Neural Substrates of Memory and Decisions

Loren Frank

Center for Integrative Neuroscience

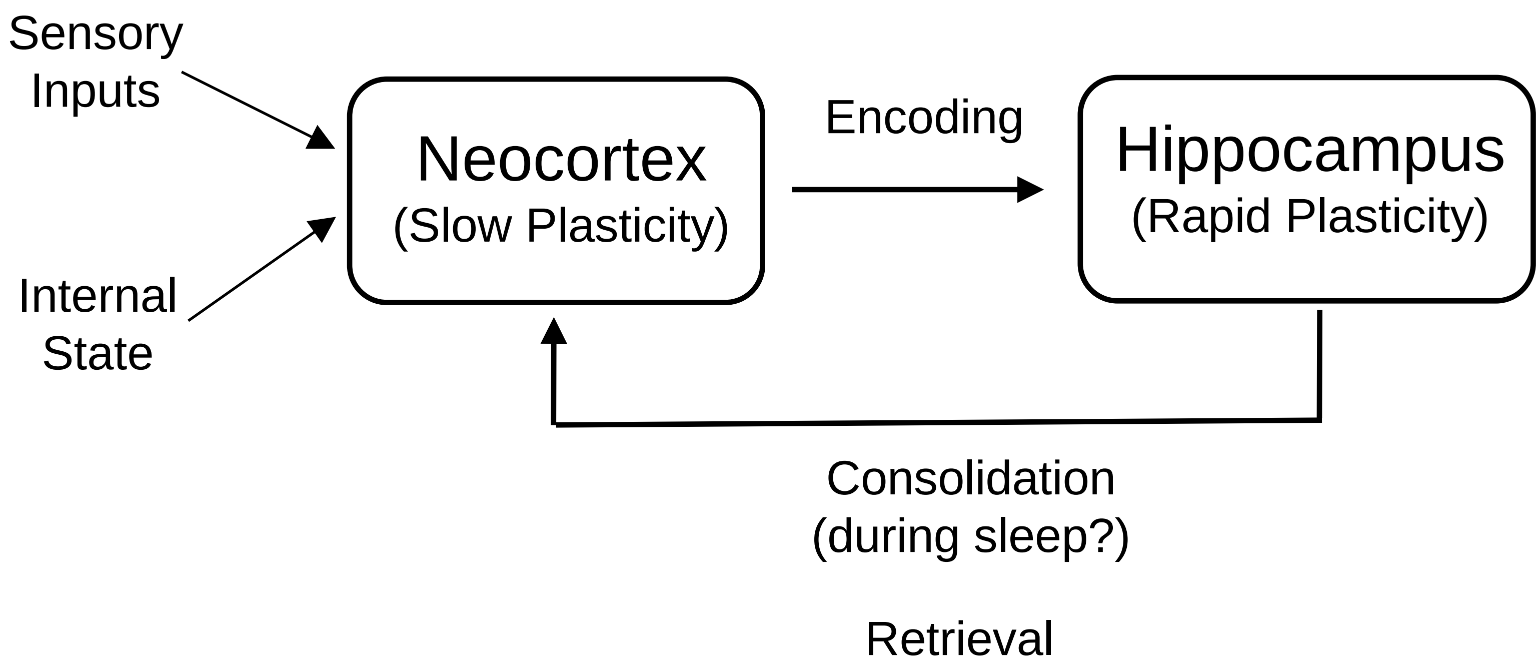
University of California, San Francisco

Musings on Memory

- What is a memory?
  - Reactivation of a pattern of neural activity related to that present during the actual experience
    - Fast

- What is a memory good for?
  - Guiding decisions

Learning and the Hippocampal Circuit



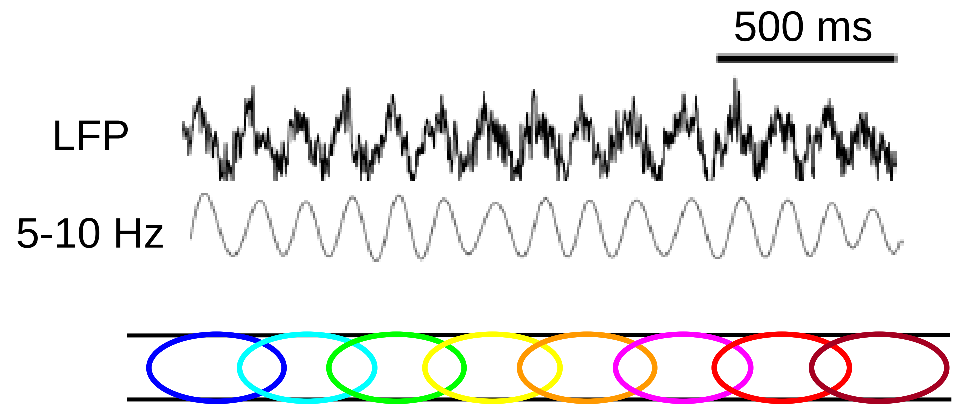
What patterns of neural activity support encoding, consolidation and retrieval?

