Neurophysiological correlates of the influences of spatial context on hippocampal reactivation in a rodent reconsolidation paradigm

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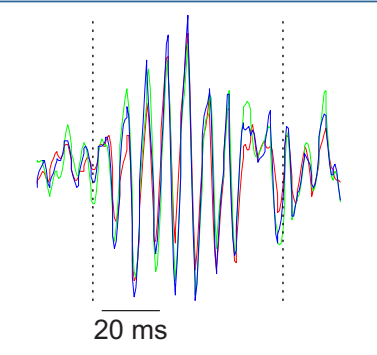
Introduction

- Sharp-wave ripples (SPWs) are high-frequency hippocampal oscillations implicated in memory consolidation.
- This is frequently demonstrated by reactivation in slow-wave sleep of recently active place cells in the rat CA1 hippocampal region, though "preactivation" has also been described (Dragoi and Tonegawa, 2011).
- Reactivation is thought to reflect pre-existing dynamics, spatial context, cognitive demand, novelty, or some combination (Grosmark et al., 2015, Kovacs et al., 2016; Larkin et al., 2014; Girardeau et al., 2014).
- We previously found significant correlations between SPW density and performance when rats were tested on set learning up to six hours later (Nagl et al., submitted).
- We study the contributions of SPWs to (re)consolidation after cognitively demanding set learning or after passive stimulus-response-type learning.
- We use a computational model of spontaneous SPW activity to simulate reconsolidation outcomes as a function of the shared overlap of place cells in same vs. different learning contexts (Malerba et al., 2016).

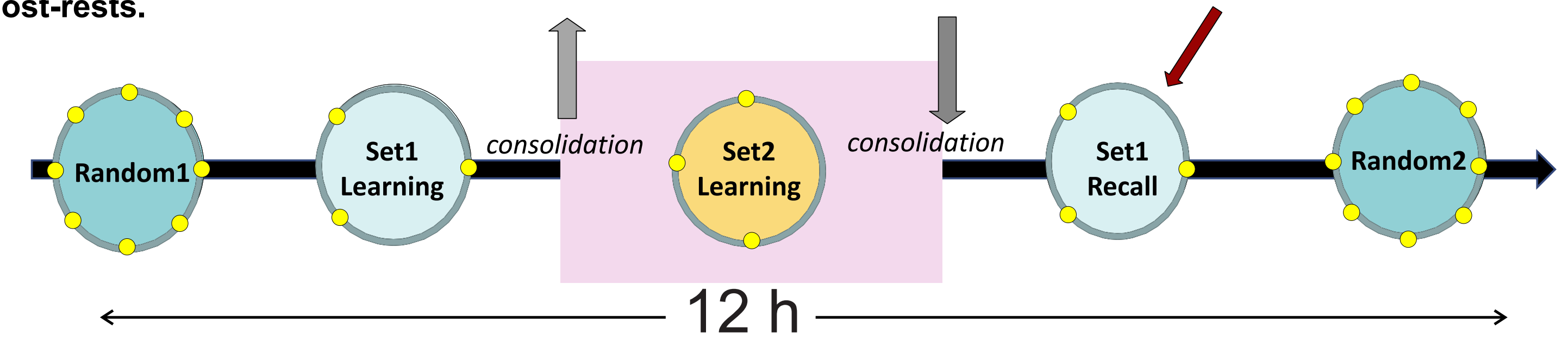
Experimental Methods



Recordings (14-tetrode hyperdrives) were obtained from the right dorsal CA1 of adult Brown-Norway rats.

Tasks involved the retrieval of sugar water rewards from a cued subset of 8 feeders.

