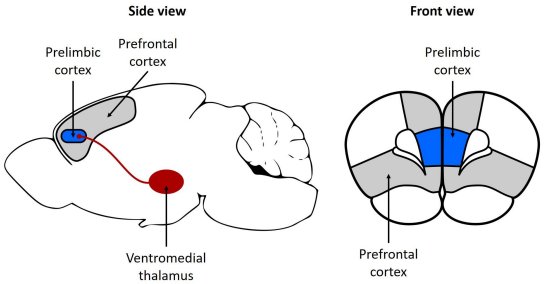
different strategy = opposite coherence in spike timing

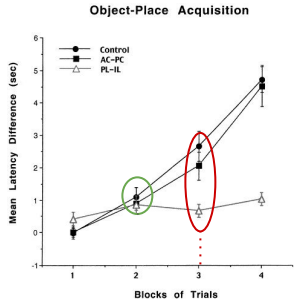
Kesner et al., The role of the prefrontal cortex in object–place learning: a test of the attribute specificity model, Behav. Brain Research (2003)

The objective: Find out the role of the PFC in paired-learning tests and test the attribute specificity model of the PFC
The task: The rat had to remember which object/spatial location pairs were associated with reward. Two different objects and two spatial locations served as stimuli. One object was associated with food reward in one spatial location, but not the other.
The timing of the experiment: All rats completed **pre-training within a 2-week period**. After surgery, 10 rewarded and 10 non-rewarded trials were given daily until the rats were given 320 trials (**16 jours sans weekend**).
The lesions: Since humans with prefrontal cortex damage have difficulty learning a paired associate task, lesions were made in the subregions of the prefrontal cortex in the rats.

The results/output: Rats with prelimbic cortex - infralimbic cortex lesions **did not learn the task**. Whenever higher order processing is required to solve a task, the data support an attribute-specificity model of prefrontal cortex function in that the PL–IL cortices support both object and place attribute information.







240 single trials

Rajji et al., The Role of CA3 Hippocampal NMDA Receptors in Paired Associate Learning, Journal of Neurosc. (2006)

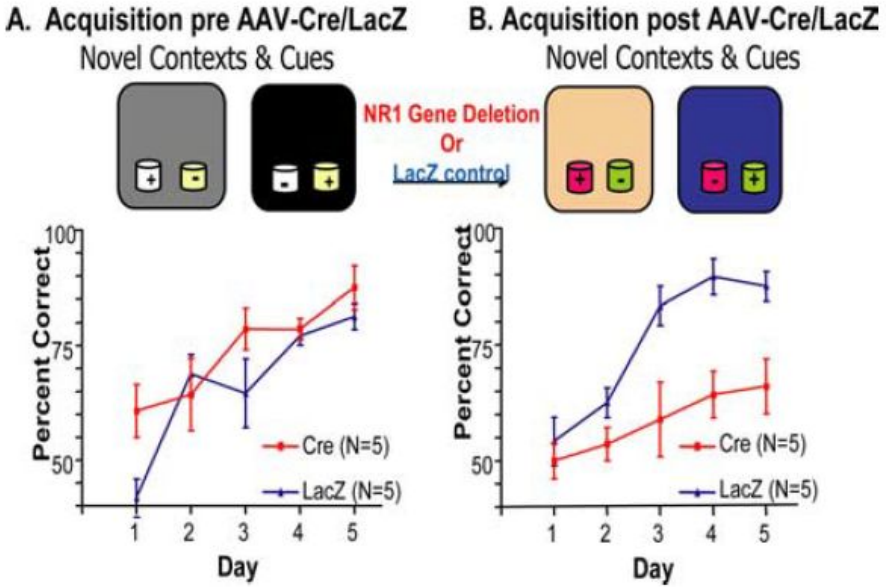
The objective: test whether hippocampal CA3 NMDARs also play a special role in pattern separation when learning requires distinguishing complex environmental contingencies.

The task: Each mouse was exposed to one set of odor/context reward assignments, and subjects and controls were counterbalanced with respect to the sets. Each set consisted of two contexts (CX1 and CX2) and two cups filled with two different scents: “A” and “B.” In CX1, the cup with A-scented sand was baited with chocolate, whereas in CX2, the B-scented cup was baited.

The timing of the experiment: For the acquisition phase, each mouse underwent pseudorandom order constrained by not having more than two trials of the same cup.The intertrial interval was 15–20 min. Ten days after the injections, all mice u originally trained. Acquisition of a novel paired associates problem after injection set of contexts and scents was used for each mouse.

The knockout: use of a viral vector technique to induce a temporally and anatom function.

The results/output: shows that learning novel paired associations between speci CA3 NR1 genes in 30% of the dorsal hippocampus was sufficient to disrupt new previously acquired paired associates and does not affect the ability to discrimin familiar. The findings suggest that CA3 NMDA receptors specifically support the



But: thalamic nuclei also play an important role

- Proof of connections between the PFC and the posteromedial region, lateral region (and to a lesser extent the anterior region).

- Both AT and LT lesions severely **impaired odour–place paired-associate learning**.

Inter-stimuli delays

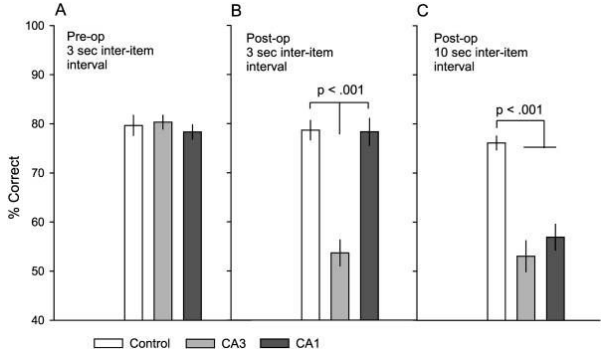
While emphasis was put on the critical role of the hippocampus in the spatial component of episodic-like memory, animal studies has previously shown that the structure is also decisive in forming temporal associations **not inevitably involving space and bridging the temporal gaps that do not present external cues** (such as inter-stimuli delays), and eventually connecting discontinuous events that forms one's continuous memories

Two articles:

- Farovik et al. 2010
- MacDonald et al. 2011

Farovik et al., Distinct roles for dorsal CA3 and CA1 in memory for sequential nonspatial events, Learning Memory (2010)

The objective: Investigated the hippocampal ability to deal with sequential **nonspatial events** on rats with induced hippocampal lesions.
The task: Animals were first presented with 10 odor PA with odors presented one at a time in a pair. After a specific delay, animals were exposed to the same 10 PA, and had to discern if the pair was displayed in the **same order as in the first trial or in the reverse order**. Depending on “old” or “new” order, animals would have to dig or return home.
The timing of the experiment:criterion of 75% correct across 20 consecutive trials
The output: % correct completion of learned task
The results: When the delay between the first and second sequence was 3 seconds, bilateral dorsal CA3 lesions critically disturbed memory, while dorsal CA1 lesions did not alter the animal's learning. When delay increases to 10 seconds, both dorsal CA1 and CA3 lesions drastically diminish rats' performance. **CA1 and CA3 function are disparate by the length of the delay.**

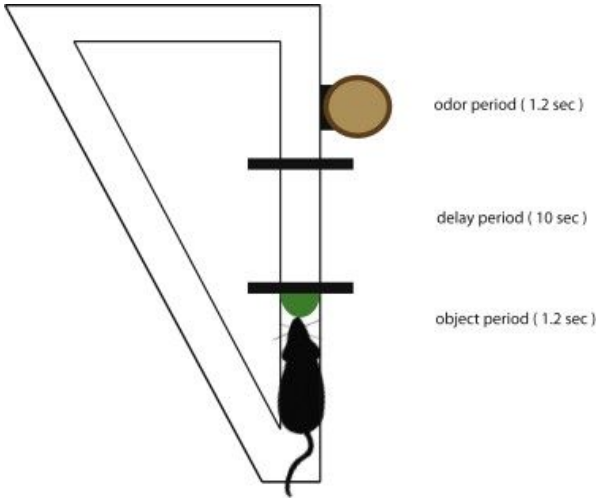


MacDonald et al., Hippocampal “Time Cells” Bridge the Gap in Memory for Discontiguous Events, Neuron (2011)

The objective: Identify and study **the dynamics of hippocampal cells in discontinuous events**

The task: **Object-Delay-Odor** Sequences where rats were to remember the order of a sequence of stimuli. Then the rat had to either dig in the sand to retrieve a buried reward (go response) or no reward was available in the odor pot and a reward could be obtained at a separate location (no go).
The timing of the experiment: average performance was 77% ± 5% (range 71%–84%)