Example of CA1 Neural Activity

Cell
1
2
3
4
5
6
7
8
9
10

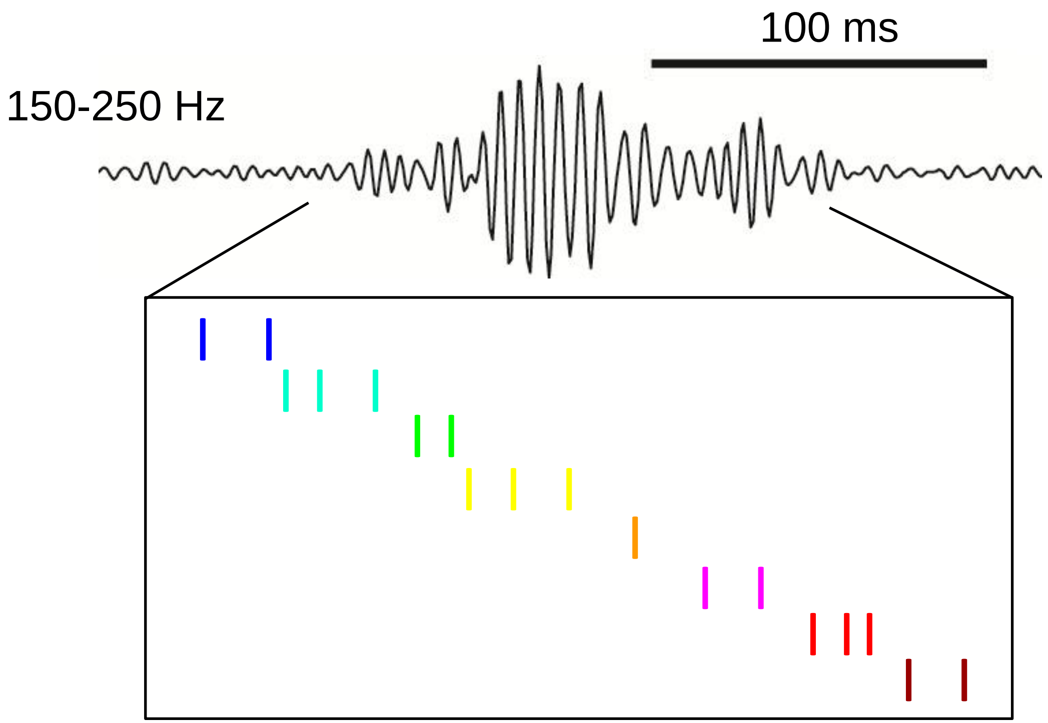
Activity Patterns in the Hippocampus

Place Fields and Theta

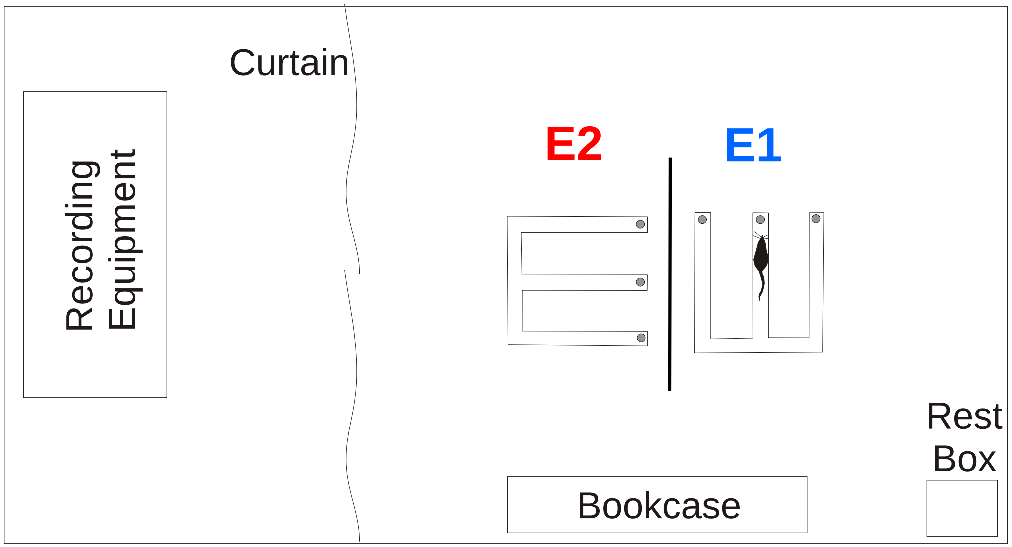


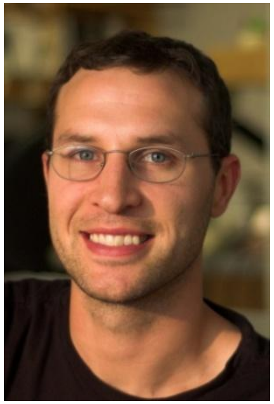
Sharp-Wave Ripples
(Ripples / SWRs)

Replay / Reactivation
of memory sequences
during SWRs

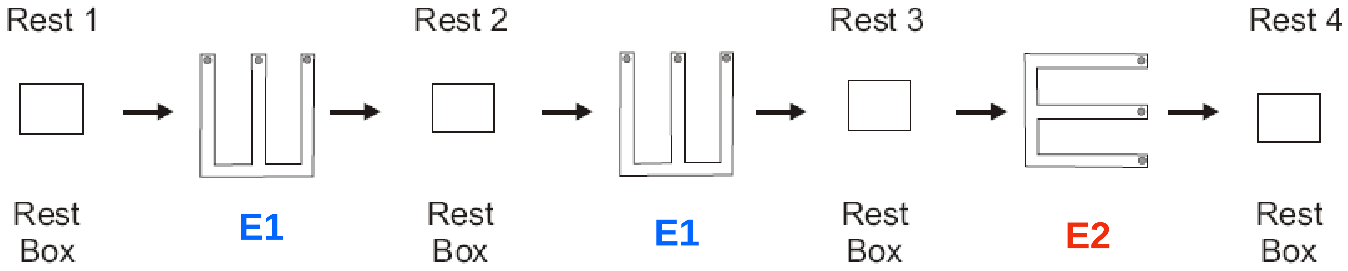


Methods - Behavior



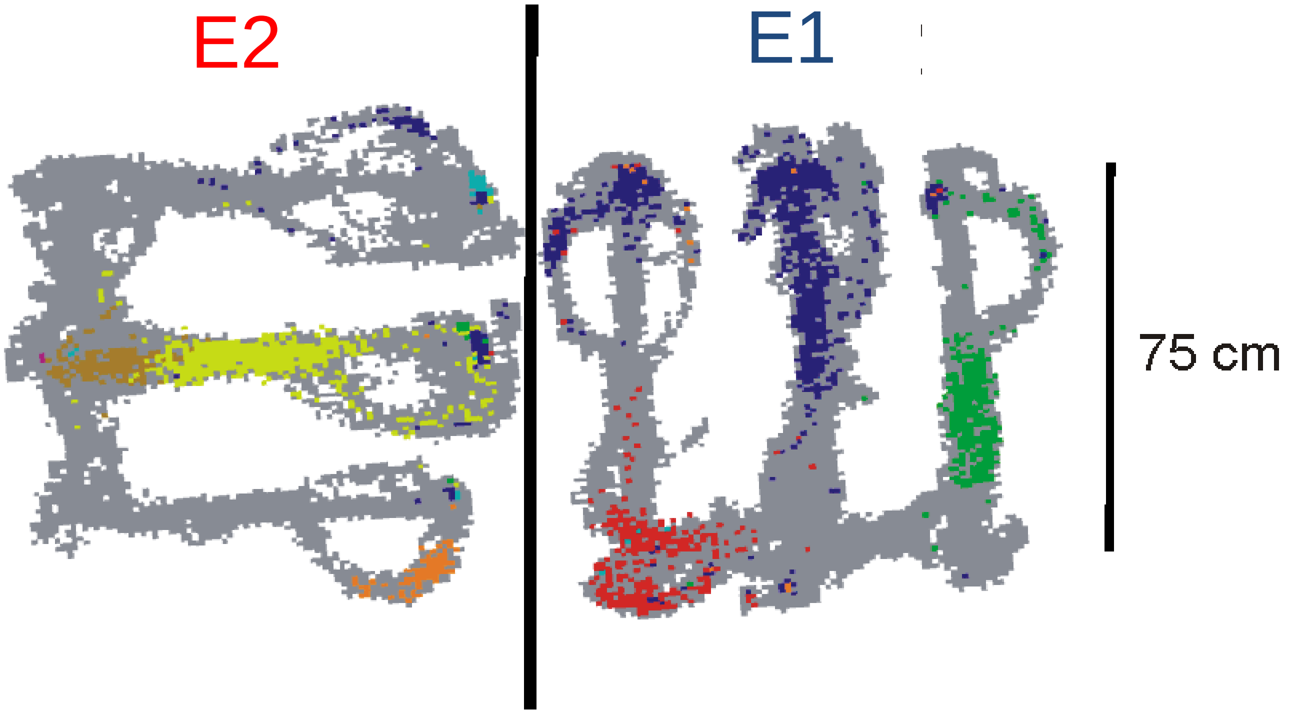


Mattias Karlsson



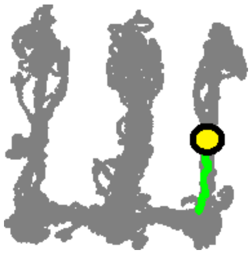
Karlsson and Frank, *Nature Neuroscience* (2009)

