Sleep Spindles and Reactivation in the Rodent Medial Prefrontal Cortex During Context-Dependent Memory Reconsolidation

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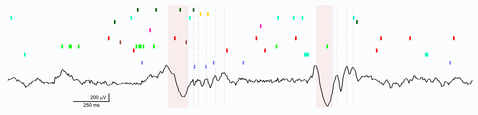
Introduction

• Sleep spindles are hypothesized to contribute to memory consolidation because their density increases during sleep immediately after learning in both rats and humans (1,2). The relationship between spindle density and recall performance is still unclear.

• Reactivation occurs in the prefrontal cortex during sleep (3,4). The extent to which reactivation depends on sleep spindles is unknown.

• We use a spatial memory reconsolidation task and record from the rat medial prefrontal cortex to study the relationship between recall performance, spindle density, and reactivation during post-learning sleep epochs.

• Delay differential analysis (DDA) is a time-domain classification framework that can be used for sleep spindle detection (5). We compare the method to a Hilbert-transform approach and to manual spindle extraction.



Methods

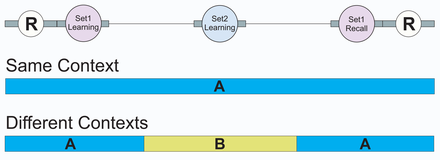
Rats get sugar water rewards at each of 8 feeders cued randomly with a blinking light.

Single cells and local field potentials are recorded using a 14-tetrode hyperdrive targeted at the medial prefrontal cortex.

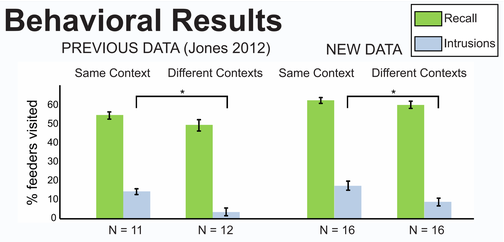
Two different “sets” of 3 feeders are cued for 75 rewards in each learning task, followed by a non-cued, free recall period to assess learning.

Learning and recall criterion: 15 consecutive correct feeder visits (max. two 15 second time-outs).

At the end of the day, rats are tested on the first set.

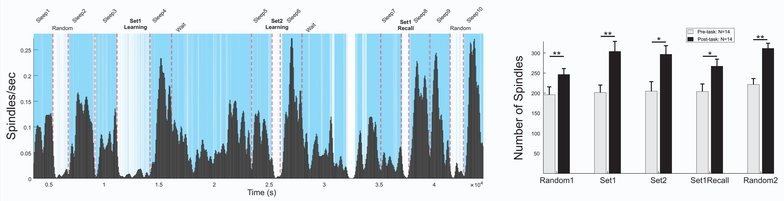


Behavioral Results

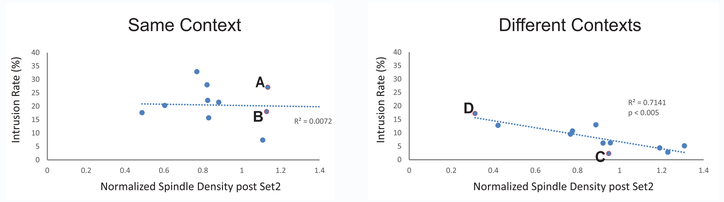


Recall performance is the same in both conditions. Rats make fewer Set2 intrusions during recall when the sets are learned in different contexts.

Pre- vs. Post-Learning Spindle Density

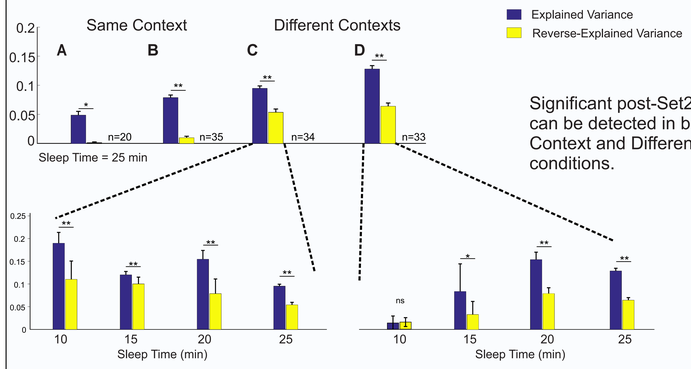


Spindle density increases after learning and learning-free spatial tasks.