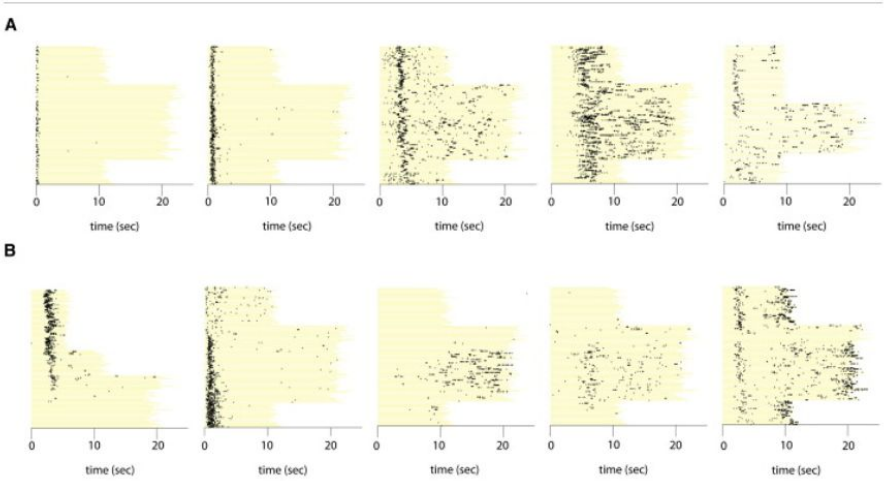
The output: multiple tetrode arrays recording of the pyramidal cell layer of dorsal CA1



MacDonald et al., Hippocampal “Time Cells” Bridge the Gap in Memory for Discontiguous Events, Neuron (2011)

The results:

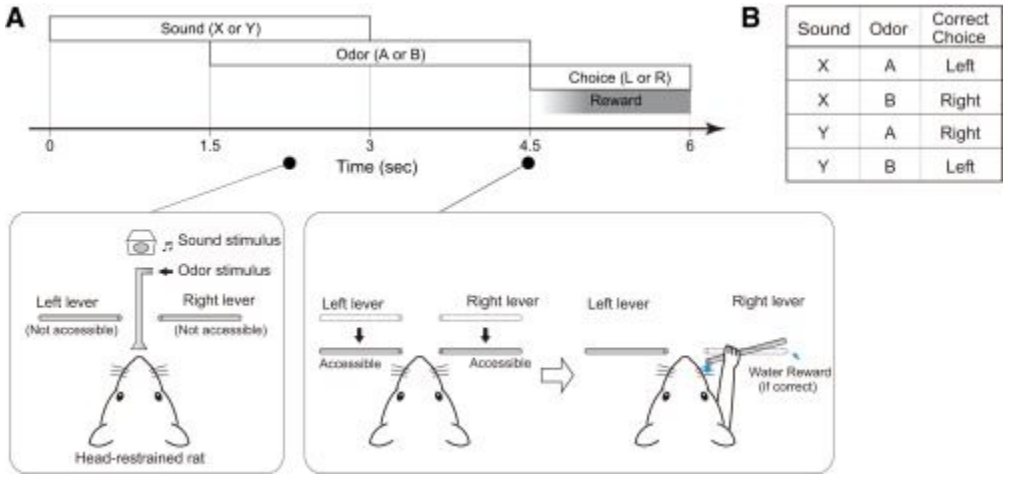
- Recordings of neuronal ensembles from the CA1 reveal the existence of specific cells that **fire concurrently and at successive time within the delay** between object and odor : “time cells”. They generate a temporal signal although influences of variables such as the animal's location, direction, speed or velocity are statistically taken out.
- Moreover, **the temporal firing patterns of time cells adapt and change** when the length of delay period was modified while keeping behavior and spatial cues unaltered. While some time cells **fired at absolute or relative time to the beginning of the delay**, most of them followed **different firing patterns** as the length of the delay changed.



2 - Minutes cells, event cells, event-specific time cells

Terada et al., Temporal and Rate Coding for Discrete Event Sequences in the Hippocampus, Neuron (2017)

The objective: we investigated rate and temporal coding of hippocampal CA1 neurons in rats performing a cue-combination task



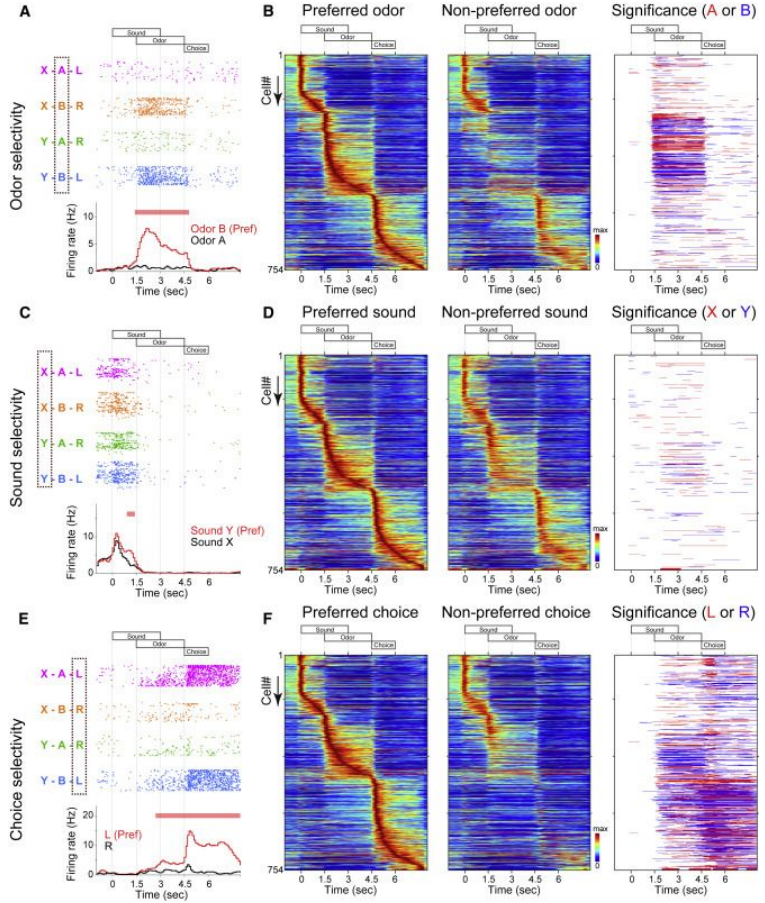
B

Sound	Odor	Correct Choice
X	A	Left
X	B	Right
Y	A	Right
Y	B	Left

Terada et al., Temporal and Rate Coding for Discrete Event Sequences in the Hippocampus, Neuron (2017)

The results:

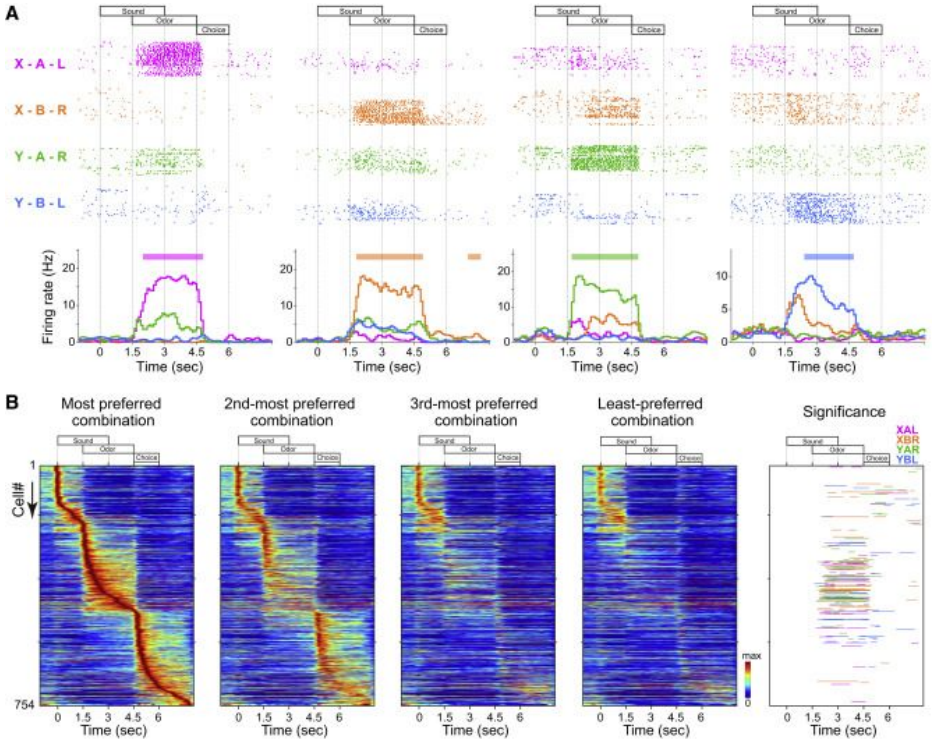
- The majority of CA1 neurons displayed **sensory cue-, combination-, or choice-specific** (simply, “event”-specific) elevated discharge activities (in a non-spatial decision-making task)



