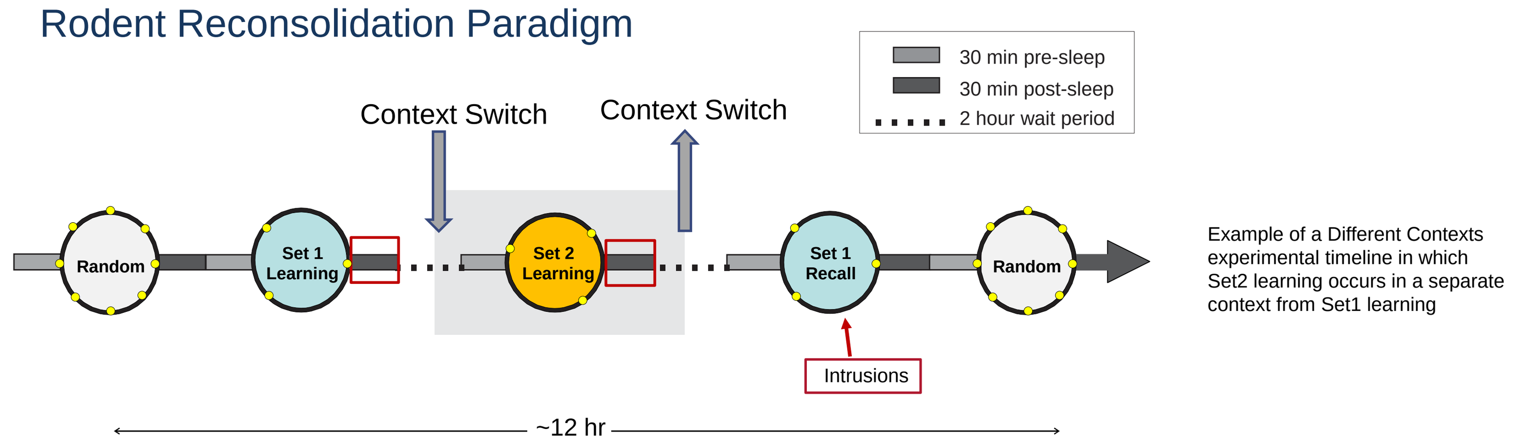
Reactivation of Interfering memories in the hippocampus shapes memory performance: a computational study.

Paola Malerba[1], Stephanie Nagl[2], Jean-Marc Fellous[2], Maxim Bazhenov[1]
[1]University of California San Diego, Department of Medicine, [2]University of Arizona, Department of Psychology

Neuronal replay is considered a mechanism by which the interaction of hippocampal and cortical activity during sleep can result in memory consolidation. In particular, reactivation of patterns coding for recently learned tasks is known to happen at least in part during sharp-wave ripples (SWRs), which are short-lived highly synchronous events which start in area CA3 and propagate to area CA1, where stratum pyramidale shows high frequency (>150Hz) ripples. Here we study how reactivation of multiple memories during sleep can inform performance on later recall.
Using a reconsolidation paradigm, our rodent data show that the reactivation of competing memories is related to memory recall performance. Specifically, when two different sets of locations (Set1 and Set2) were learned, the amount of Set1 place cell reactivation during the SWRs recorded in sleep after learning Set2 correlated with lower performance when recalling Set1. Furthermore, if the two sets were learned in different contexts, this "interference" was reduced.
We investigate how sleep reactivation of different memories can influence their respective recall performances in a biophysical model of CA3-CA1 spontaneous SWR activity. In the model, we represent Set1 and Set2 by groups of pyramidal cells in both CA3 and CA1 with enhanced synaptic connections among them. After quantifying the spontaneously emergent reactivation of Set1 and Set2, we modify network connections according to the degree of shared reactivation, to represent the cumulative effect of reactivation-induced synaptic plasticity. We then quantify the recall performance of both Sets by stimulating a small portion of cells belonging to a given set and measuring the spike pattern completion. We introduce a similarity measure between the two memories, by gradually changing the degree of overlap between Set1 and Set2 cells. We find that the degree of similarity between the two sets influences their common reactivation during sleep and the degree of intrusions of cells from the wrong Set during memory recall tests. Within the range of similarity considered, we identify which configuration of Set 1 and Set2 overlap can account for behavioral performance in the same or different context.
We conclude that memories with similar representation in the CA3-CA1 network can undergo spontaneous reactivation during sleep which will encode their degree of similarity. In turn the mixed reactivation can result in synaptic plasticity shaping recall performance. We predict that testing recall of memories learned in contexts with gradual level of differentiation will show a proportional level of intrusions during sleep, and hence in performance.