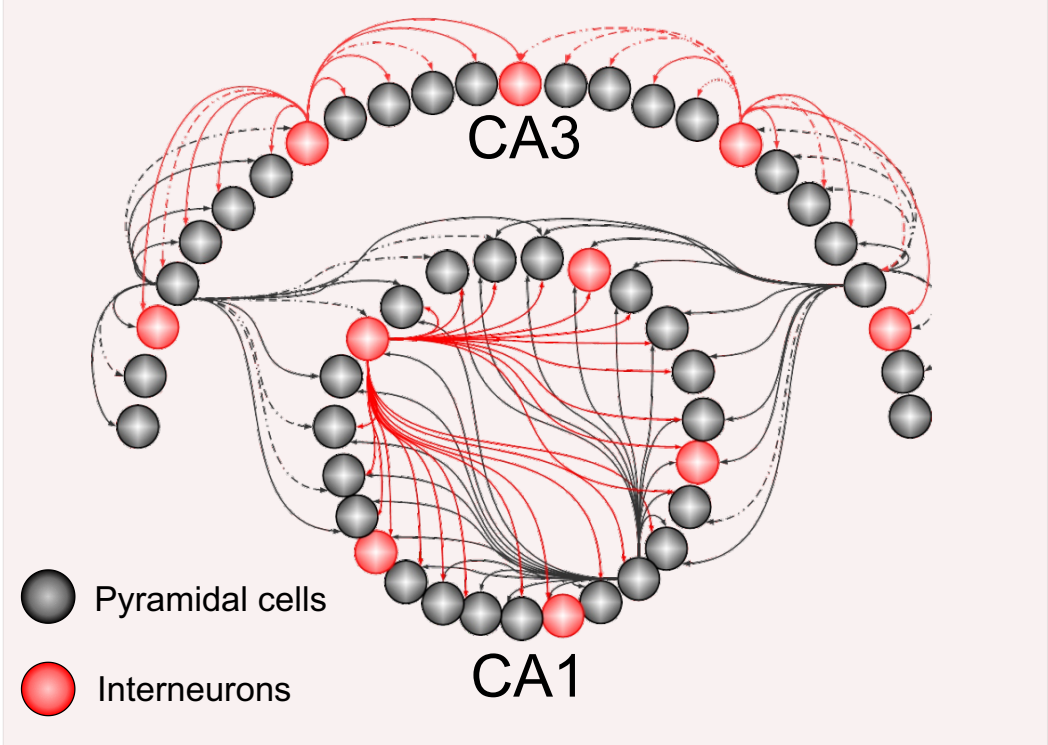
Set-Learning Experiments



Each task was flanked by **30-minute pre- and post-rests.**

"Set" = 3 feeders that could provide reward in random order.
Learning/Recall criterion = rats visited 15 consecutive non-cued feeders that were part of the Set.

Computational Model



CA3 ⟶ CA1 model of spontaneous SPW activity

(Malerba et al., 2016)
Poster EEE12

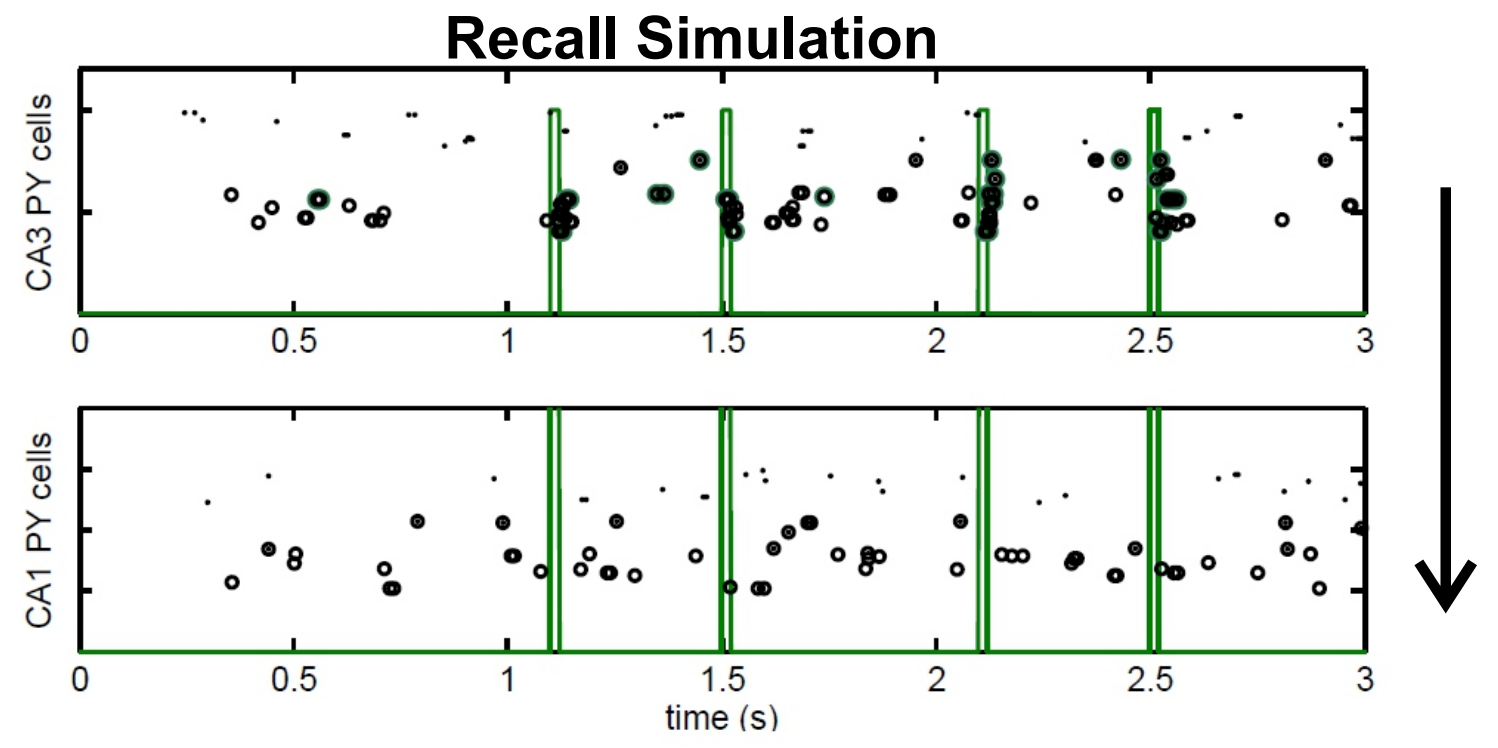
Set1 represented by 50 CA3 pyramidal (PY) cells (indexes 400-600)
36 CA1 PY cells (indexes 205-335)