In the Different Contexts condition, higher spindle density after learning Set2 predicts fewer intrusions during Set1 recall.

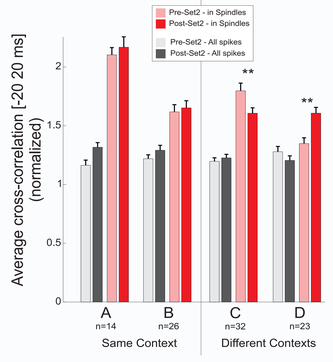
Set2 Reactivation



Significant post-Set2 reactivation can be detected in both Same Context and Different Contexts conditions.

Lower intrusion rate in the Different Contexts condition may be related to earlier reactivation in the first 30 minutes of sleep after Set2 learrning.

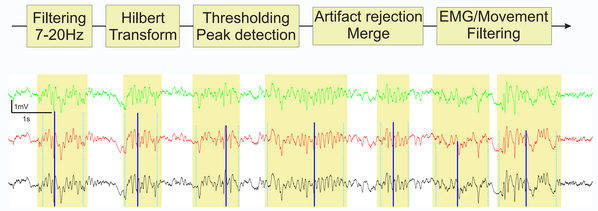
Post-Set2 Reactivating Cells and Spindles



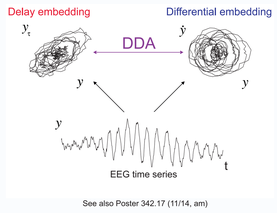
- The average pairwise correlations of all cells contributing to reactivation is higher in spindles than in the overall rest epoch.
- In the Same Context condition, the correlation does not change after learning.
- In the Different Contexts condition, a decrease in correlation correlates with a decrease in intrusion and vice versa.

Methods: Spindle Detection

Hilbert Transform



Delay Differential Analysis



Creates a low-dimensional feature space by relating two types of embeddings in functional form:

i.e. $\dot{x} = a_1x_1+a_2x_2+a_2x_1^2$ where $x_i=x(t-\tau_i)$

The model is trained on human intracranial data.
Spindles are detected when a weighted sum of the coefficients exceeds a set threshold.

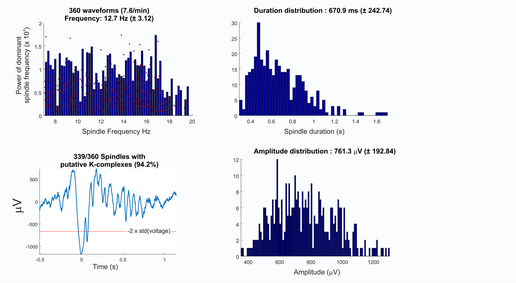
See also Poster 342.17 (11/14, am)

Inter-Algorithm Agreement

	Experiment 1			Experiment 2		
	Channel 1	Channel 2	Channel 3	Channel 1	Channel 2	Channel 3
Cohen’s κ: DDA vs. hand scoring	0.15	0.20	0.16	0.25	0.24	0.23
Cohen’s κ: Hilbert method vs. hand scoring	0.33	0.33	0.33	0.57	0.57	0.57
Cohen’s κ: DDA vs. Hilbert method	0.11	0.15	0.12	0.17	0.16	0.16