Rodent Reconsolidation Paradigm



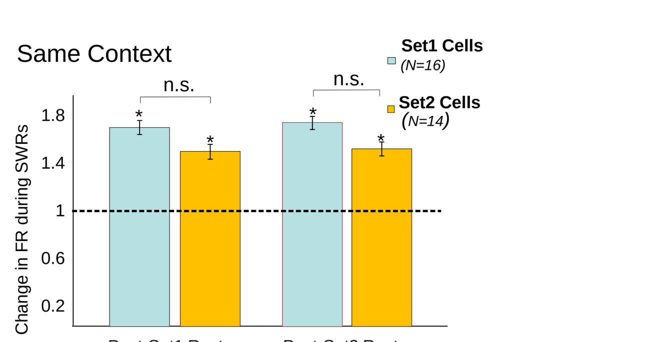
Example of a Different Contexts experimental timeline in which Set2 learning occurs in a separate context from Set1 learning

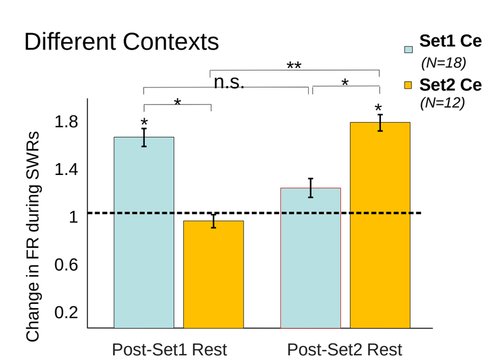
- N = 4 Brown Norway rats
  - 14 Same Context experiments
  - 14 Different Contexts experiments
- Each Context = unique combination of carpet, maze color, local cues, global cues, curtain configuration and scent

- Set: Three-non-overlapping feeder locations viable for reward in random order. Light cue on first 75 rewards, after which cue-delay phase begins
- Intrusion error: Calculated as the percent of feeders visited during Set1 Recall that belonged to Set2
- Set1 Recall criterion: Rat receives one initial light cue, and then proceeds directly to cue-delay phase

Results

Cells in the Different Contexts, but not the Same Context condition, show higher firing rate in SWRs than baseline following the task in which they were selectively active.

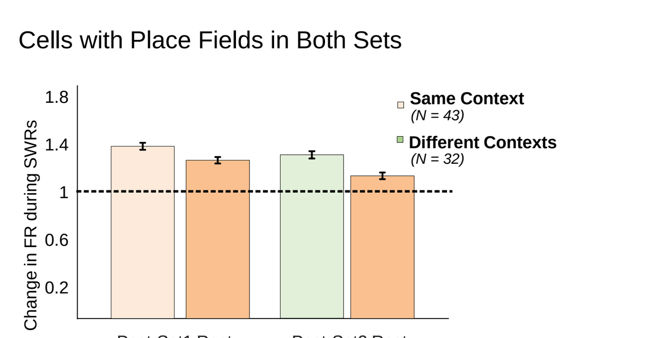


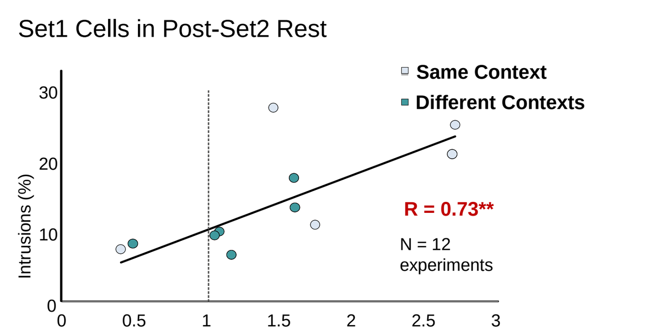


- Set-specific cells show higher firing rate from baseline in SWRs in the Same Context condition, but do not significantly differ from each other in either post-learning rest session

- When Set2 is learned in a different context, the firing rate of Set1 cells in SWRs is significantly reduced in Post-Set2 Rest ripples