Terada et al., Temporal and Rate Coding for Discrete Event Sequences in the Hippocampus, Neuron (2017)

The results:

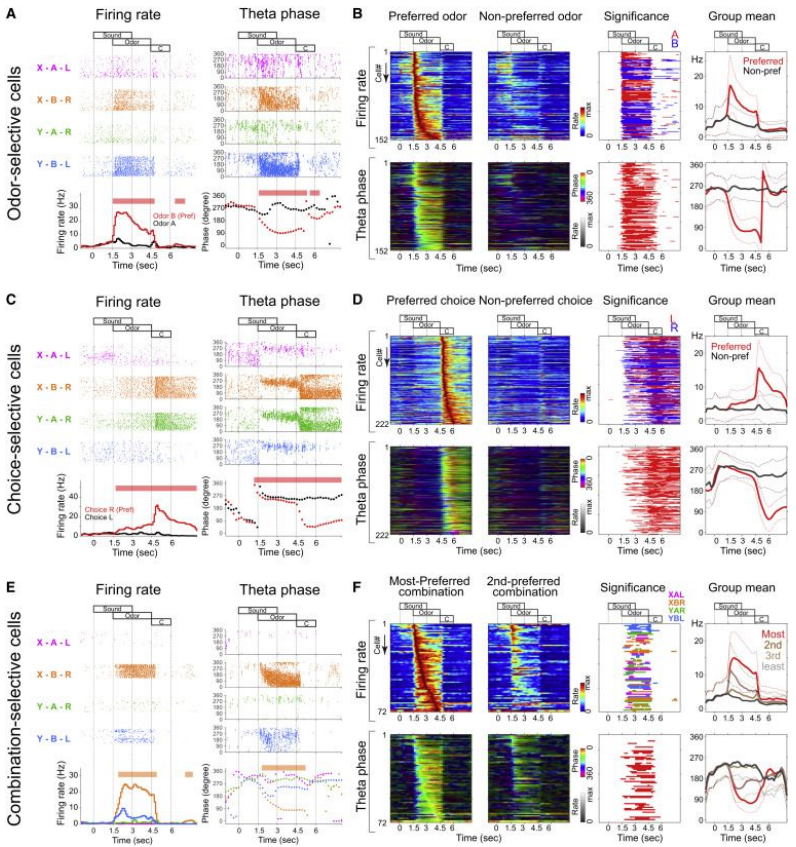
- Note that the sustained activity of **combination-selective neurons** often outlasted the only period of concurrent presentation of the sound and odor indicating that combination-selective neurons represent **conjunctive information of the two sensory cues associated with choice**.



Terada et al., Temporal and Rate Coding for Discrete Event Sequences in the Hippocampus, Neuron (2017)

The results:

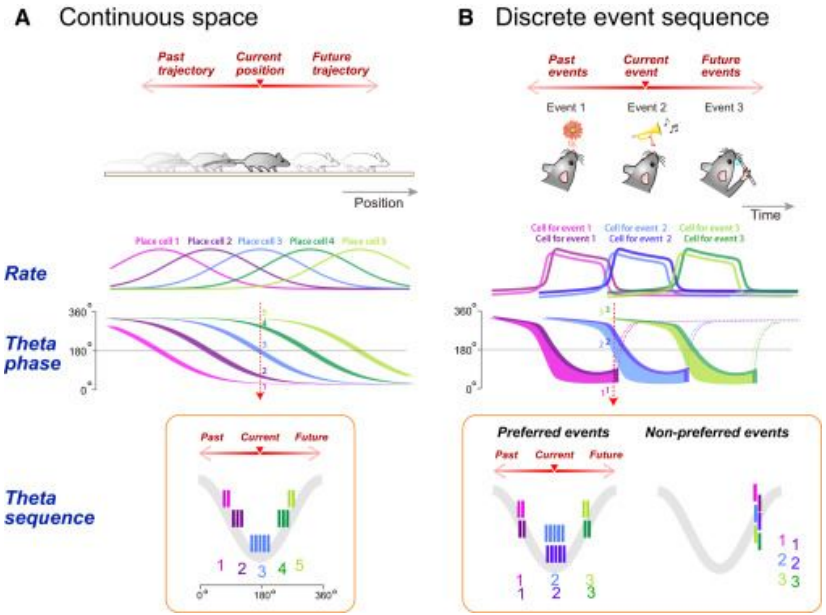
- These event cells underwent **low firing rates on late phases of theta oscillation before event onset**, **transient theta phase precession** at event onset, followed by **sustained phase locking to the early theta phases** during the remainder of the stimulus presentation period.



Terada et al., Temporal and Rate Coding for Discrete Event Sequences in the Hippocampus, Neuron (2017)

<u>The conclusion:</u>

- Event sequences of past, current, and future are thus discretely presented in theta cycles.
- There is a discretization of the cell assemblies activity by the structure of the task

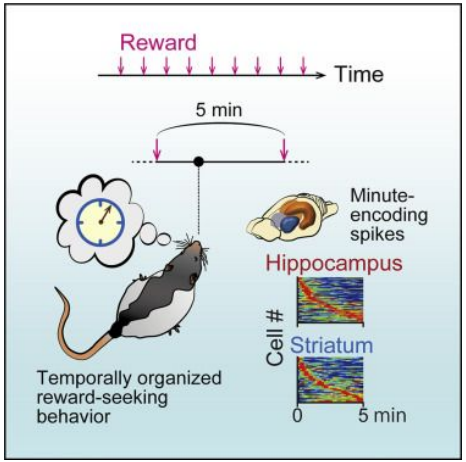


Shikano et al., Minute-encoding neurons in hippocampal-striatal circuits, Current Biology (2021)

The objective: Time cells in the range of minutes?

The results: These results indicate that **minute encoding in the hippocampal-striatal circuit first develops as animals initially learn** repetitive changes in temporal contexts.

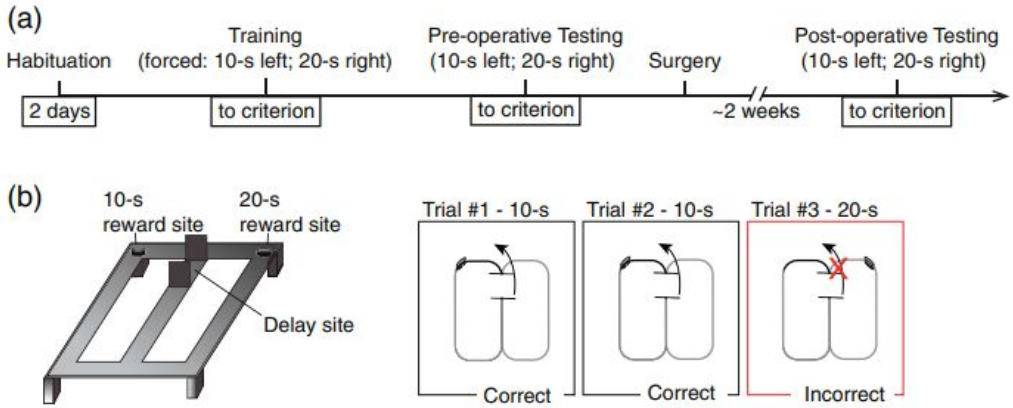
Minute-encoding neurons found in this study appear analogous to cells that encode seconds observed from previous studies:
(1) each neuron encodes **discrete time** periods
(2) their time fields cover an **entire time period**, as represented by the sequential emergence of the time fields
(3) their time fields become broader the later they appear
(4) their time fields **develop as animals gain experience with the task**
(5) their time fields are scalable, correlated with animal's timing behavior



Sabariego et al., In the temporal organization of episodic memory, the hippocampus supports the experience of elapsed time, Hippocampus (2020)

The objective: The study of time cells have not used **time duration as a variable** that animals **need to be aware of to solve the task**.