Overall Spindle Characteristics

	Hand Scoring	DDA	Hilbert	Other Rat Data (Eschenko et al. 2006)	Human Data (Warby et al., 2014) (Andrillon et al., 2011) (Dehghani et al., 2011a,b)
Frequency (Hz)	12.7 ± 3.2	12.3 ± 3.3	12.1 ± 3.2	12-15	10-16
Amplitude (μV)	693.5 ± 171.5	617.5 ± 218.8	429.8 ±154.6	300-700	~30 (scalp EEG)
Duration (ms)	617.1 ± 218.8	1237 ± 453.6	1021 ± 839.4	830	500-1200
Density (/min)	~5.1	~15.8	~12.1	6.5-7.5	1.8-4.3



Conclusions and Interpretations

• **Sleep spindle density increases after learning, retrieval, and learning-free spatial tasks.**
- We replicate the known correlation of increased spindle density with learning and retrieval.
- We show that this increase also occurs in the absence of explicit learning.

• **Higher spindle density after Set2 learning is correlated with fewer intrusions in Set1 recall when rats learn Sets in different contexts.**
- Prefrontal cortex spindle density may contribute to the ability to distinguish between different memories on the basis of context.

• **Reactivation assessed by explained variance does not depend on spindle-related activity.**
- Population reactivation occurs within and outside of spindles.

• **Pairwise neural cross-correlations in reactivating epochs are stronger during spindles and their change after learning depends on context.**
- Pre-existing pairwise correlations between cells do not change after Set2 learning in the Same Context condition.
- Correlations between cells change after Set2 in the Different Contexts condition. These changes may relate to later memory performance.

• **Automatic spindle detection methods appear to give similar results.**
- DDA and Hilbert transform spindle detection have higher rates of agreement with human ratings than with each other.
- The Hilbert transform uses consensus among three channels to detect spindles, while DDA uses a single channel. False positives and negatives may differ for this reason, but automatically detected spindles do not differ qualitatively.

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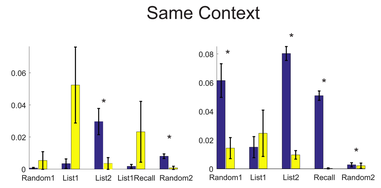
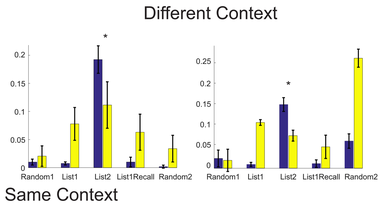
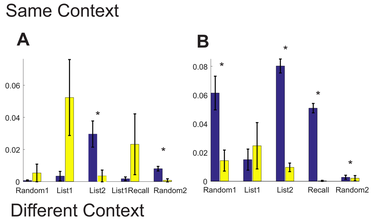
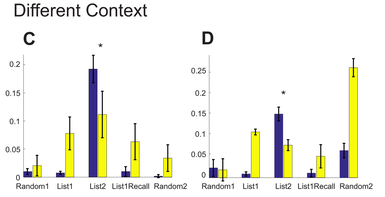




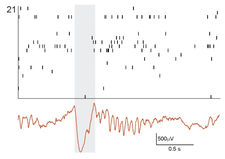




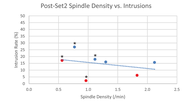
N = 13 same context
N = 11 different contexts

N = 7 same context
N = 4 different contexts

N = 2 same context
N = 2 different context



Human data suggest that post-learning spindle density is predictive of recall performance in a rewarded task ().



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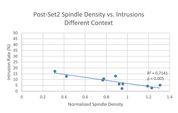
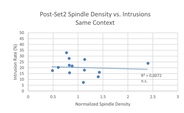
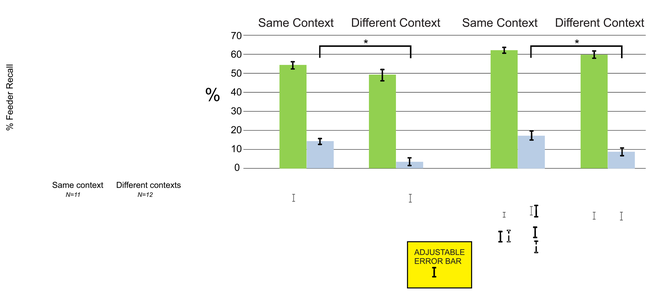
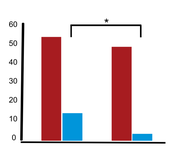
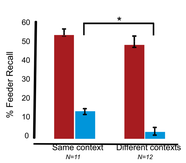
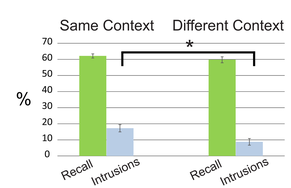