All error bars represent SEM. ** p < 0.01 * p < 0.05



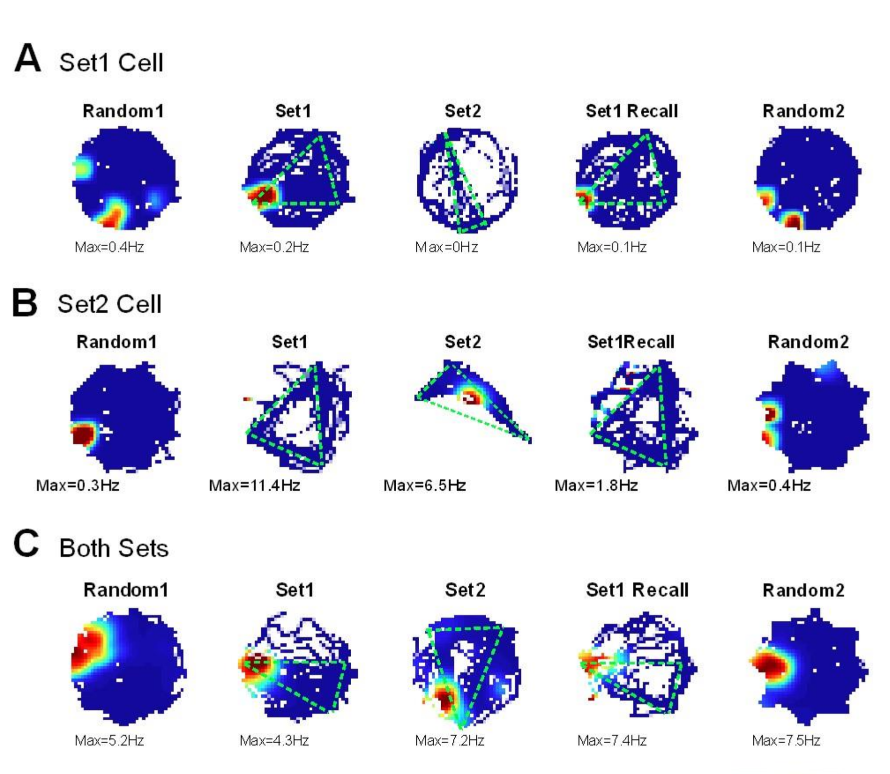


- Cells that had place fields overlapping at least 10% with both Set1 and Set2 during learning sessions did not show significantly altered firing rate from Post-Set1 Rest to Post-Set2 Rest in either condition

- Higher firing rate of Set1 cells in Post-Set2 Rest SPWs correlates with higher intrusions in both experimental conditions

Place Cell Categorization

Single unit recordings from dorsal CA1



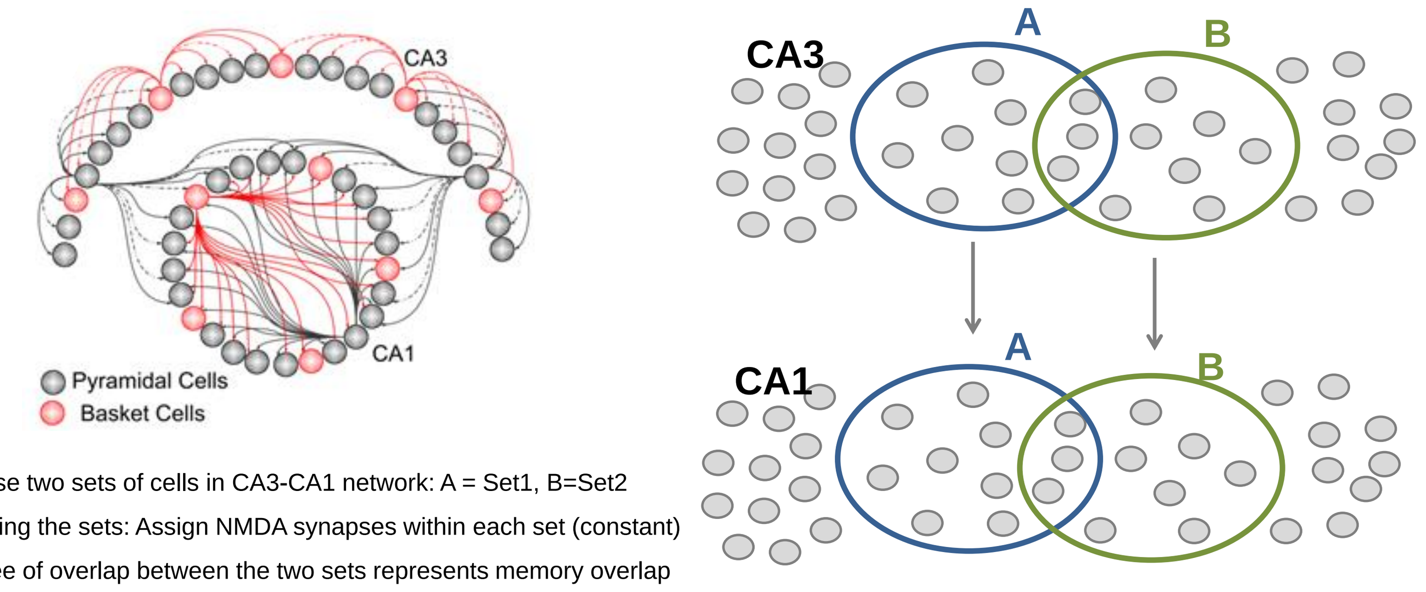
Examples of the three categories used to putatively characterize distal CA1 place cells in relation to the tasks. Blue represents actual track data. Dotted lines represent idealized trajectories for the particular Set. All Set learning data taken from the cue-delayed portion of the task.

Set1 Cell: Place field (PF) shared > 10% overlap with Set1 trajectory and < 1% overlap with Set2 trajectory.