Set2 represented by 50 CA3 PY cells (indexes 800-1000)
36 CA 1 PY cells (indexes 465-595)

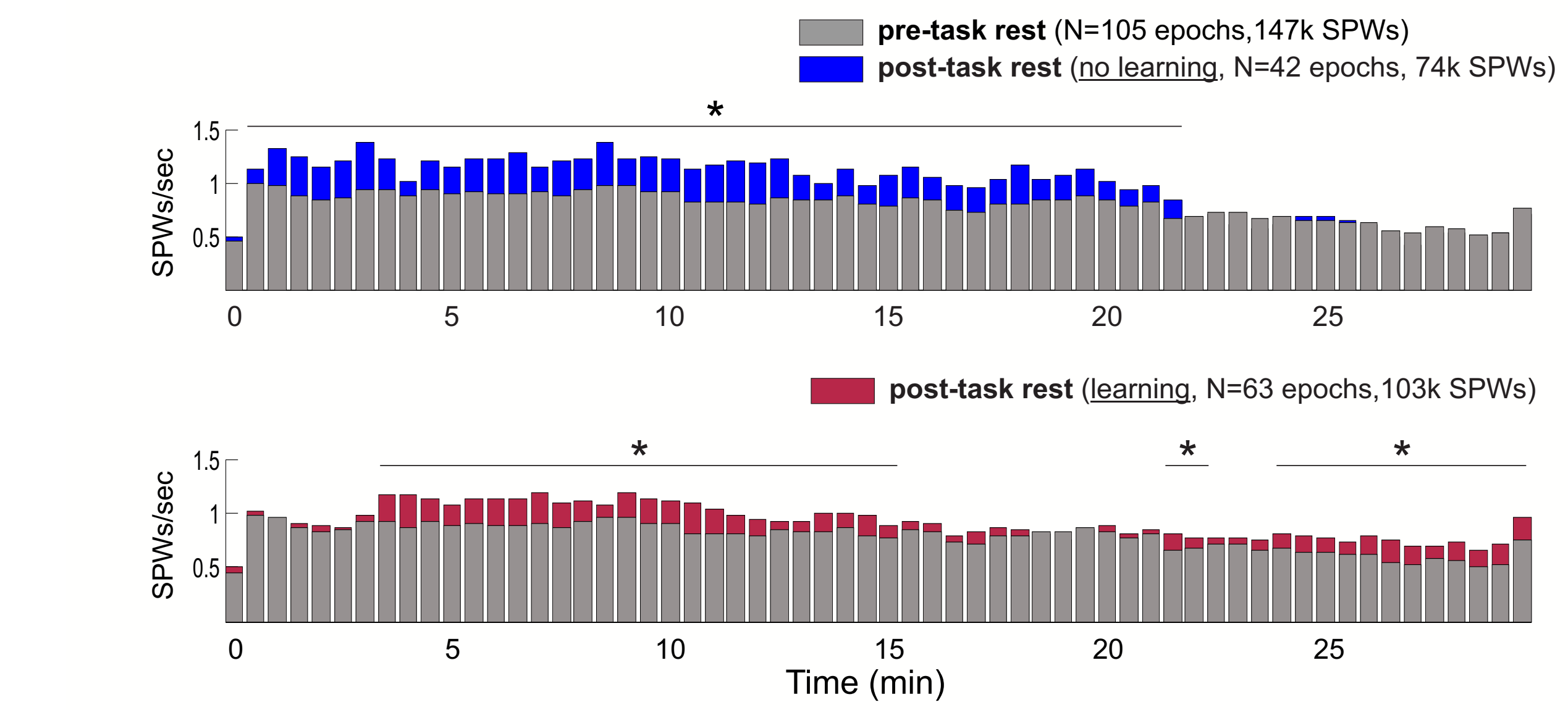
% Overlap introduced by discarding proportional number of cells in Set1 and Set2 and replacing them with the same cells taken from unused indices (600-800/335-465) in CA3 and CA1.