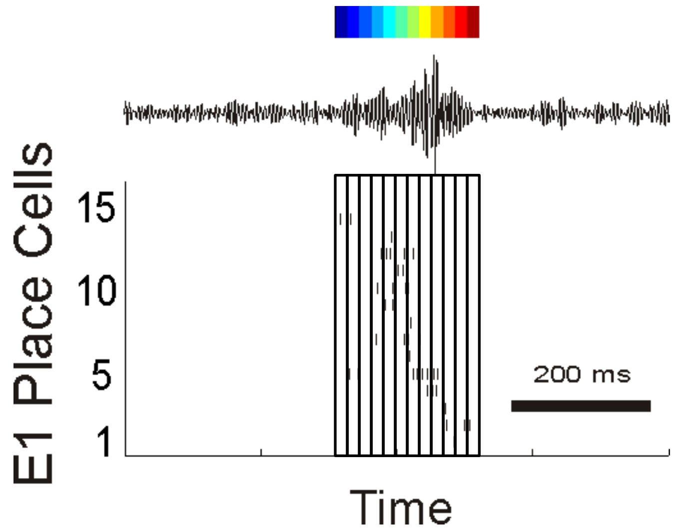
Distinct Representations of Distinct Environments



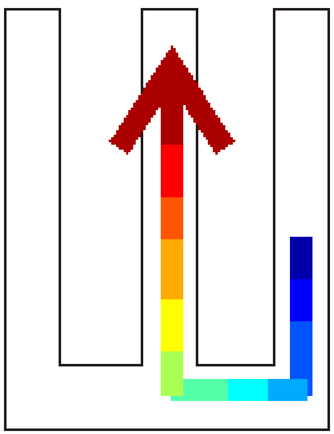
Awake Replay Activity

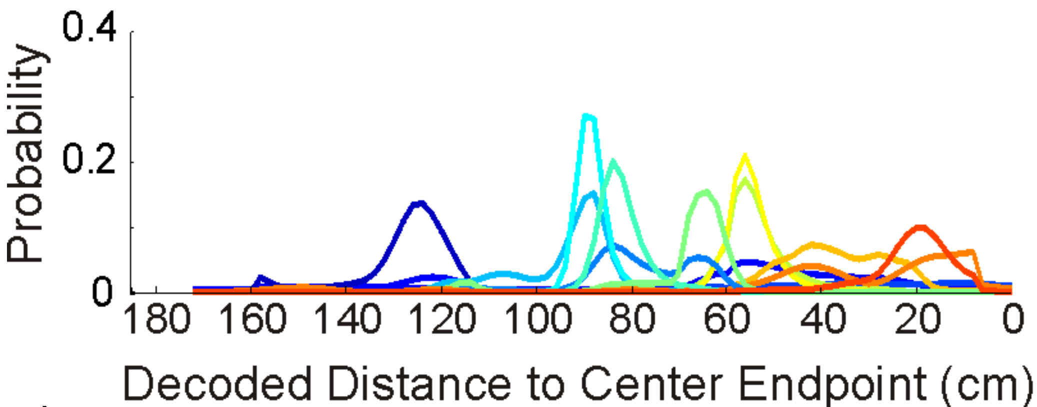
Actual Trajectory





Decoded Trajectory

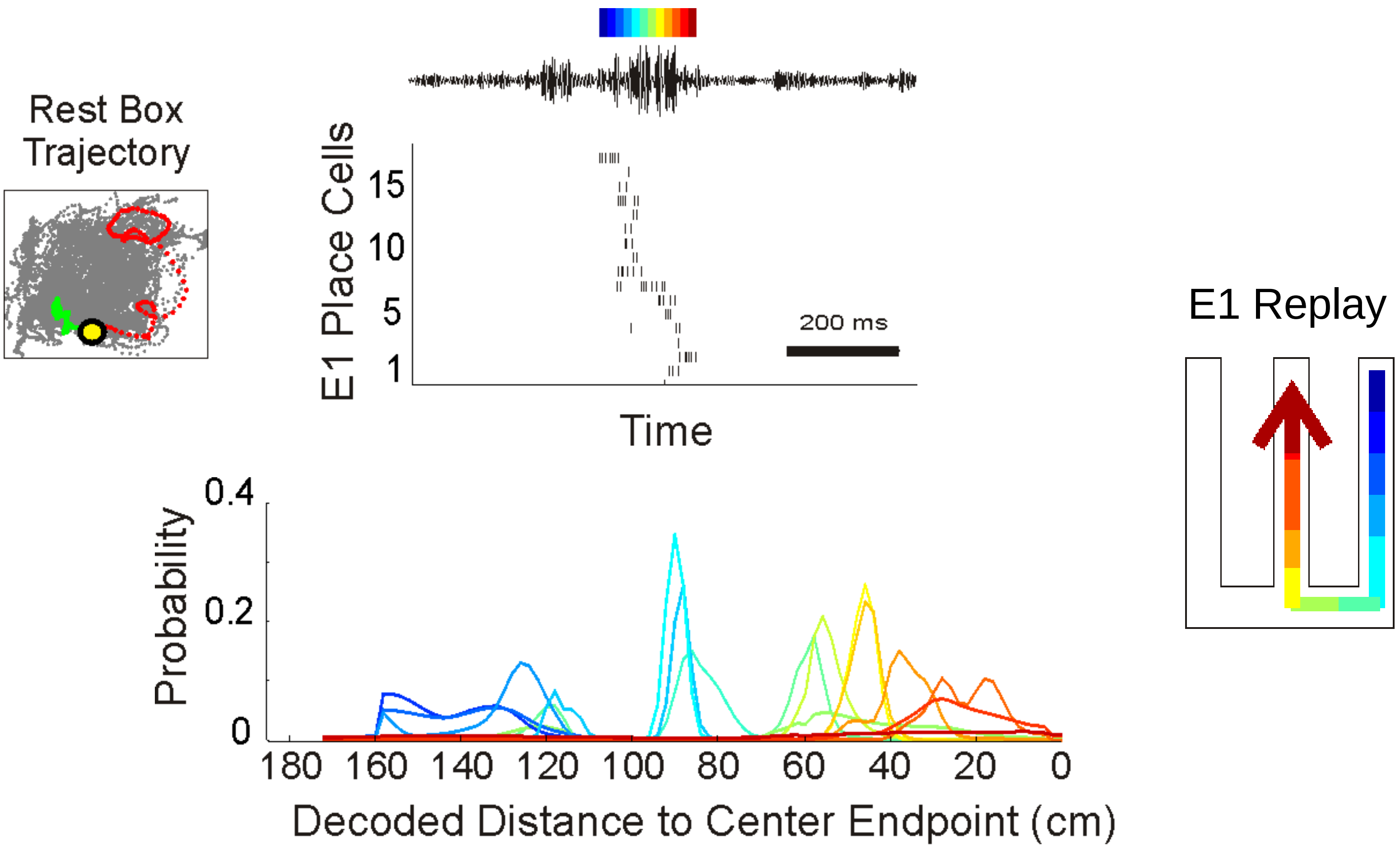




Kudrimoti et. al. (1999)
Foster and Wilson (2006)
Diba and Buzsaki (2007)