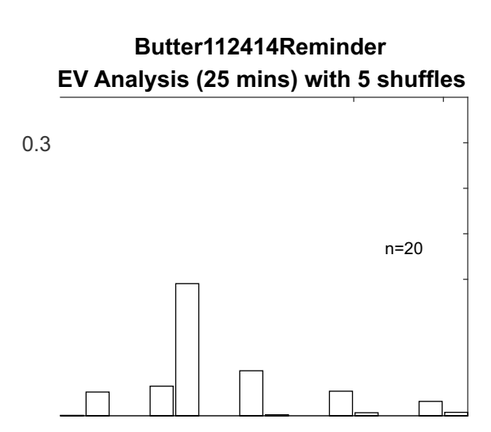


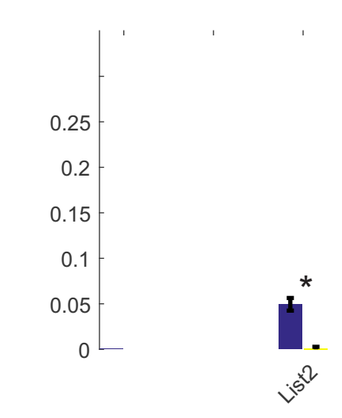


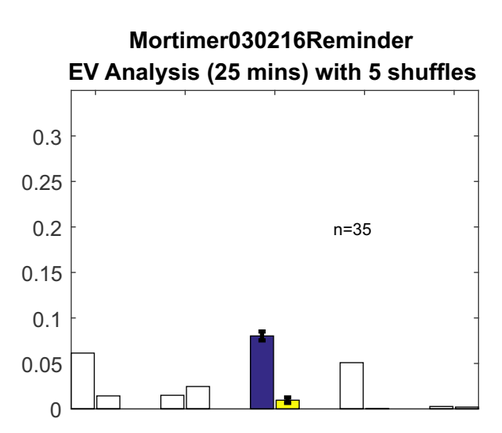


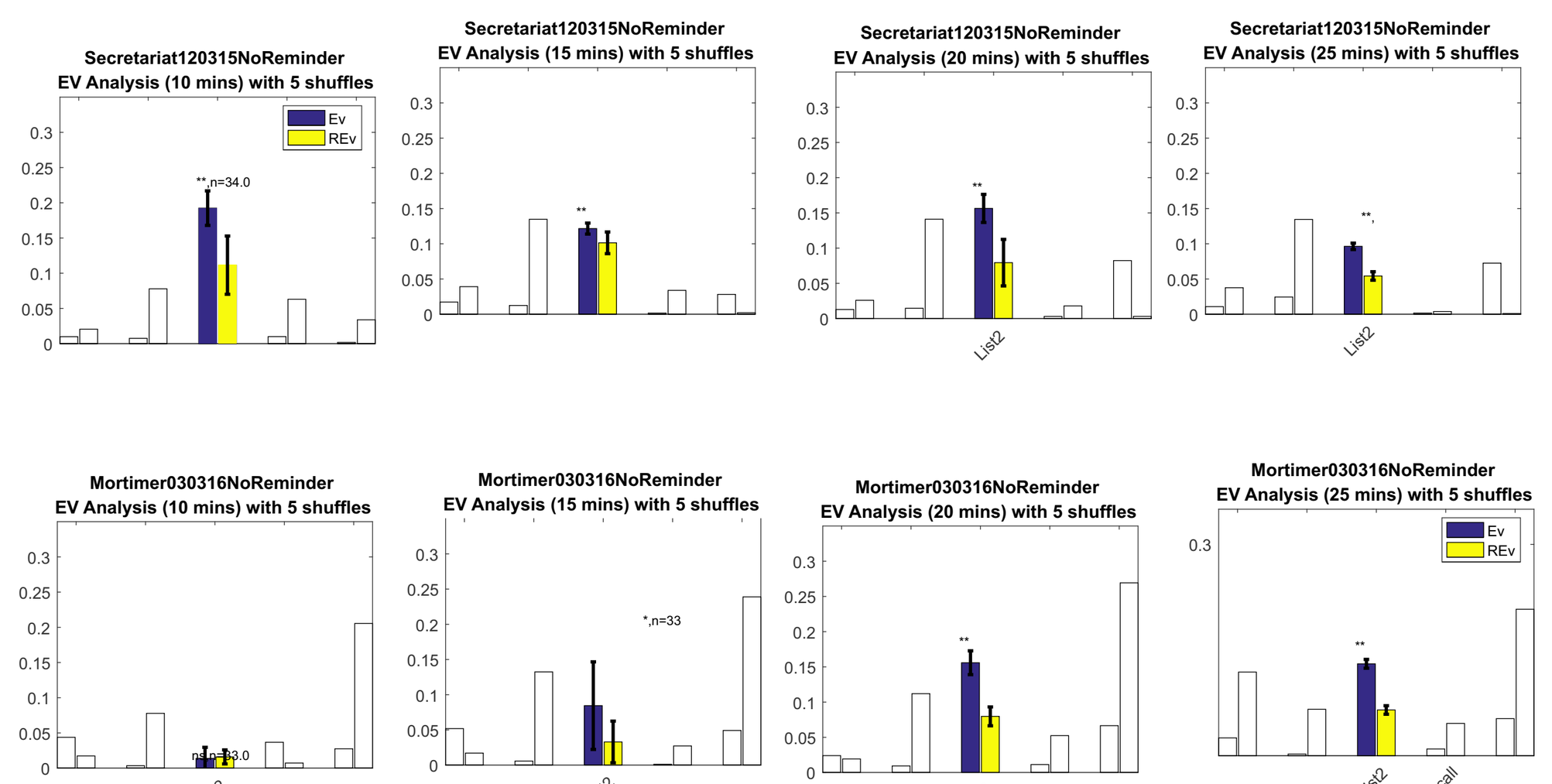


	Our Study (motionless epochs)	Other Rat Data (Eschenko et al. 2006, Sullivan et al. 2014)	Human Data (Warby et al. 2014, Andrillon et al. 2011, Dehghani et al. 2011)
Frequency (Hz)	**14** (± 1.85)	12-15	10-16
Amplitude (μV)	**470** (± 196)	300-700	~30 (scalp EEG)
Duration (ms)	**857** (± 450)	750-900	500-1200
Density (/min)	**2.7** (± 0.25)	1.2-3.4	1.8-4.3


Butter112414Reminder
EV Analysis (25 mins) with 5 shuffles




Mortimer030216Reminder
EV Analysis (25 mins) with 5 shuffles


Secretariat120315NoReminder
EV Analysis (10 mins) with 5 shuffles
Secretariat120315NoReminder
EV Analysis (15 mins) with 5 shuffles
Secretariat120315NoReminder
EV Analysis (20 mins) with 5 shuffles
Secretariat120315NoReminder
EV Analysis (25 mins) with 5 shuffles
Mortimer030316NoReminder
EV Analysis (10 mins) with 5 shuffles
Mortimer030316NoReminder
EV Analysis (15 mins) with 5 shuffles
Mortimer030316NoReminder
EV Analysis (20 mins) with 5 shuffles
Mortimer030316NoReminder
EV Analysis (25 mins) with 5 shuffles

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