NMDA synapses among all cells within a Set in CA3 and from that Set to CA1 are turned ON (all with the same strength).

Recall = A fraction of Set1 cells stimulated in CA3 (20 ms DC current,10x in 5 sec).



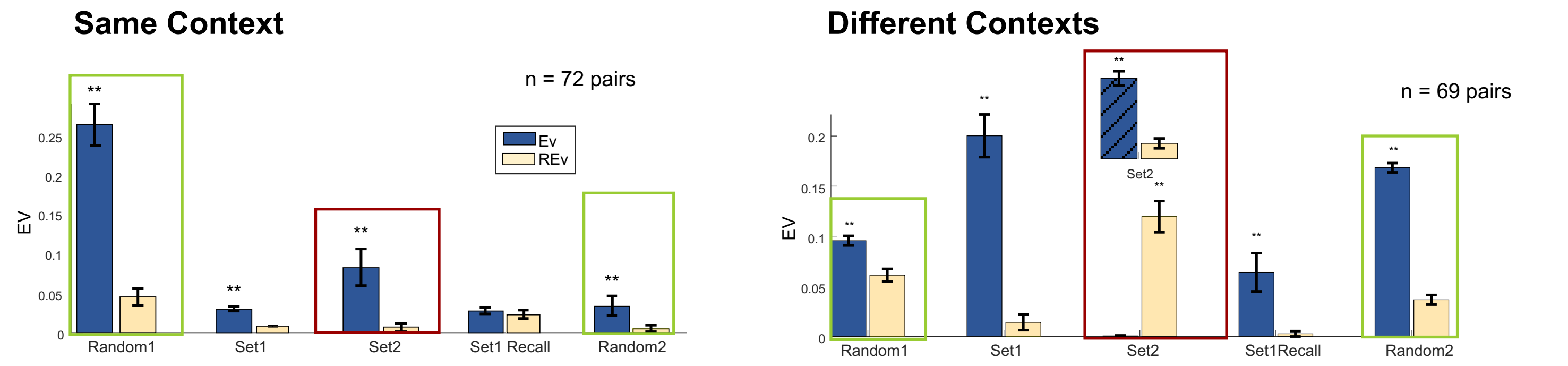
SPW Density



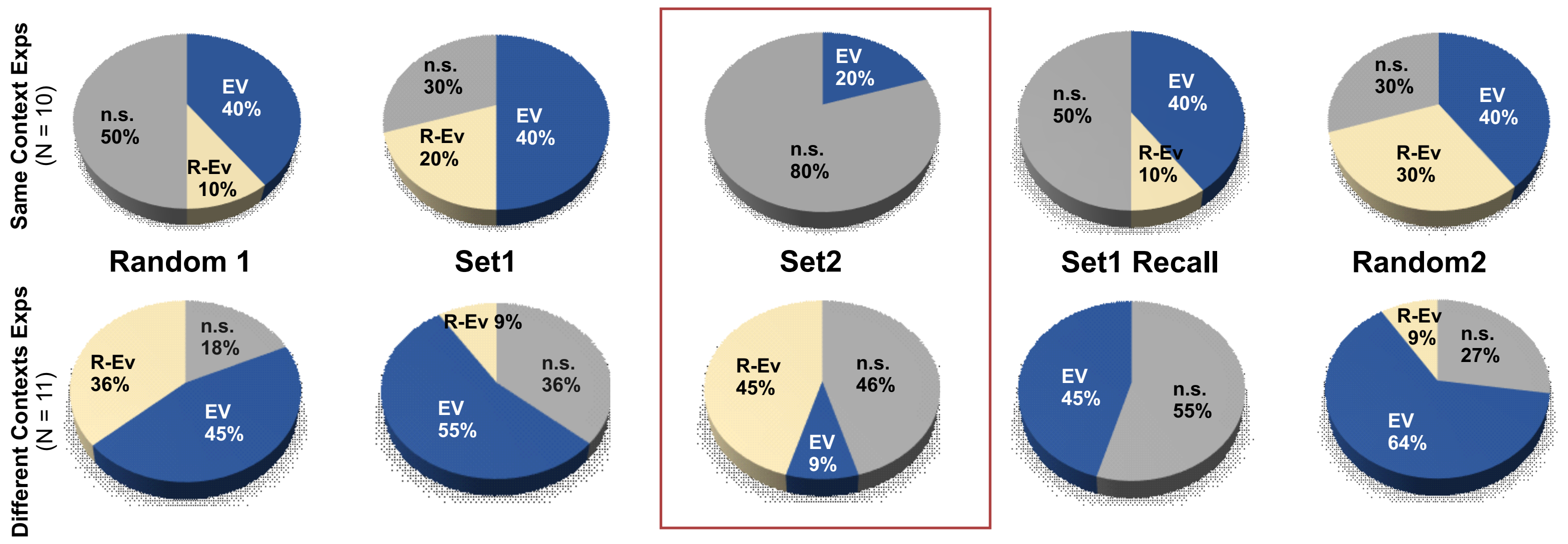
- Higher SPW density occurs after Random spatial navigation epochs in which the rat cannot learn a sequence (blue). SPW density after Set learning is delayed, longer lasting and fragmented (red).