Karlsson and Frank, *Nature Neuroscience* (2009)

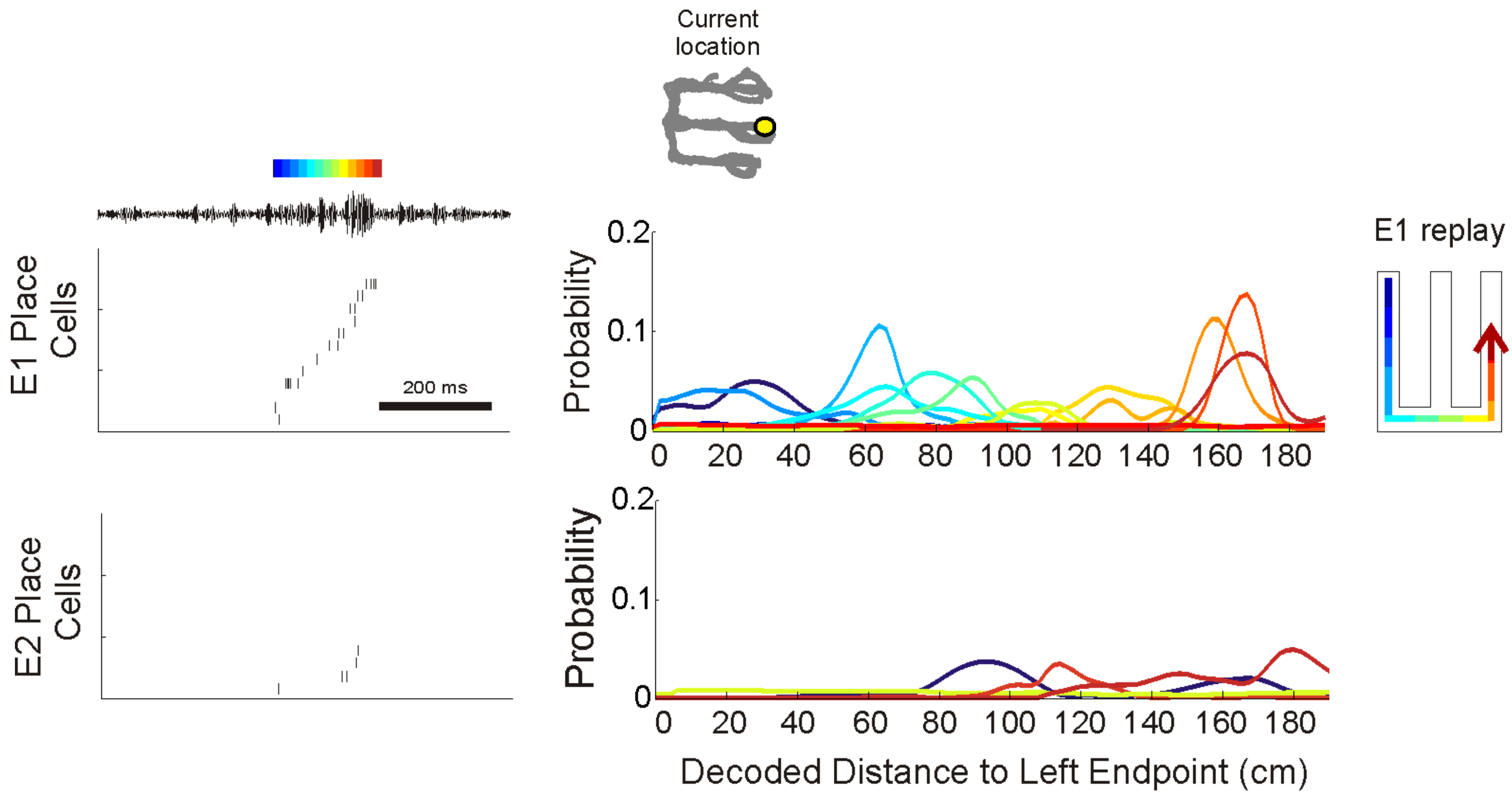
Awake Replay of Remote Experiences



256 / 580 (44%) candidate events significant. $p < 10^{-10}$

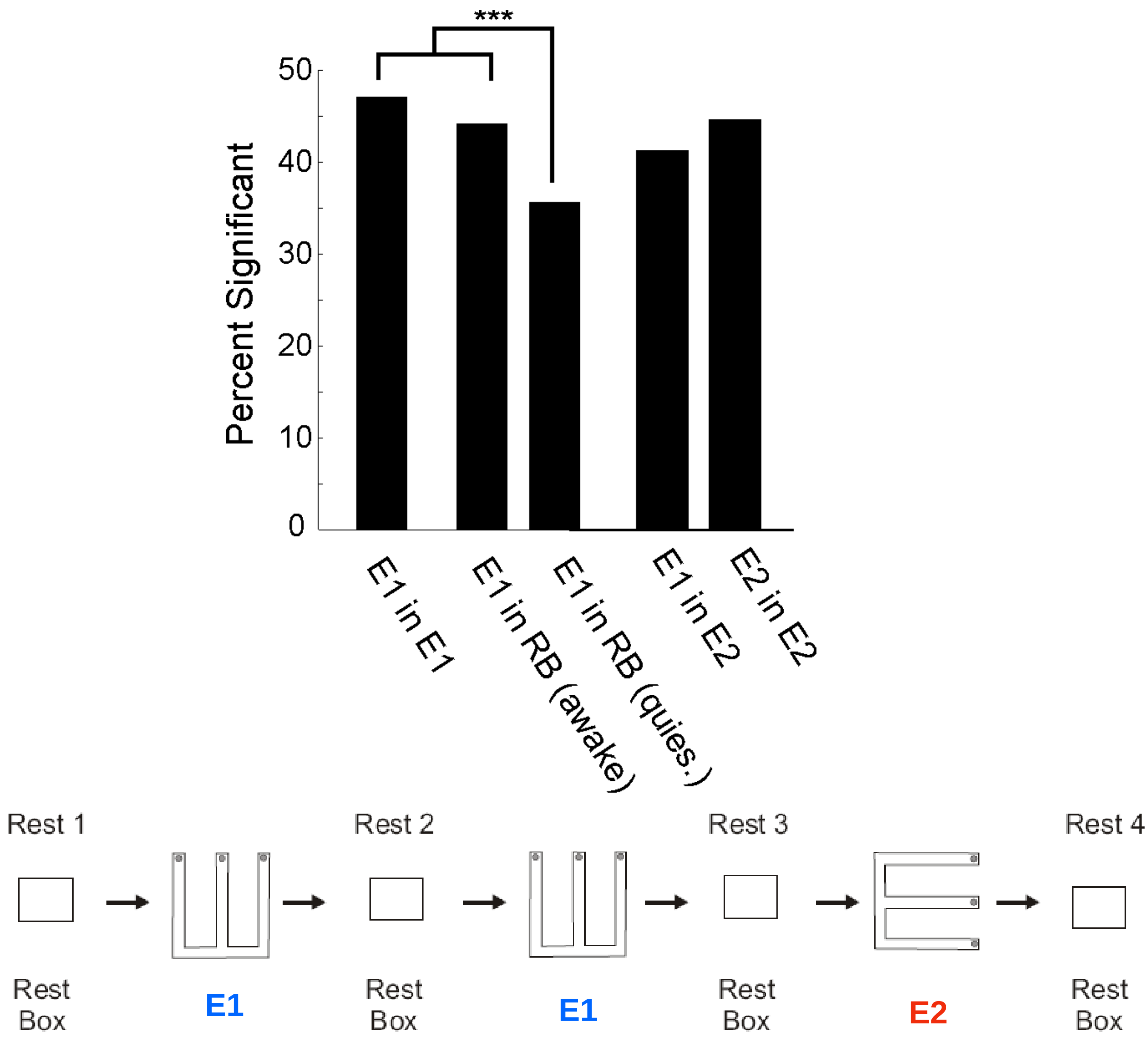
Karlsson and Frank, *Nature Neuroscience* (2009)