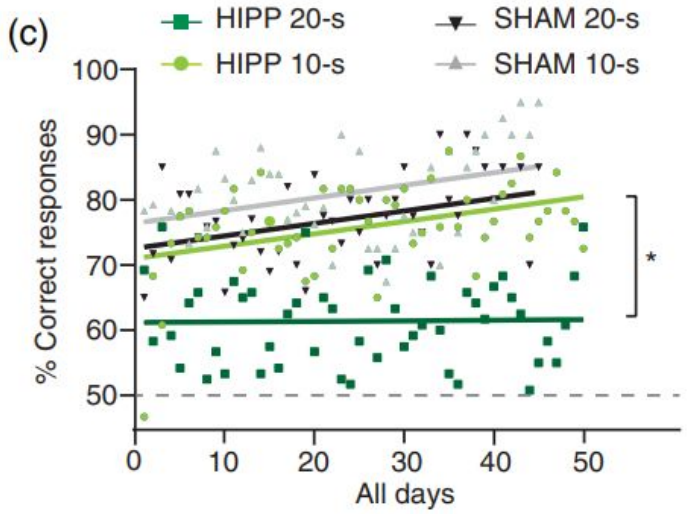
The task: The time duration discrimination (TDD) task required rats to make a correct left- or right-turn out of a central delay box depending on the duration of the preceding 10- or 20-s delay.



Sabariego et al., In the temporal organization of episodic memory, the hippocampus supports the experience of elapsed time, Hippocampus (2020)

<u>The results:</u>
Hippocampal lesions resulted in a impairment in discriminating elapsed time only during the longer delay trials.

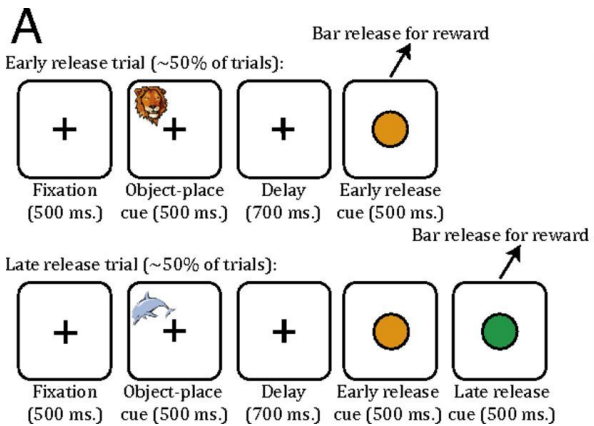
<u>Their hypothesis:</u>
The complexities and amount of information required to be maintained **exceeds the capacity of the rodent prefrontal cortex**, rats are forced to **solve spatial tasks using long-term memory resources**.



Sakon et al., Context-dependent incremental timing cells in the primate hippocampus, *PNAS* (2014)

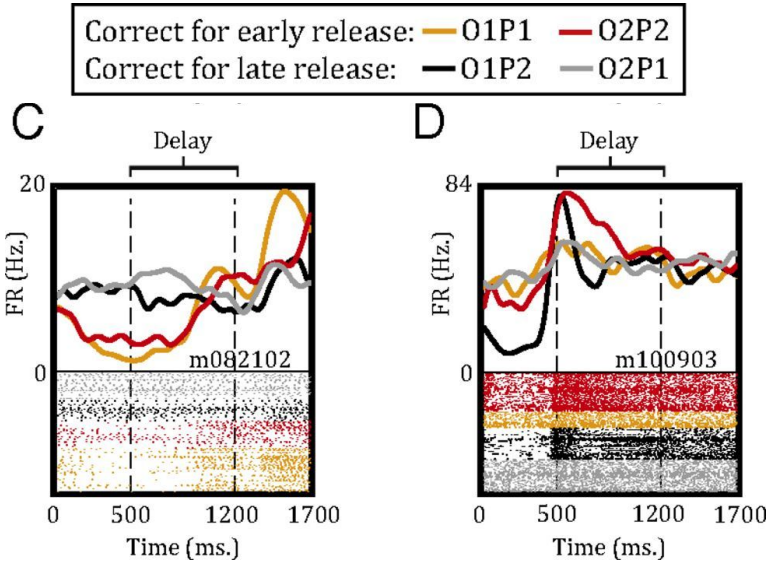
The results: found hippocampal cells with firing rates that incrementally increased or decreased across the delay: **incremental timing cells** (ITCs) of 3 categories:

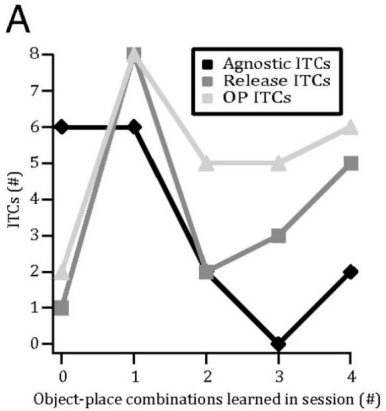
1. Agnostic ITCs did not distinguish between different trial types
2. cells tracking time depending on the behavioral action required for a correct response
3. cells tracking time only for those trials cued with a specific OP combination.



Sakon et al., Context-dependent incremental timing cells in the primate hippocampus, *PNAS* (2014)

Release-selective and OP-selective ITCs were found almost exclusively during sessions in which at least one new association was learned and the number of associations learned by the animal was significantly increased when these selective ITCs were recorded.





De Corte et al., The dorsal hippocampus' role in context-based timing in rodents (pre print), BioRXiv (2022)

https://www.biorxiv.org/content/10.1101/2022.01.10.475732v1.full

To act proactively, we must predict when future events will occur. Individuals generate temporal predictions using cues that indicate an event will happen after a certain duration elapses. Neural models of timing focus on how the brain represents these cue-duration associations. However, these models often overlook the fact that situational factors frequently modulate temporal expectations. For example, in realistic environments, the intervals associated with different cues will often covary due to a common underlying cause. According to the 'common cause hypothesis,' observers anticipate this covariance such that, when one cue's interval changes, temporal expectations for other cues shift in the same direction.

Kartik K. Sreenivasan1, and Mark D'Esposito,The what, where and how Nat Rev Neurosci. 2019*

"delay" = between sample presentation/sample stimulus and the response

The work reviewed above suggests three key points about delay activity. First, although delay activity has classically been described as sustained activation of highly tuned neurons or neural populations, the abundance of evidence for time-varying forms of delay activity and population coding indicates that a broader view of delay activity is necessary.

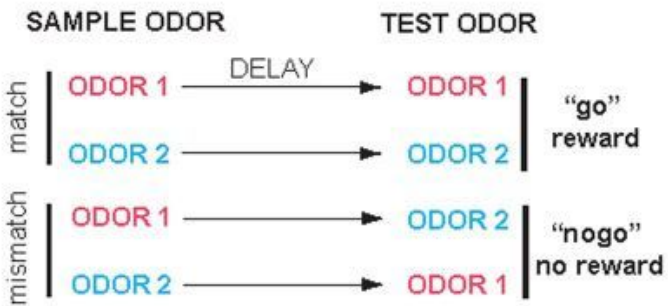
Extracellular recordings have documented increases in spike rate (relative to a pre-trial baseline) that persist throughout WM delays; for brevity, this finding is referred to as 'delay spiking' (Fig. 1a). Delay spiking is found in rodent PFC[8,9]; in various regions in the brains of non-human primates (NHPs), including prefrontal, parietal and sensory cortices[2,3,10–14]; and in human medial temporal lobe (MTL)[15,16].

Distinct Hippocampal Time Cell Sequences Represent Odor Memories in Immobilized Rats, Christopher J. MacDonald, Stephen Carrow, Ryan Place, and Howard Eichenbaum (J.Neurosci. 2013)

Pareil mais chez le rat

Odor memory was represented by a temporally organized ensemble of time cells composed mostly of neurons that were **unique to each memory** and some that fired at the same or different moments among multiple memories

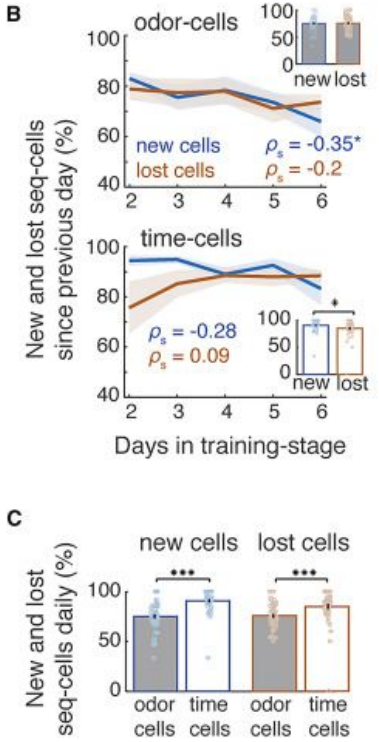
→ Hippocampal neurons encode successive brief moments that compose the flow of time within a distinct memory (without movement and spatial location).



Taxidis et al., Differential Emergence and Stability of Sensory and Temporal Representations in Context-Specific Hippocampal Sequences, Neuron 2020

On se demandait: si on change le delay, same time cells mais what about les event cells?