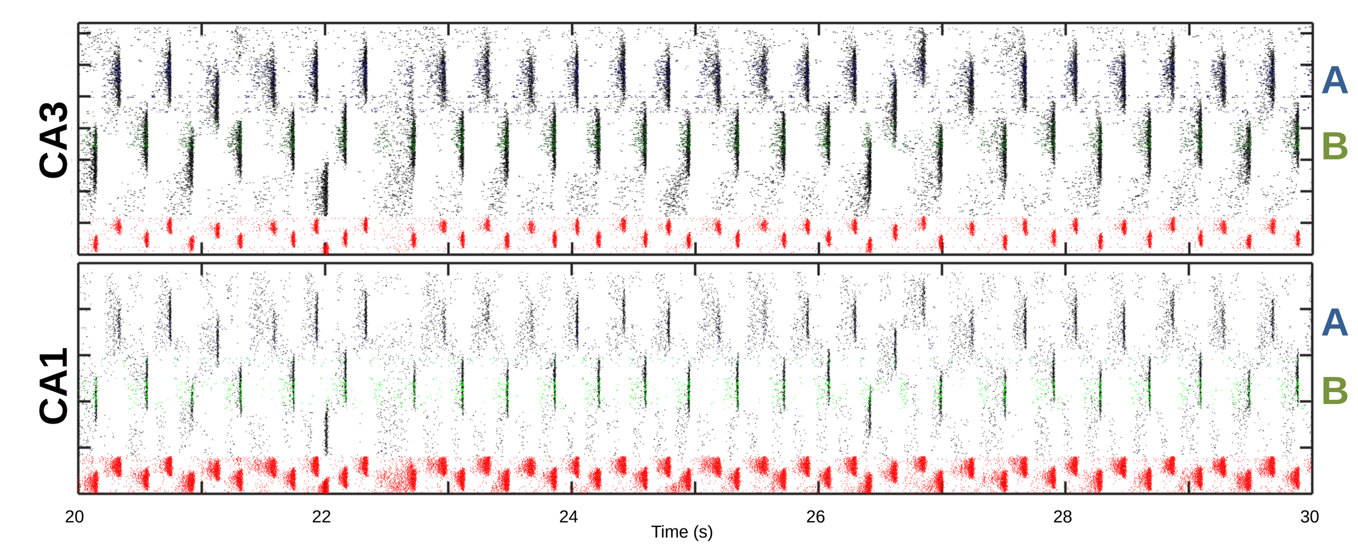
Set2 Cell: PF > 10% overlap with Set2 trajectory and < 1% overlap with Set2 trajectory

Both Sets: PF > 10% overlap with Set1 trajectory and > 10% overlap with Set2 trajectory

Biophysical Model of SWR activity with Set1 and Set2 cells

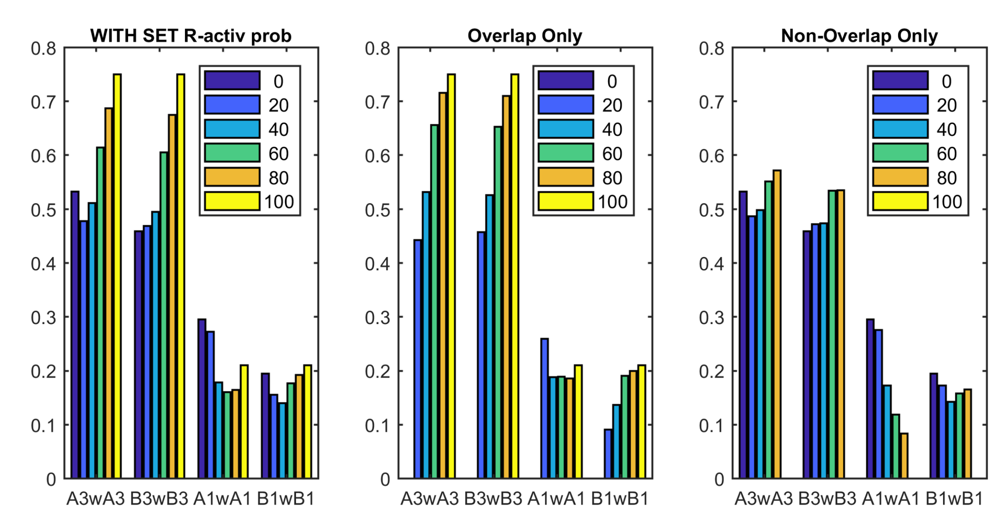


- Choose two sets of cells in CA3-CA1 network: A = Set1, B=Set2
- Learning the sets: Assign NMDA synapses within each set (constant)
- Degree of overlap between the two sets represents memory overlap



Example of sleep model activity, spikes in time are represented with dots. Different cells on different rows. The overlap Between A and B is set at 20%. Black = Pyramidal cells, Red = Basket Cells, Blue = Cells of Set A, Green = Cells of set B