Awake Replay of E1 in E2

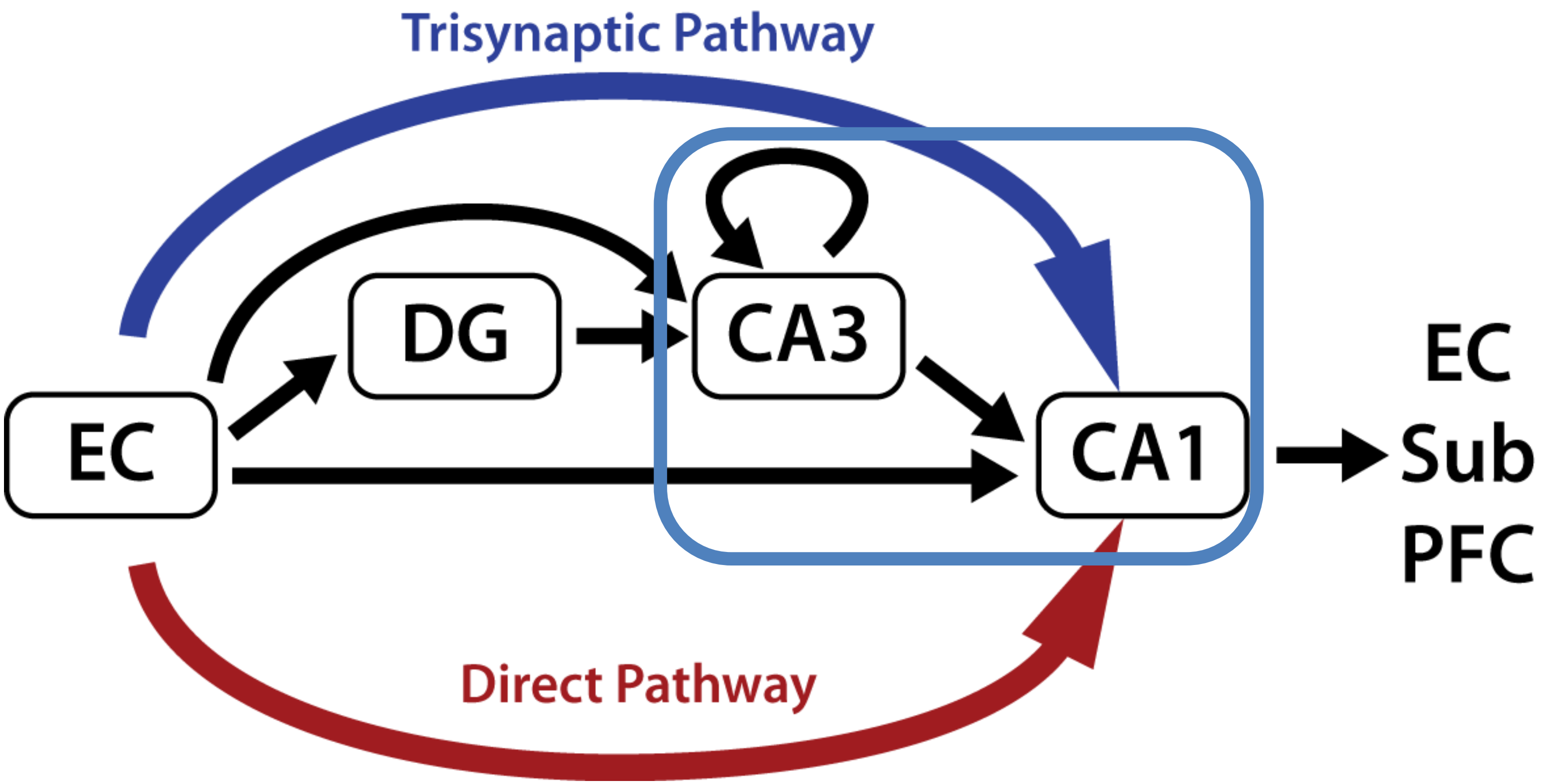


Karlsson and Frank, *Nature Neuroscience* (2009)

Awake Replay Across Environments



Replay and Anatomical Pathways to CA1



Reactivation enhanced by

Novelty (Cheng and Frank, Neuron, 2008)
Reward (Singer and Frank, Neuron, 2009)

Questions

- Do awake SWRs contribute to memory-guided decision-making?

- How does memory replay during SWRs inform subsequent decisions?

Questions

- Do awake SWRs contribute to memory-guided decision-making?

- How does memory replay during SWRs inform subsequent decisions?

Hypotheses

- Awake replay could serve as a continuous mechanism for memory consolidation

- Awake replay could be important for memory recall for guiding ongoing behavior.

Carr, Jadhav and Frank, *Nature Neurosci. (*2011)

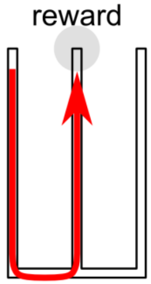
Question:

Does specific disruption of hippocampal SWRs in the awake state impair learning?