- Odor-cells were reliably activated and **retained stable fields** during changes in trial structure and across days.
- Time-cells exhibited sparse and **dynamic fields that remapped in both cases**.
- During task training, but not in untrained task exposure, time-cell ensembles increased in size, whereas odor-cell numbers remained stable.



Possible strategies in PA learning (in the litterature)

Smith et al., Age-related impairments on the touchscreen paired associates learning (PAL) task in male rats, Neurobiology of aging (2022)

- Select a stimulus based on a single feature domain (either its location or its identity) without considering the stimulus-location association (response-driven bias). If persistent, this stimulus or location bias would interfere with task acquisition.
  → **Egocentric response-based strategy**

- The implementation of reward heuristics, where the choice selection on a trial is a function of the reward or lack thereof received on the immediately preceding trial.
  → **Stimulus/Location win-stay**
  → **Stimulus/Location lose-shift**

Comme pas de PA avec spatial dans la litterature, pas d'autres

What has been shown/proven already:

- *mPFC neuronal activity was more concerned with representing a particular type (or types) of event relatively independent of its associated spatial location, and such coding for event-types gradually developed over time during learning.*
- *The above results strongly suggest a positive relationship between learning stage and the proportion of neurons whose spiking activities were significantly phase locked to theta oscillations across CA1 and mPFC. Activity in the two regions became more coordinated during the postylearning stage when object-in place strategy was used.*
- *Rats with prelimbic cortex - infralimbic cortex lesions did not learn the task and difference appeared at trial 240 approx.*
- *CA1 and CA3 function are disparate by the length of the delay between two elements (two odor pairs).*
- *Time cells firing patterns adapt and change when the length of delay period was modified while keeping behavior and spatial cues unaltered.*
- *Neuron events discretize the theta phase?*
- *Modification du délai post-learning (shikano et al.) in minutes*
- *JR Manns, MW Howard, H Eichenbaum, Gradual changes in hippocampal activity support remembering the order of events. Neuron 56, 530–540 (2007).*
- *Time cells found in rodents, NHP and humans. In rodents: CA1, CA3, mPFC and striatum*
- *Does the adaptation of time cells when a delay change affect the event cells (do they remain the same, does the brain consider this to be a “novel” event)*

What can be interesting to look at (not found in the litterature so far)

- To what extent a modification of the **ISI post-learning** affect the mice memory? How does the animal behave when given this new delay?
- Paired associates task with a **timing cue** (arm of the maze + waiting time) → Shikano + Sabariego mais en paired associates? “Time” as the event/cue, how does that affect the time cells for example?
- **Does/to what extent ISI affect the strategy** used in paired-associates learning? (to study the strategies we would have to change the forced closed door in the central arm).
- Changing the length of the delay period on a trial-by-trial basis in order to determine how context dependent ITCs respond in the face of changing task parameters.

“Temporality” of episodic memory? à quel niveau?

- ISI → WM & its load
- inter trial interval → memory retrieving, “delay activity”
- temporality of learning → multiple trials at once or few sporadic on various days?

3 - Time & event cells recap, cognitive “charge”, time as a coding term?

Time cells in the litterature

Global definition:

Time cells reliably fire at specific and consistent moments, or “time fields,” within a longer time interval (Umbach et al., 2020).

General characteristics (*but I don’t see a “precise” consensus*):

(1) each neuron encodes **discrete time** periods
(2) their time fields cover an **entire time period**, as represented by the sequential emergence of the time fields
(3) their time fields become broader the later they appear
(4) their time fields **develop as animals gain experience with the task**
(5) their time fields are scalable, correlated with animal’s timing behavior

Time cells in the litterature - “subtypes”

Category	Model?	When?	Characteristics
“Time cells” *(McDonalds et al., 2011)*	Rats (CA1)	ISI (0-20s)	- **fire concurrently and at successive time within the delay** between object&odor - generate a temporal signal although influences of variables such as the animal's location, direction, speed or velocity are statistically taken out - **temporal firing patterns adapt and change** when the length of delay period was modified while keeping behavior and spatial cues unaltered
“Minute encoding neurons” *(Shikano et al., 2021)*	Rats (CA1 & dorsal striatum)	Delay between a reward & reward (5min-8min)	- share the **same similarities** as second-range time cells
“Agnostic incremental timing cells”	Primate (HPC)	Delay between Object-Place presentation & action to take (700-1200ms)	- incrementally changed their FR during the delay period **similarly for all cues and trial types** - majority of agnostic ITCs cannot be explained by anticipatory or cue dissipating signals
“Release-selective ITCs”	//	//	- showed an incremental rise or fall in FR across the delay period **selective to either early release trials or late release trials** - //
“OP-selective ITCs”	//	//	- fired significantly differently to **particular OP combinations (with a min. of 15 trials)**. - the majority of those only showed this incremental change for a **single OP combination**. - //

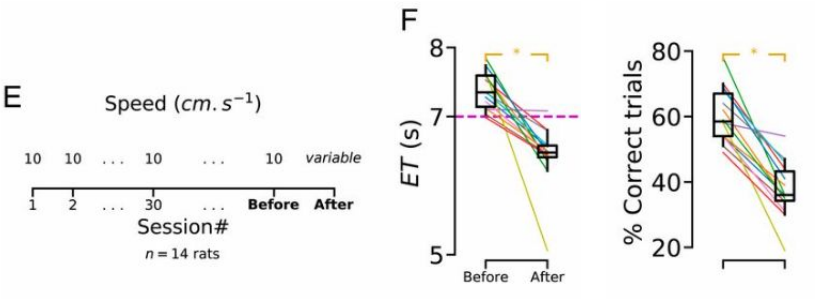
Time cells in the litterature - “subtypes”

Category	Model?	When?	Characteristics
“Temporally periodic cells” (Aghajan et al., 2022 preprint)	Human (entorhinal cortex mainly)	free watching of a 47min movie	- modulate their activity in a **periodic manner across different timescales**—from s to min - **remapped** their dominant periodicity to shorter timescales during the subsequent recognition memory task - when movie was presented at two different speeds, a significant % of TPCs maintained their timescales, suggesting a **degree of invariance with respect to the narrative content.**
“Ramping cells” (Tsao et al., 2018)	*Rats (entorhinal cortex)*	*?*	*pas d’accès à l’article Nature –* - *rather **long firing rate timescales** in which the firing may ramp down toward 0 over many minutes and in some cases may ramp or jump up from low rates to these high rates before starting another decrease in firing over a long period*
“Temporal context cells” (Bright et al. 2019)	Primate (entorhinal cortex)	free-viewing task with a 5s period after presentation of an image (this being the interest time)	- showing large deviations from baseline firing shortly after image onset but relaxing back to baseline at different rates. - the range of relaxation rates allowed for the time since image onset to be decoded on the scale of seconds. - carry info about when an event took place + the identity of that event.
“Temporal context cells” (Howard&Hasselmo, 2020 preprint)	Primate (entorhinal cortex)	Based on Tsao et al., 2018 and Bright et al. 2019	- the theory of their model: time cells in the HPC can be described as a compressed estimate of events as a function of the past (concept of memory being compressed), while TCC (entorhinal) are a Laplace transform of the function of the past.

Safaie et al., Turning the body into a clock: Accurate timing is facilitated by simple stereotyped interactions with the environment, PNAS (2020)

The objective: Elucidating the coding of time and its link with spatial navigation: does motor routines improve timing accuracy?
The task: freely moving animals on a motorized treadmill could obtain a reward if they approached it after a fixed interval (7sec)

The results: Most animals took advantage of the same motor routine whose execution resulted in the precise timing of their reward approaches. When proficient animals did not follow this routine, their temporal accuracy decreased. When trained with a task to remove the routine, the animals didn't reach comparable level of accuracy.



→ As animals use disembodied internal neuronal representations of time, we absolutely need to block the animal as mostly as possible

Toso et al., Time coding in rat dorsolateral striatum, Neuron (2021)

The objective:
assess the role of DLS in time coding

The task:
comparison of the durations of two sequential vibrations + in vivo recordings

The results:
1- DLS did not show a stronger representation of the stimulus duration compared to other delays/time spans.
2- While **higher intensity vibrations were perceived as longer, time decoded from DLS activity was not affected**
3- DLS did not encode stimulus duration differently on correct versus incorrect trials
4- Observation of a persistent activity in DLS of those cells even when time is not relevant in the task

→ **Time is inherent of the dorsolateral striatum, has no link with the rat doings**

Tunes et al., Time encoding migrates from prefrontal cortex to dorsal striatum during learning of a self-timed response duration task, eLife (2022)

The objective: We investigated how the time encoding evolves when animals learn to time a 1.5 s interval

The task: Animals had to remain in a nose poke for at least 1.5 s to receive access to the sucrose solution, limited to three licks, after which the access gate closes. Rats go from naive- to proficient-level timing performance within a single session.