Different distribution of reactivation in Set2 based on context condition

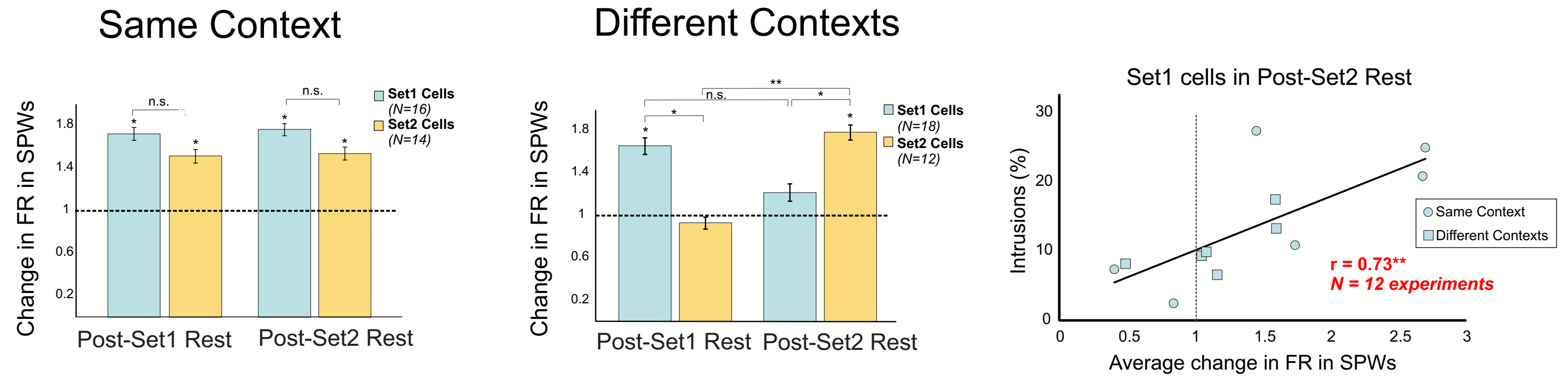
(First 15 min of post-rests)



- In these representative examples, EV analyses indicate that Post-Random rests often contain high levels of reactivation (green boxes).
- A subset of Different Contexts experiments, but no Same Context experiment, show significant reverse EV for Set2 learning (red boxes).