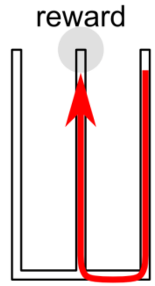
Behavioral Paradigm

W-track : Hippocampus dependent spatial alternation task

Kim and Frank, PLoS One, 2009

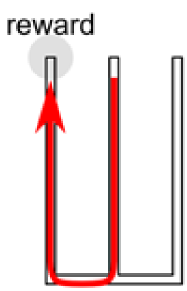


left → center
(inbound)

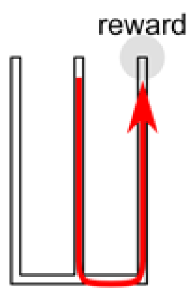


right → center
(inbound)

Inbound Trials



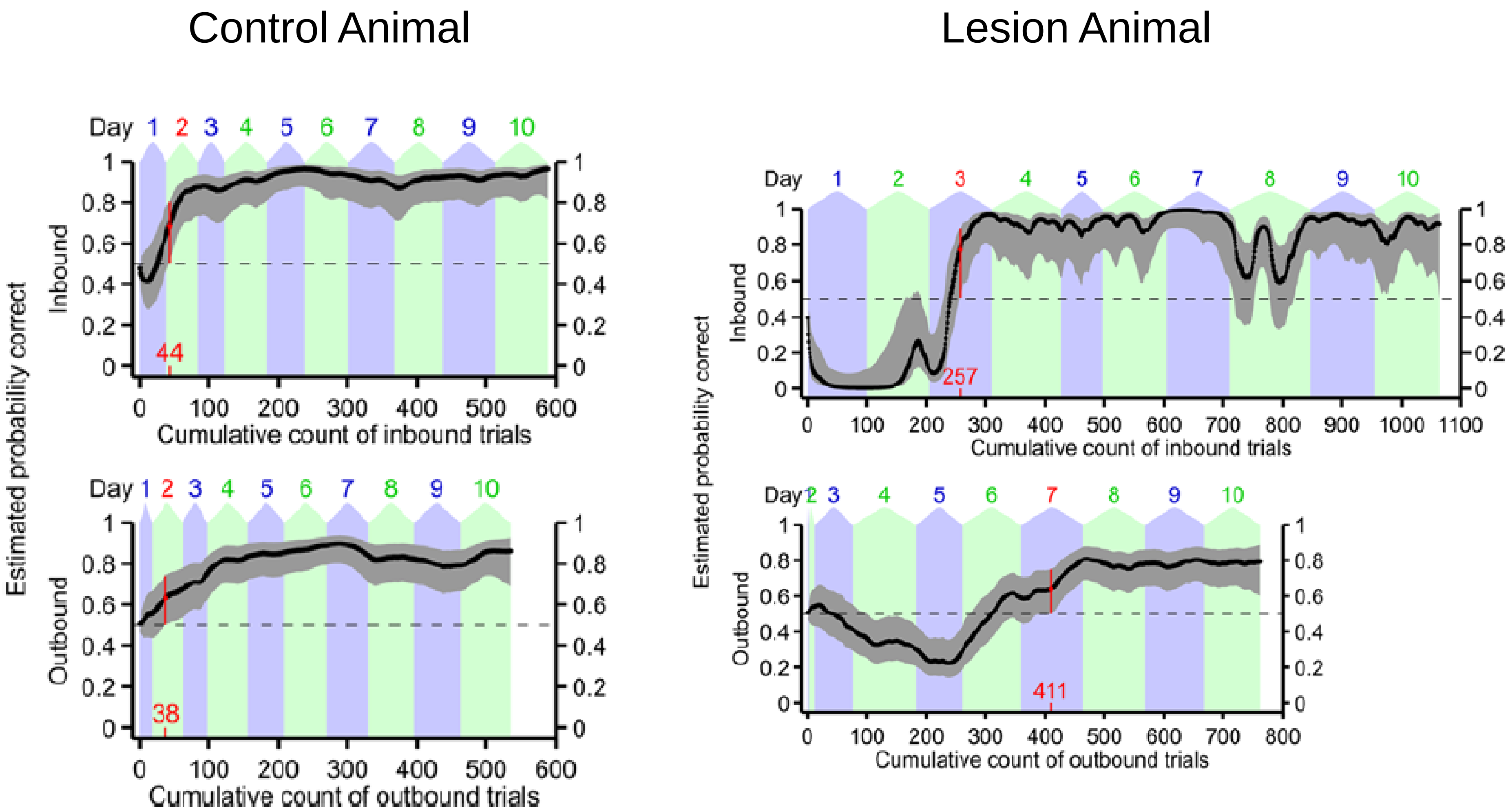
center → left
(outbound)



center → right
(outbound)

Outbound Trials

W-Track Task – Effect of lesions



Kim and Frank*, PLoS One (2009)*

Method: Smith et. al*., J. Neurosci.* (2004)

Methods: Specific Disruption of Awake SWRs

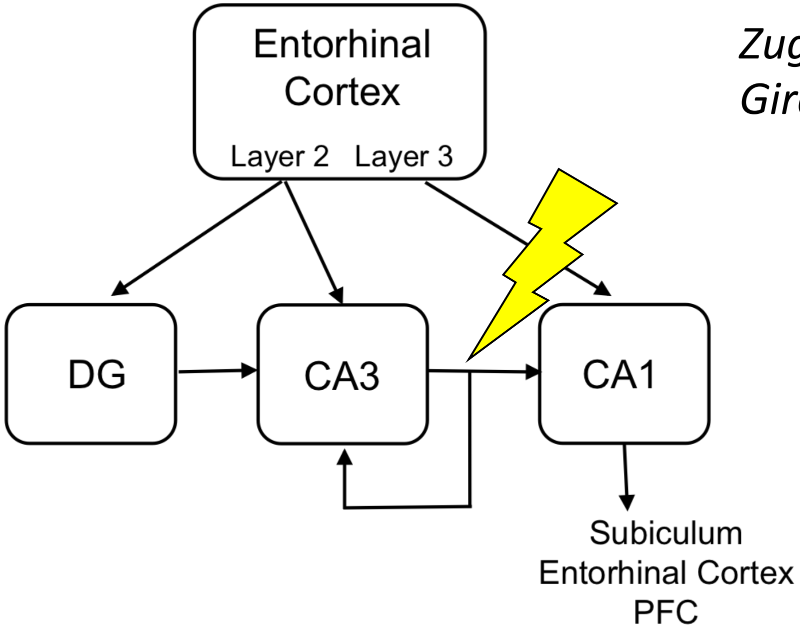
- Real-time fast detection of ripples

  - Simultaneous detection of SWRs on multiple electrodes in CA1 (n = 6).

  - Speed threshold to avoid false positives.

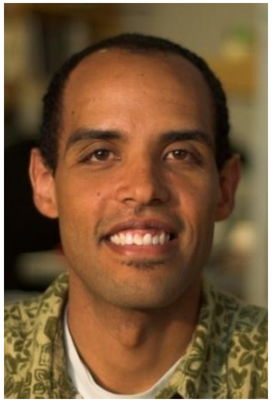
- Disruption of ripple activity triggered by real-time detection.

  - Stimulation in ventral Hippocampal Commissure (vHC) disrupts ripple activity and associated hippocampal output.