The results: Early in training the dynamics of the medial prefrontal cortex provides the best code for time, but later in training the striatum provides a better code. (If a brain area is involved in the encoding of that interval, a trial-dependent and more structured spiking activity must emerge due to learning.)

Event cells in the litterature - “Subtypes” or similar cells

Subtypes:

Category	Model?	When?	Definition/characteristics
“event cells” (Terada et al., 2017)	Rats (CA1)	Integration of sound and odor cues associated with left or right lever pulls	Sensory cue-, combination-, or choice-specific (simply, “event”-specific) elevated discharge activities, which were sustained throughout the event period. These event cells underwent transient theta phase precession at event onset, followed by sustained phase locking to the early theta phases.
“event-specific neurons” (Mazuski et al., preprint 2021)	Rats (basolateral amygdala)	freely-moving rats as they interacted with different ethological stimuli: male or female rats, a moving toy and food.	Over 20% of neurons showed highly tuned *event-specific* responses to a single class of stimuli. Firing persisted in 30% of these responsive cells for minutes after the removal of the eliciting stimulus. Neural information flowed directionally from event-specific neurons to less specific neurons with changes in connection strength after removal of the stimulus. We propose that the basolateral amygdala identifies specific ethological events, with circuit-wide activity driven by the event-specific neurons during and after the termination of those events likely facilitating active short-term memory consolidation.
“context-specific	*Rats (just*	*hippocampal neuronal activity was*	*Pyramidal neurons developed robust context-specific responses to*

4 - Sequential relationship among events, temporal information over different timescale, time awareness in mice

Shahbaba et al., Hippocampal ensembles represent sequential relationships among an extended sequence of nonspatial events, Nature Communications (2022)

Mau et al., The Same Hippocampal CA1 Population Simultaneously Codes Temporal Information over Multiple Timescales, Current Biology (2018)

5 - Protocols

Basics of our task

- We chose/stick with paired associates memory paradigm because it is described in the literature as a **classic paradigm** to test episodic memory in **both animals and humans**

- We chose/stick with a **spatial navigation task** because of the HMJB objectives/interests and the brain region involved

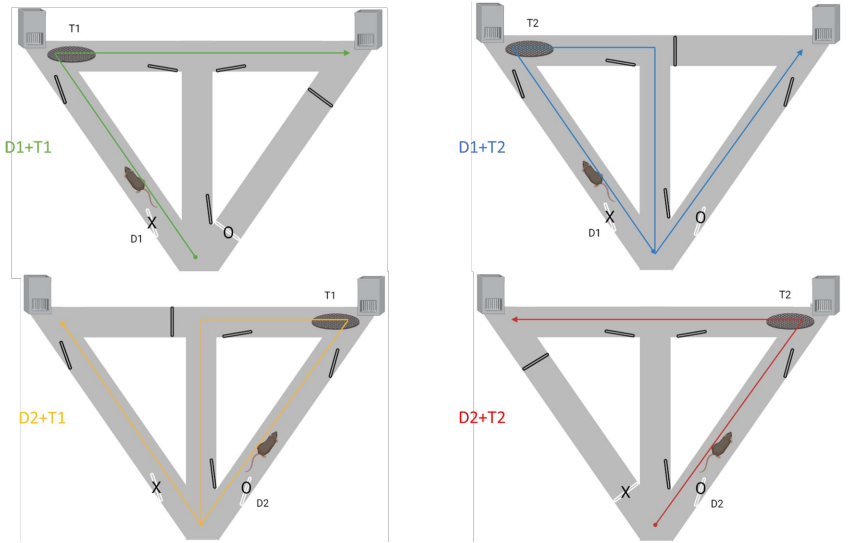
- We chose/stick with the addition of a **temporal aspect in the task** because of the eXplAIn objectives/interests

What is tricky with the current protocol?

Testing at the same time:

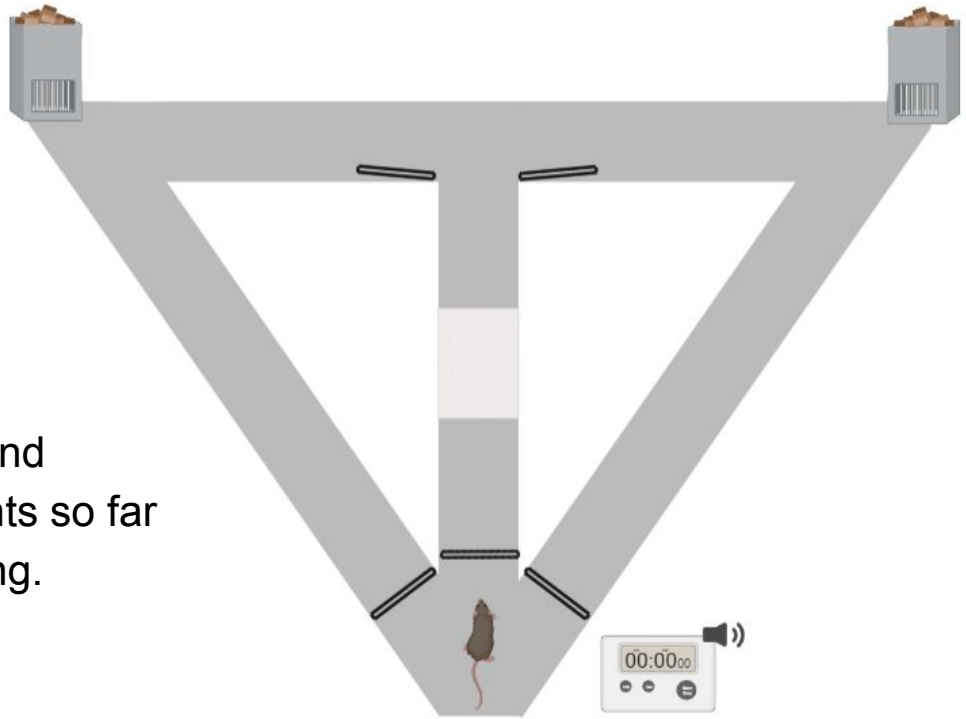
- cognitive and physical effort
- autonoetic consciousness (time)
- spatial memory
- paired associates learning
- time and its effect on learning path that vary in their difficulty and length

There is a need to simplify the task and prioritize what's important.



1st proposition: XOR with timing cue

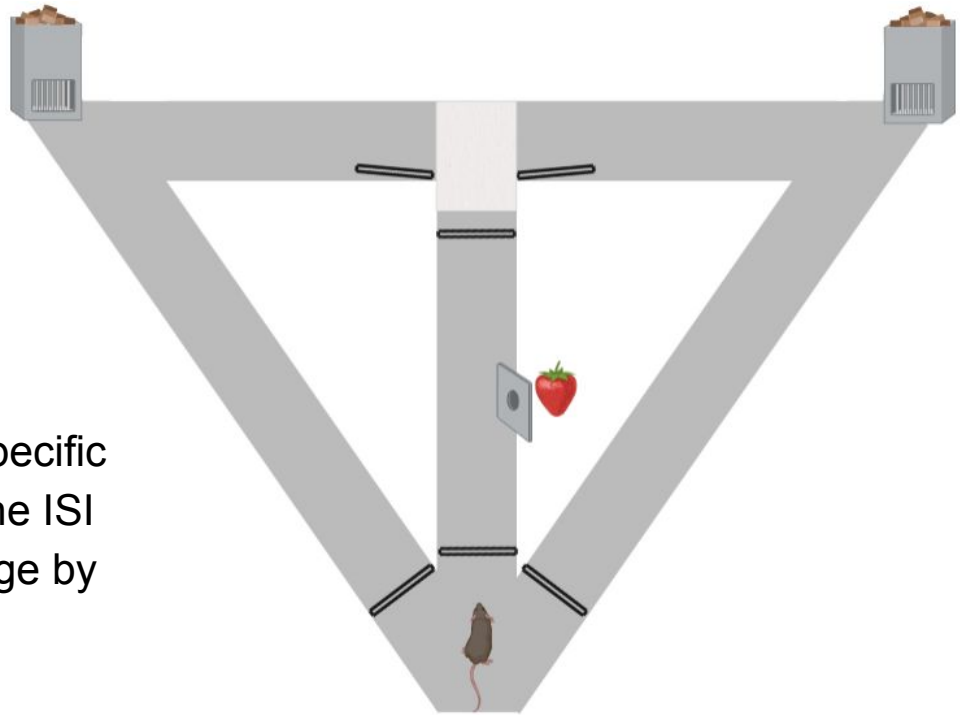
5sec + Texture 1 = LEFT
30sec + Texture 2 = LEFT
5sec + Texture 2 = RIGHT
30sec + Texture 1 = RIGHT



- The delay starts & ends with a sound
- XOR has not been tested on rodents so far and might be cognitively challenging.