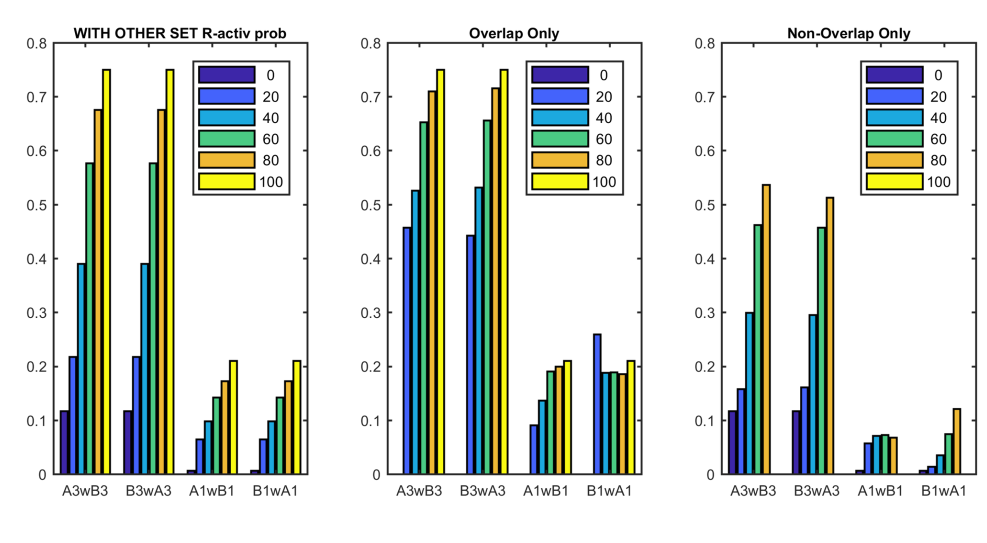
Co-activation of cells in Set A and Set B during sleep depends on Overlap

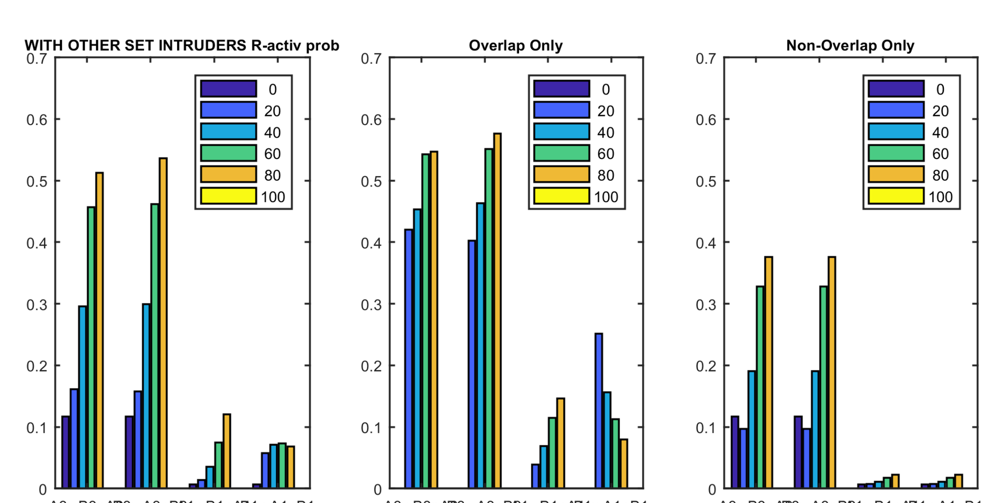


Average across 10 simulations, 50s each

- Overlap promotes activation of cells within the same set in CA3, less in CA1
- In CA3 more overlap creates more co-activation in cells within the overlap, but not in the others
- Set A and B in CA1 show different profiles when only overlap or only non-overlap cells are considered: recent learning interacts with past learning in network reactivation

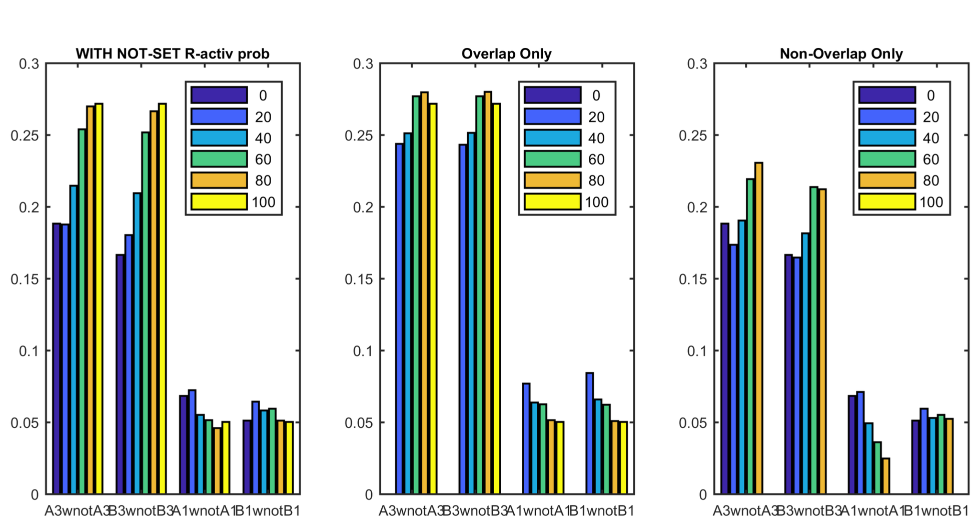
- Overlap promotes activation of cells within the opposite set in both CA3 and CA1
- In CA3 cells in the overlap and not in the overlap reactivate more with cells from the other set
- In CA1, A cells in the overlap increase their activation with cells from the other set but not those out of the overlap. B cells show the opposite behavior.