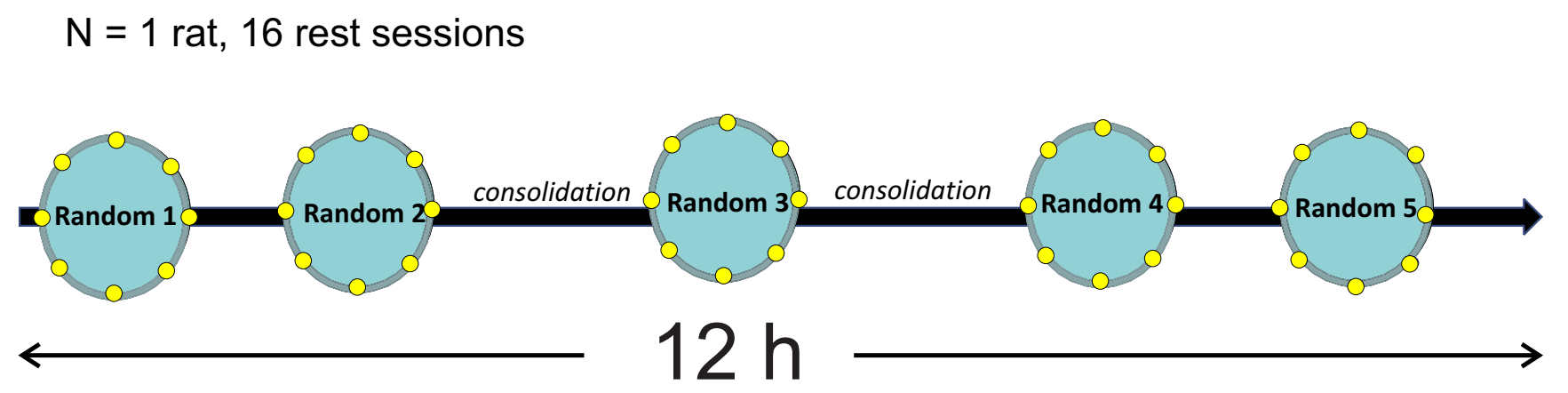


Single Cells in SPWs



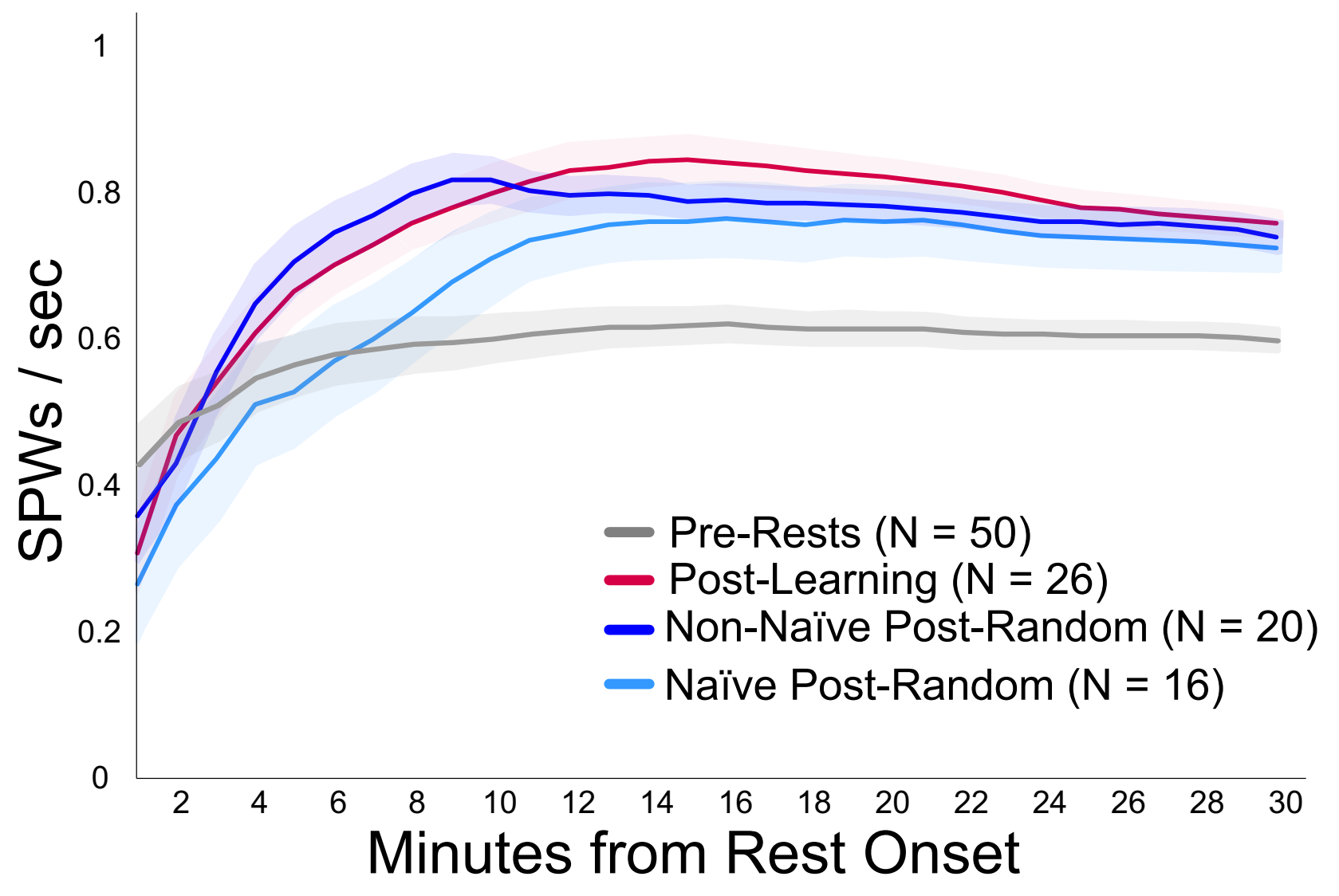
- Higher firing rates (FR) of Set1 cells during Post-Set2 Rest are correlated with more intrusions during Recall regardless of condition.
- This effect is more prominent in the Same Context condition, when Set1 and Set2 cells do not show a significant difference in FR change from baseline compared to each other.
- Different Contexts experiments show a reduction of FR of Set1 cells after Set2 learning, perhaps due to less context-bound overlap in the neuronal ensemble linked to the two sets.