2nd proposition: XOR without timing cue

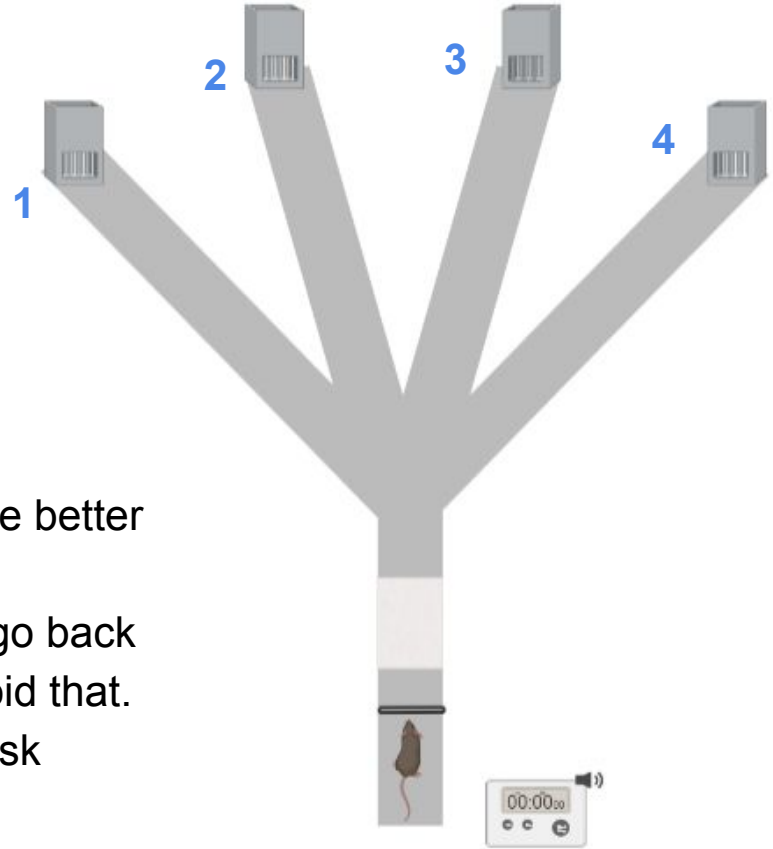
Ordor 1 + Texture 1 = LEFT
Odor 2 + Texture 2 = LEFT
Odor 1 + Texture 2 = RIGHT
Odor 2 + Texture 1 = RIGHT



- The odor can be presented for a specific period of time and we can act on the ISI
- Reduce the XOR cognitive challenge by removing the timing cue

3rd proposition: 4 combinations with 5 arms maze

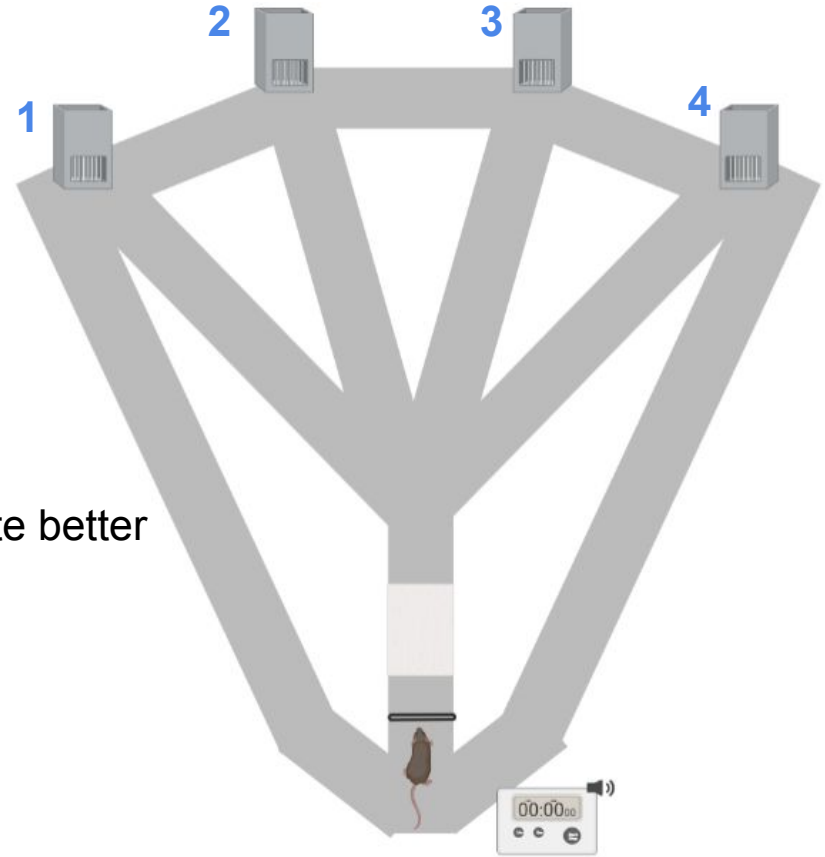
5sec + Texture 1 = Arm 1
30sec + Texture 2 = Arm 2
5sec + Texture 2 = Arm 3
30sec + Texture 1 = Arm 4



- The delay starts & ends with a sound
- The 4 arms allow the animal to differentiate better the 4 combinations.
- BUT animal has to make a turnaround to go back to starting box or to be manipulated to avoid that.
- BUT we are losing the “spatiality” of the task

3rd proposition: 4 combinations with 5 arms maze

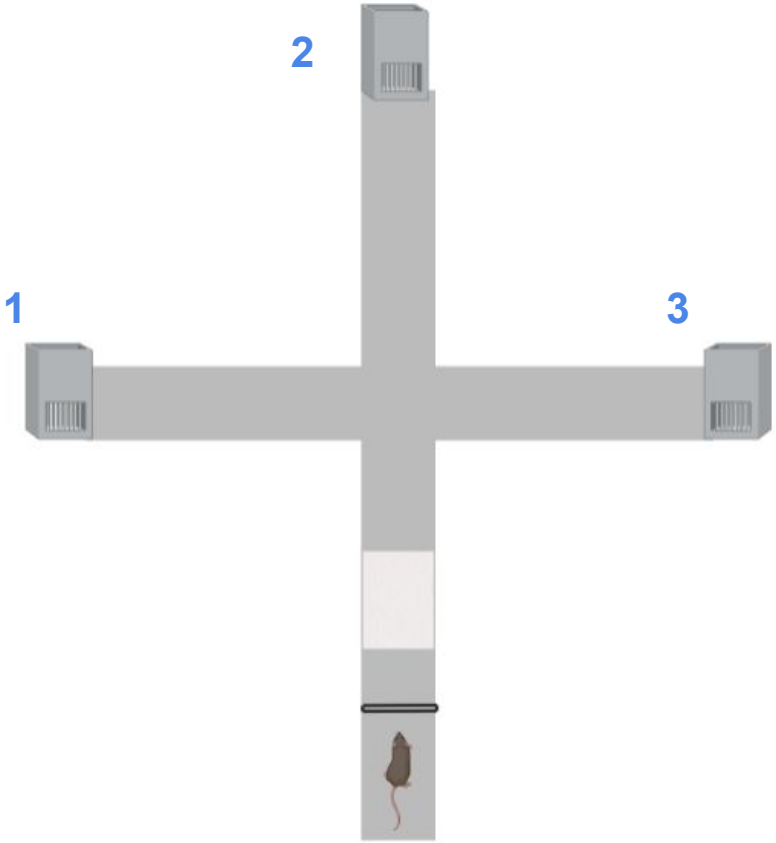
5sec + Texture 1 = Arm 1
30sec + Texture 2 = Arm 2
5sec + Texture 2 = Arm 3
30sec + Texture 1 = Arm 4



- The delay starts & ends with a sound
- The 4 arms allow the animal to differentiate better the 4 combinations.
- BUT we are losing the “spatiality”

5th proposition: 3 combinations with cross maze?

5sec + Texture 1 = 1
30sec + Texture 1 = 2
5sec + Texture 2 = 3
30sec + Texture 2 = 1



- The delay starts with a sound and end with a sound.
- The 3 arms allow the animal to differentiate
- Mentally challenging??? Only one OR compared to 2 OR in the XOR
- BUT we are losing the “spatiality”

Report

contrainte temporelle niveau info
coACA reinforcement learning: l'intéret du papier d'Ashwin c'est qu'on a la durée des états cognitifs, donc on aimerait contraindre cette durée (ces états cognitifs) et voir l'impact que ca a sur l'animal (chunking) donc ca ouvre la porte à appliquer coACA sur une nouvelle expé avec contrainte d'une durée
contrainte hérité de l'etat de l'art du machine learning, respect de la contrainte, montage d'un nouvel expe., et qu'on peut appliquer coACA

Report outline

1.