Zugaro, et al., 2005;
Girardeau, et al., 2009; Ego-Stengel, et al., 2010

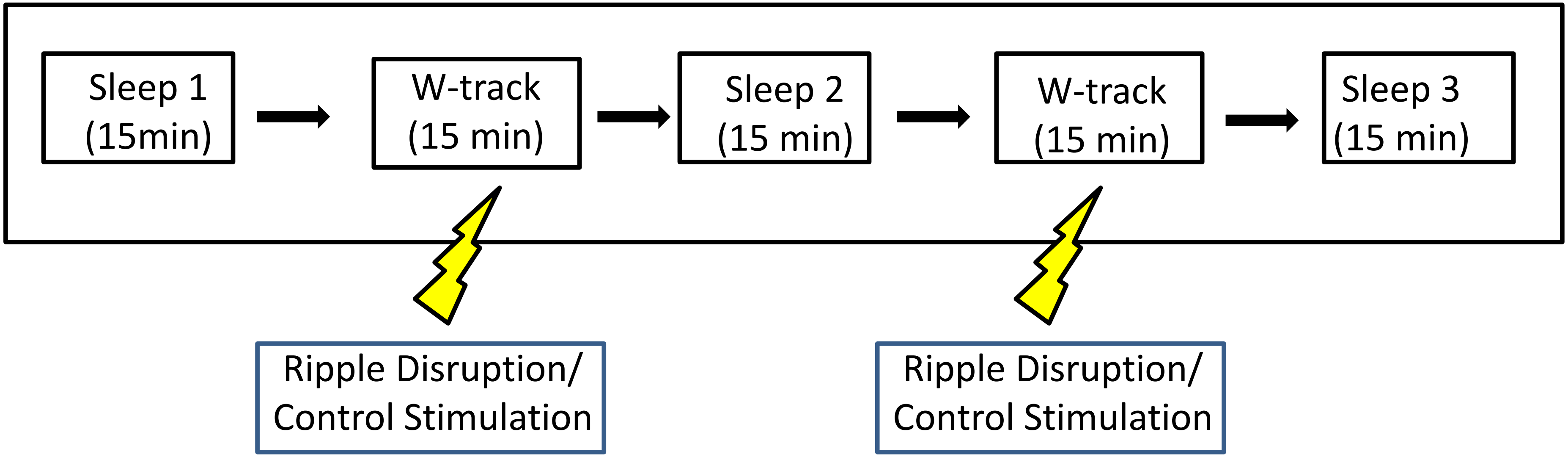
Shantanu Jadhav



Caleb Kemere

Ripple Disruption During Behavior

8 days of behavior for each animal



Behavioral Groups

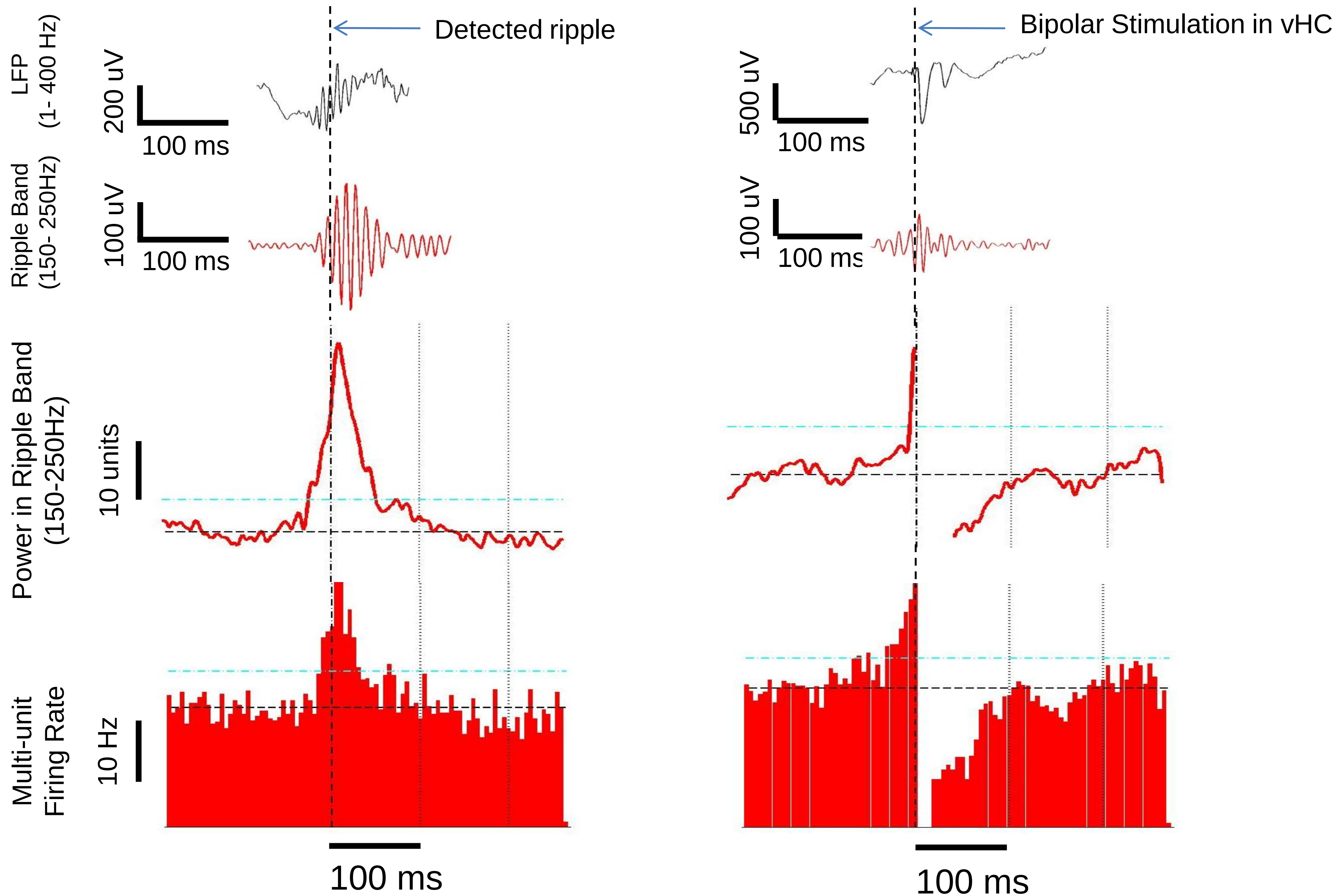
○ Ripple Disruption Group (n=6)

■ Control Stimulation Group (n=4)
Stimulation follows each ripple by 150-200 ms

□ Normal Group (n=4)
Unoperated, unstimulated Controls

Jadhav et. al., *Science* (2012)