- Overlap promotes activation of cells with intruders in both CA3 and CA1.
- In CA3 cells in the overlap and not in the overlap reactivate more with intruders cells
- In CA1, cells not in the overlap do not activate with intruders. Cells in the overlap reactivate more with intruders for increasing overlap for set A and less for set B.

- Overlap promotes non-specific activation of set cells in CA3
- In CA1 the selectivity of set B is not dependent on overlap, and the selectivity of set A improves with overlap
- Differential rules of ripple activation in CA3 and CA1 influence the content of ripple replay.



Consolidation: using co-activation during sleep to shape connections after sleep

Frequency Index of one cell = fraction of all ripples in which it spikes [F(c1)]

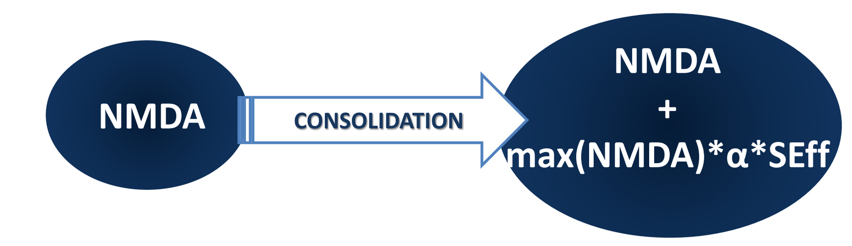
Frequency Index of two cells = fraction of all ripples in which they spike together [F(c1,c2)]

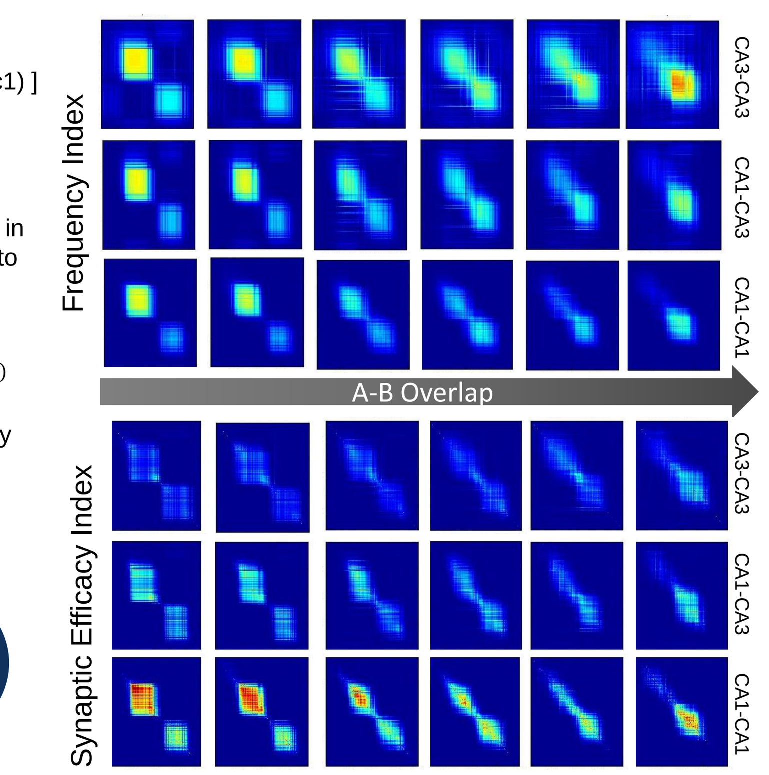
Cells in sets A and B reactivate during sleep with many cells not included in either sets. This stays true at all overlap levels tested. For consolidation to be effective, it has to be selective.