Notes zoom

Learning forcé ou exploratoire?

Sabariego et al., In the temporal organization of episodic memory, the hippocampus supports the experience of elapsed time, Hippocampus (2020) → to test the time forced first then free to criterion

Terada (2017) → Training periods of rats for this task were 7~9 weeks. In the first stages of leaning, the odor cues were randomly presented in each trial whereas the auditory cue was fixed one type of sound (i.e., odor-discrimination task in one sound context; ~1 week). In the second stage, the auditory cue was now fixed to the other type of sound (i.e., reverse leaning of odor-discrimination task in the other sound context; ~1 week). In the third stage, we repeat this process but gradually decrease the numbers of sessions between reversals of sound cues (~2 weeks). In the fourth stage, we introduced sound reversal within a single session. We gradually increase the frequency of sound reversals in a session (~2 weeks). In the last stage, presentations of sound and odor cues were totally randomized (~2 weeks).

Rajji et al. on mice (2006) → Before the AAV injections, mice (AAV–*Cre* group, $n = 7$; AAV–*LacZ* group, $n = 6$) were trained for 5 d on the paired associates problem; all mice reached a level of >75% correct of eight trials by day 4, and this level was maintained on retesting with eight trials on day 5

Favorik et al. (2010) → Animals were trained in successive stages. Initially, rats were trained to dig for reward (one Froot Loop) buried in a cup filled with unscented sand. Once the animals had learned to dig reliably to retrieve the reward, they were introduced to the task.

Kesner et al. (2003) → All rats completed pretraining within a 2-week period, with the total time spent at each stage tailored to the individual rat. First, the rats were introduced to the testing apparatus with the food reward placed randomly throughout. The rats were then shaped only to search for food in food wells with an object nearby (not an object used during testing), and finally rats were shaped to displace an object in order to obtain food located in the well underneath.

Ross et al., The Hippocampal Horizon: Constructing and Segmenting Experience for Episodic Memory

A hippocampal network for spatial coding during immobility and sleep:
interstimuli delays place cells: When an animal is slowly moving or immobile, the self-position representation is understood to be signalled by a subset of cornu ammonis 2 (CA2) place cells, in which their firing rate displays an atypical negative correlation with speed compared to other place cells (Kay et al., 2016).

Reward-associated cells in CA1 and subiculum were found to be either active at the location after reward delivery or strikingly, before obtaining the reward (reward-predictive cells; Gauthier & Tank, 2018). Such reward-associated cells were context-dependent or context-invariant to the external virtual environment and the reward-predictive neurons were correlated with slowed running behaviour indictive of reward anticipation (Gauthier & Tank, 2018).

Another reported temporal hippocampal phenomenon was termed event-specific rate remapping (ESR) activity (Sun et al., 2020). Mice were trained to run four consecutive laps in a square maze, the environment and task was identical, apart from the first lap being rewarded in a start box, acting as a temporal marker. Calcium imaging indicated that ~30% of the given CA1 cells had a peak activity rate for a given lap number that was preserved across days, hence termed ESR, and these cells conjunctively represented place coding, but this was separable from ESR activity (Sun et al., 2020). Crucially, when each lap was rewarded following a previous day of the standard one-in-four lap reward experiment i.e., removal of the temporal marker, ESR activity was abolished. Furthermore, some cell's activity could be described as 'counting', in that they had ESR activity for lap four (the last lap before a new trial) yet showed a progressive increase across laps until displaying maximal rate for lap four (Sun et al., 2020), similar to the ramp-like activity reported in CA1 minute time cells (Shikano et al., 2021).

Interval timing and the encoding of signal duration by ensembles of cortical and striatal neurons

https://www.scopus.com/record/display.uri?eid=2-s2.0-0042666924&origin=inward&txGid=5d3d7a9a8978a365168bc4cd3d877ea9

Cognitive effort

For example, when deciding whether to perform the bare minimum at the office or to exceed expectations in the hope of promotion, one of the key costs we are evaluating is the cognitive effort required for the potentially more lucrative task. In human laboratory studies aimed at investigating the neurobiological basis of effort, the difficulty level is most often varied by increased cognitive demands such as attention or executive control (Botvinick et al, 2009; Croxson et al, 2009; McGuire and Botvinick, 2010; Naccache et al, 2005; but see Treadway et al, 2009).

The task: In order to investigate whether rats are sensitive to differences in mental effort requirements when making decisions, we therefore designed a novel rat cognitive effort task (rCET) with costs more closely analogous to human studies, and conducted some pharmacological challenges to assess the task's utility for studying the neurobiology underlying this process.

https://link.springer.com/article/10.3758/s13423-014-0772-5

The goal: The aim of the present study was to examine the impact of an essential factor of WM performance, namely cognitive load, on episodic memory.

This study shows that both working and episodic memory traces depend on the cognitive load of the concurrent task, whereas the use of rehearsal affects only working memory performance.

Usually, harder strategies involve more and/or more complex steps, require more effort to execute, and are more demanding in processing resources. In the memory domain, complex strategies based on deep encoding usually yield better performance (e.g. Craik and Lockhart, 1972, Paivio and Csapo, 1969). An example of an efficient memory strategy is mental imagery, which involves linking the word to be memorized to a corresponding visual representation (i.e., representational processing, Paivio, 1986), but it requires a relatively long time to be correctly implemented (Paivio and Csapo, 1971, Plaie and Thomas, 2008). By contrast, rote repetition involves perceptive-lexical encoding, which requires less time and fewer cognitive resources and thus leads to shallower encoding (Tulving and Thomson, 1973, Froger et al., 2012).

Cognitive computation using neural representations of time and space in the Laplace domain

The results: Time cells in the hippocampus and temporal context cells in the entorhinal cortex both code for events as a function of past time, but with very different receptive fields.

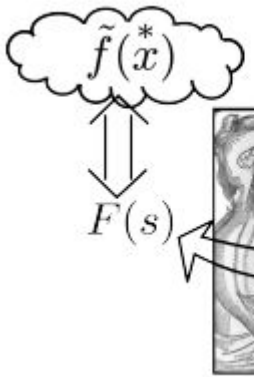
The basic idea is that the firing rate of populations of neurons represent functions out in the world. Some populations do not represent these functions directly, but rather represent the Laplace transform of functions.

The brain tries to estimate functions f(x) out in the world. The brain's estimate of this function is denoted ˜f(∗ x). In many cases, it is not practical to directly compute ˜f(∗ x). Instead the brain first estimates the Laplace transform of f(x), F(s) and then constructs ˜f(∗ x) by inverting the transform via an inverse transform operator L -1 k .

The observation that memory is less precise for less recent events has led to the proposal that this record of the past is compressed, such that the time at which recent events occurred has better resolution than events further in the past

Hippocampal cells as a compression of time:
" Hippocampal time cells have the computational properties one would expect of a compressed representation of what happened when as a function of past time. First, different external distinct sequences of hippocampal time cells (MacDonald et al., 2011; Terada et al., 2017; Taxidis et al., 2018; Cruzado et al., 2019), meaning that these populations carry information ab happened in the past. Second, hippocampal time cells show decreasing temporal accuracy further in the past. The number of cells with receptive fields around a particular value ∗ τ o go up. Moreover, the width of receptive fields go up with ∗ τ o"

Entorhinal:
Cells coding the Laplace transform of a variable x should show receptive fields that fall off like e −sx. A set of neurons coding the Laplace transform of past time τ should show receptive −sτ , with many different values of s across different neurons. Recent evidence shows that cells in the entorhinal cortex contain temporal information, like hippocampal time cells, but wit fields that are as we would expect from the Laplace transform (Figure 2C, (Bright et al., 2019)). These "temporal context cells" are analogous to findings from a rodent experiment record entorhinal cortex (Tsao et al., 2018).



Rolls et al.: The Generation of Time in the Hippocampal Memory System, Cell Reports (2019)

The objective: theory of why and how time is organized in the hippocampal system

McDonald et al., Crucial role for CA2 inputs in the sequential organization of CA1 time cells supporting memory, PNAS (2021)

https://www.pnas.org/doi/abs/10.1073/pnas.2020698118

https://www.cell.com/neuron/fulltext/S0896-6273(18)30687-1?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0896627318306871%3Fshowall%3Dtrue