Naive Random Control



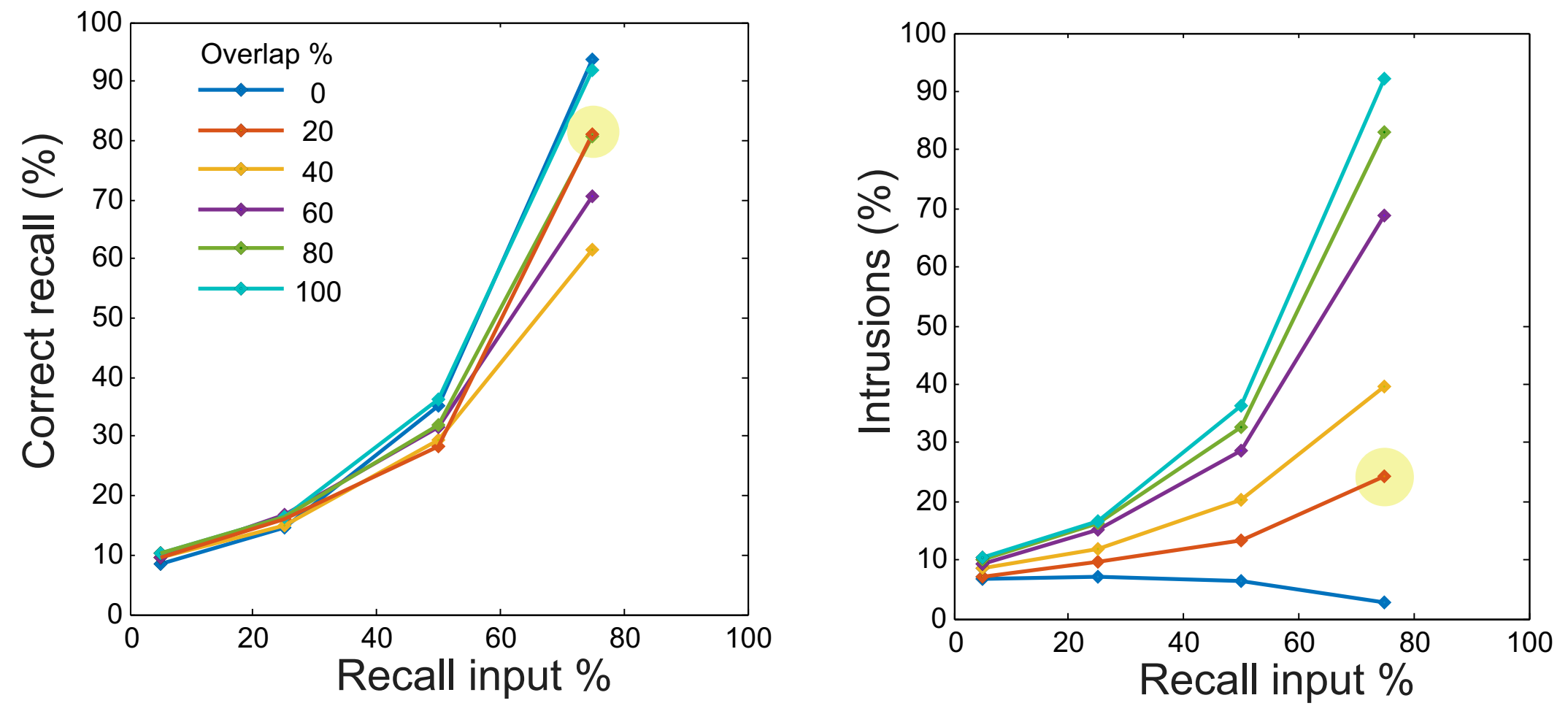
- We included a naive animal who had never learned a Set.