Synaptic Efficacy Index:

$$\mathrm{SEff}(c1,c2) = {F(c1,c2)^3}/{F(c1)F(c2)}$$

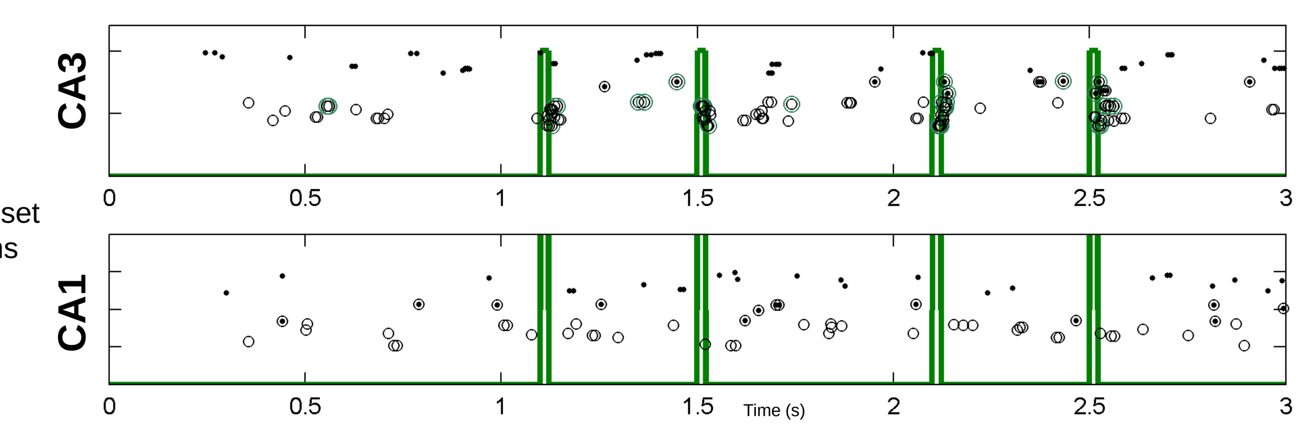
SEff is based on co-activation: high for cell pairs which activate selectively together, low for cell pairs which activate often but not only together





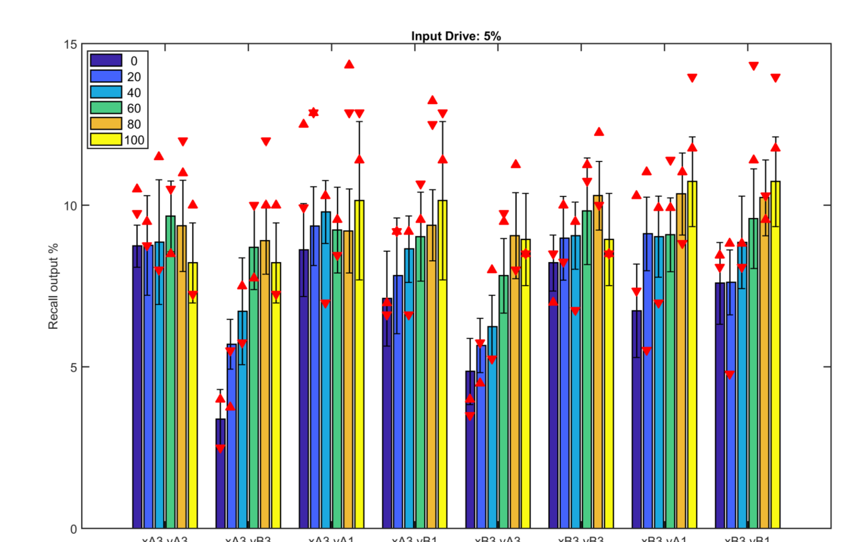
Recall: quantify set activation and intrusions in response to brief inputs

- Stimulate a some cells from set A in CA3
- Measure recall of set A or B within 200ms