Naive vs. Learning Post-Rests

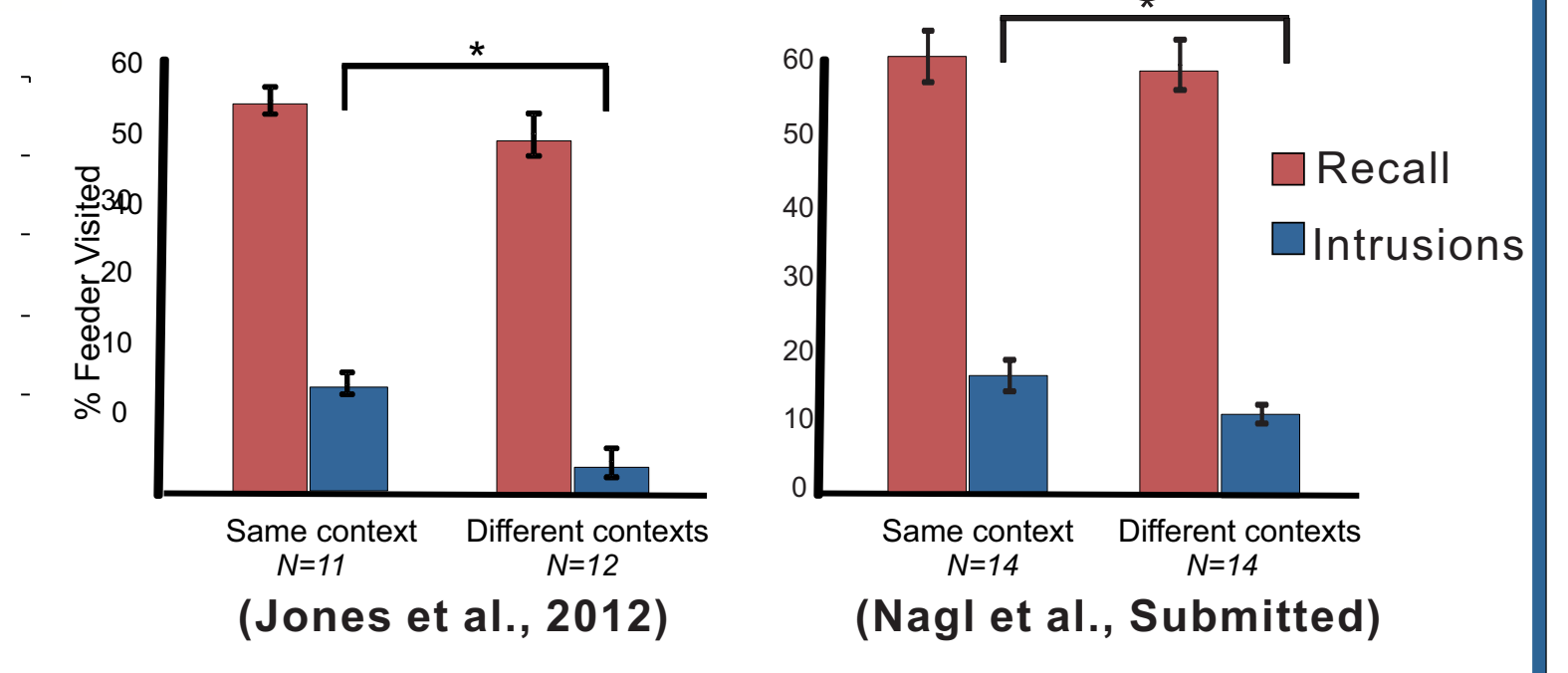


- The naive animal showed the lowest average SPW density compared to non-naive animals, though this appears transiently toward the beginning of Rest.
- Post-Random Rests from non-naive animals show a different curve profile, with high SPW density at the start of rests that levels off after about 15 minutes.

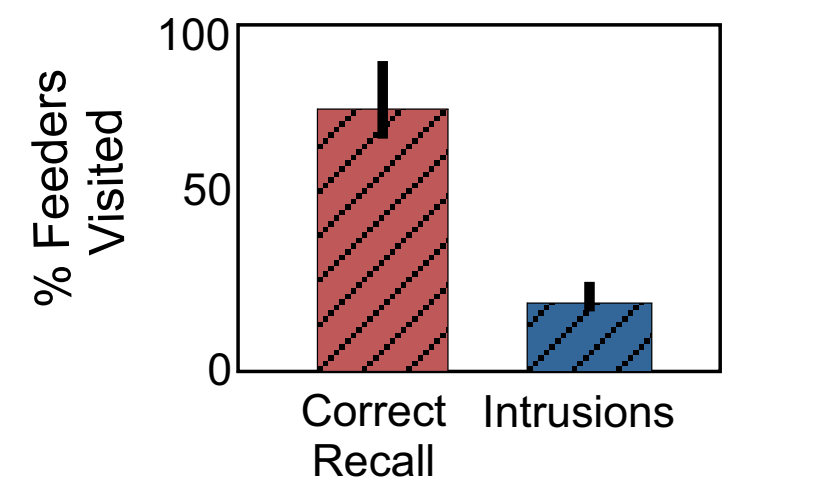
Modeling Results



Behavioral Data



20% Overlap, 75% Recall input



The model best matches the behavioral data with a 20% overlap between the cell populations for Set1 and Set2.

Discussion

- The increase in SPW density after a task showed different temporal dynamics depending on whether the task required explicit learning or was purely cue driven. Additionally, there seemed to be an effect of the presence of prior learning experience on SPW density immediately after cue driven tasks.
- EV analyses showed comparable reactivation across all epochs of the experiments in the same and different contexts conditions, with the exception of post-Set2 epochs during which some reverse-EV significance was observed in the different contexts condition only. This suggests that the presence of a new context may influence the pattern of correlations during upcoming learning episodes.
- The degree to which Set1 cells contributed to post-Set2 SPWs positively correlated with the amount of Set2 intrusions during Set1 recall in both context conditions. This suggests that intrusions may be due to a SPW-mediated increase in plasticity between Set1 and Set2 cell populations.
- A computational model of the CA3-CA1 network suggested that intrusions may be caused by a context-induced overlap of cell populations representing the memory items. Further work will focus on the changes of memory representations induced by SPWs during sleep-mediated consolidation.

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