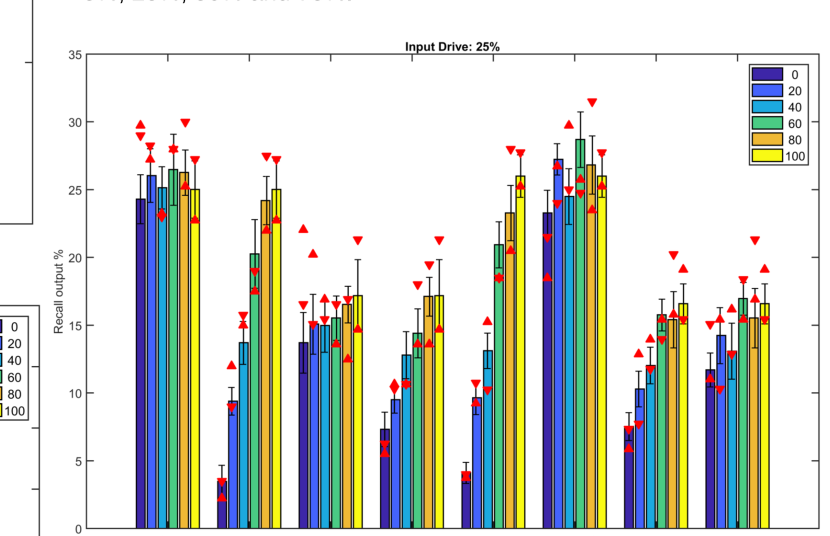


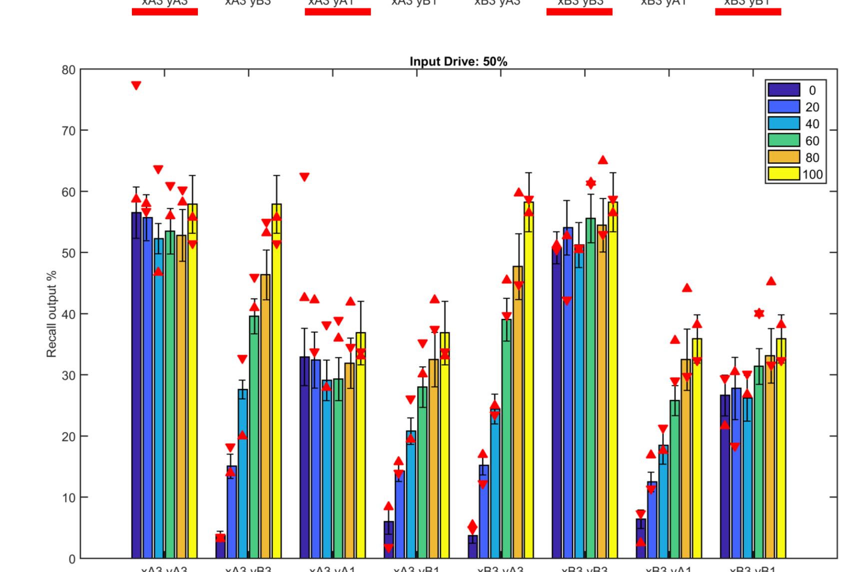
Example of awake model activity, spikes in time are represented with dots. Different cells on different rows. Overlap between A and B is 20%. Fraction of Set A cells receiving input is 25%. Black dots = Set B cells, Black circles = Set A cells, Green circles = cells receiving input
Green Trace shows when input is delivered (ONLY to CA3). The recall % for a simulation test is given by the fraction of cells in the set that spike up to 200ms after input onset, averaged across 8 input deliveries.

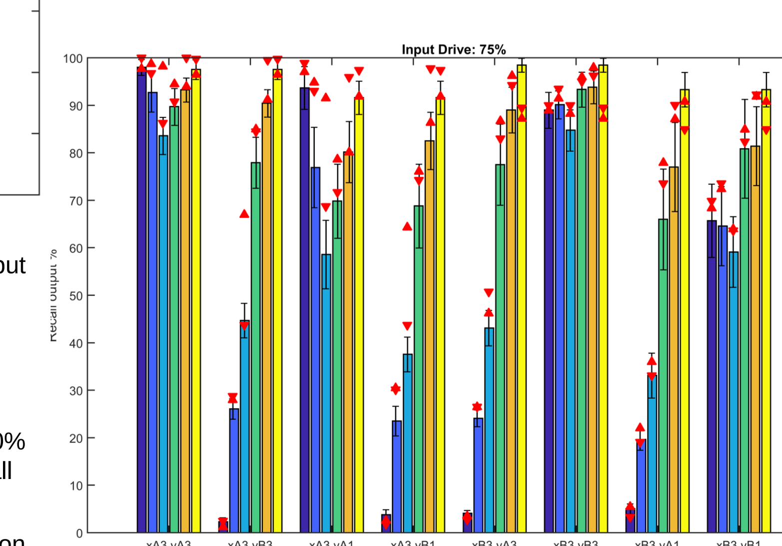
Recall shows consistent output in CA3 and CA1. Consolidation promotes correct recall and intrusions. Increased overlap promotes interferences at recall.



- xA3 yA1 = input delivered to set A in CA3, while the recall is quantified for cells in set A in CA1. red lines highlight "with set" (correct) recall
- bars: recall without consolidation (α=0). Mean: average across 10 recall tests (8 input deliveries each). Errorbars: standard deviation.
- red markers: recall with consolidation (α=1). 2 recall tests per condition are shown.
- The amount of input set receiving stimulus at recall is tested at 5%, 25%, 50% and 75%.







- Recall with other set (intrusions) depends on overlap for all input drives.
- Recall measured in CA3 is consistent with recall in CA1.
- Comparison to experimental data suggests the case of 20% overlap with 25% input drive could represent Set1 and Set2 recall
- Consolidation promotes "with set" and "with other set" reactivation at intermediate input drives

Conclusions

- Experimental results connect increased sleep co-activation of cells in different sets with increased intrusions at recall
- Model of CA3-CA1 sharp-wave ripple activity shows that co-activation of two memories can be modulated by shared synaptic connections
- Overlap promotes non-specific activation of set cells in CA3 during sleep
- Memory A and B are affected differently by overlap in CA1: newly learned memories interact with past memories during sleep
- Awake recall performance "with set" is not dependent on overlap, while recall "with other set" is.
- Sleep-dependent consolidation of selected synapses can promote recall of both correct and intruding cells.

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