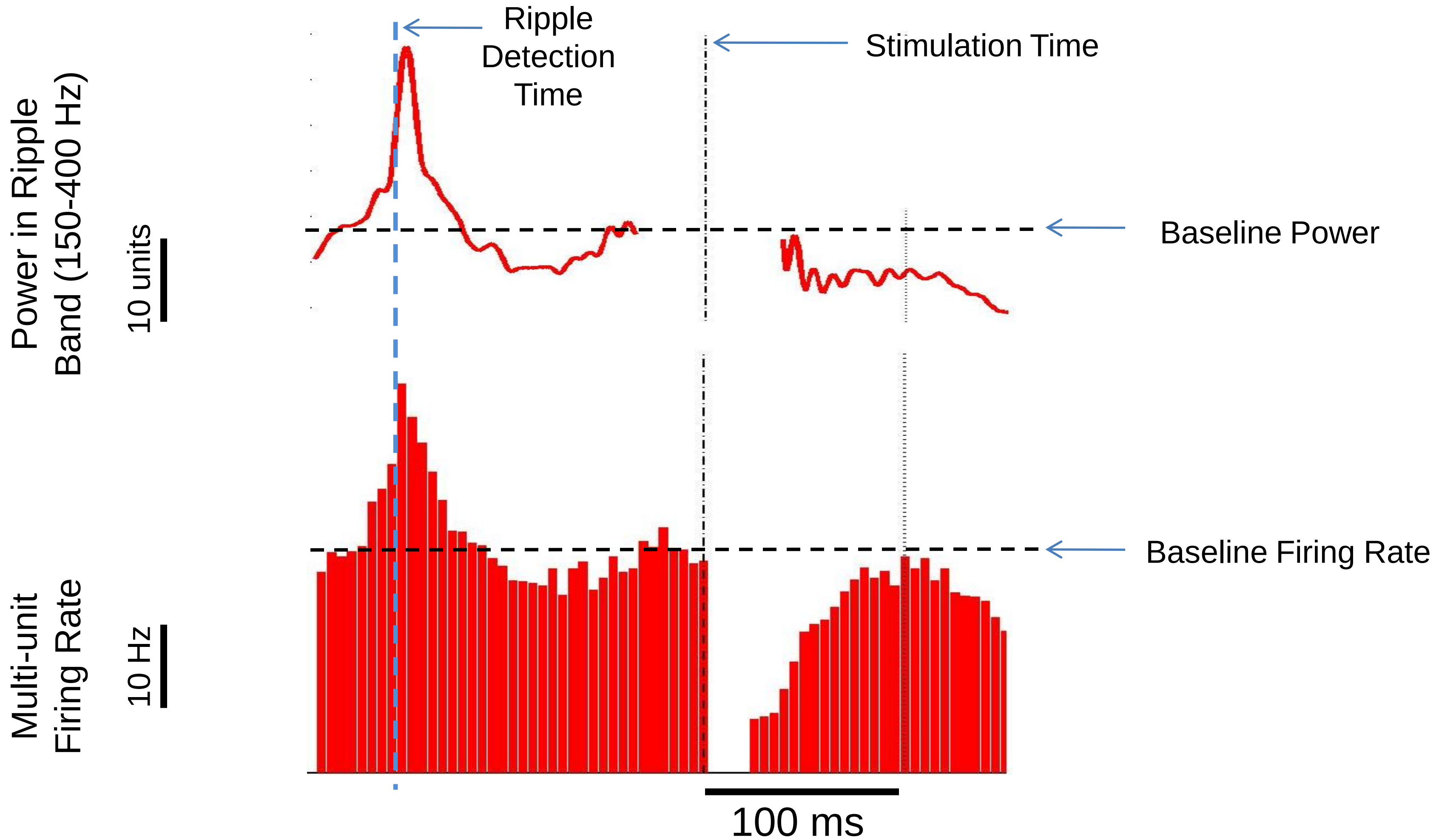
Effect of Ripple Disruption



Effect of Control Stimulation

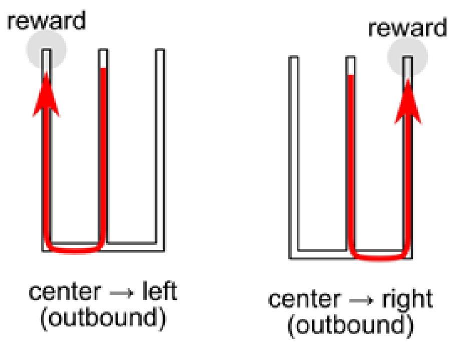
<u>Control Group</u>

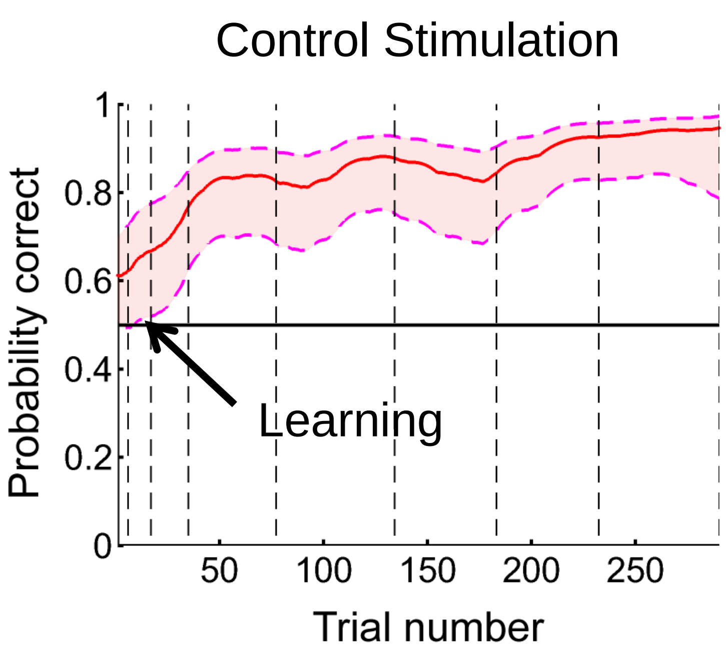
- Similar stimulation protocol with real-time detection of ripples and vHC stimulation ***<u>after</u>*** ripples with a delay of ~150 ms.

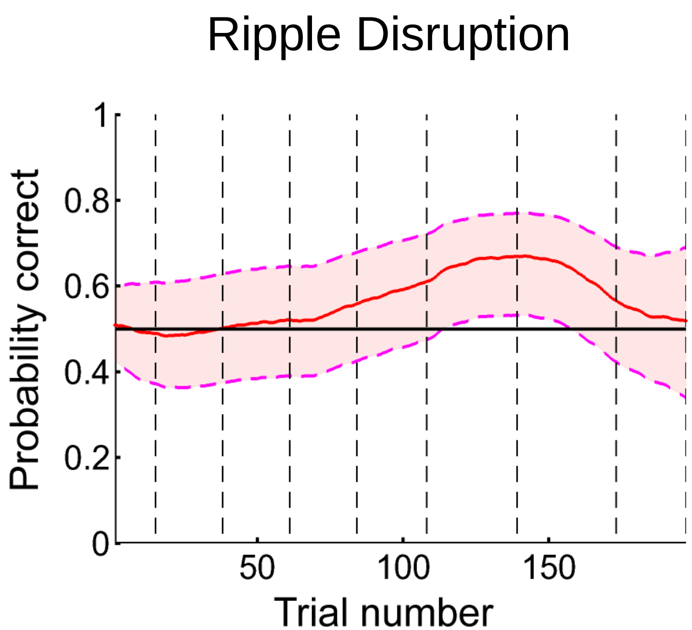


Learning – Outbound

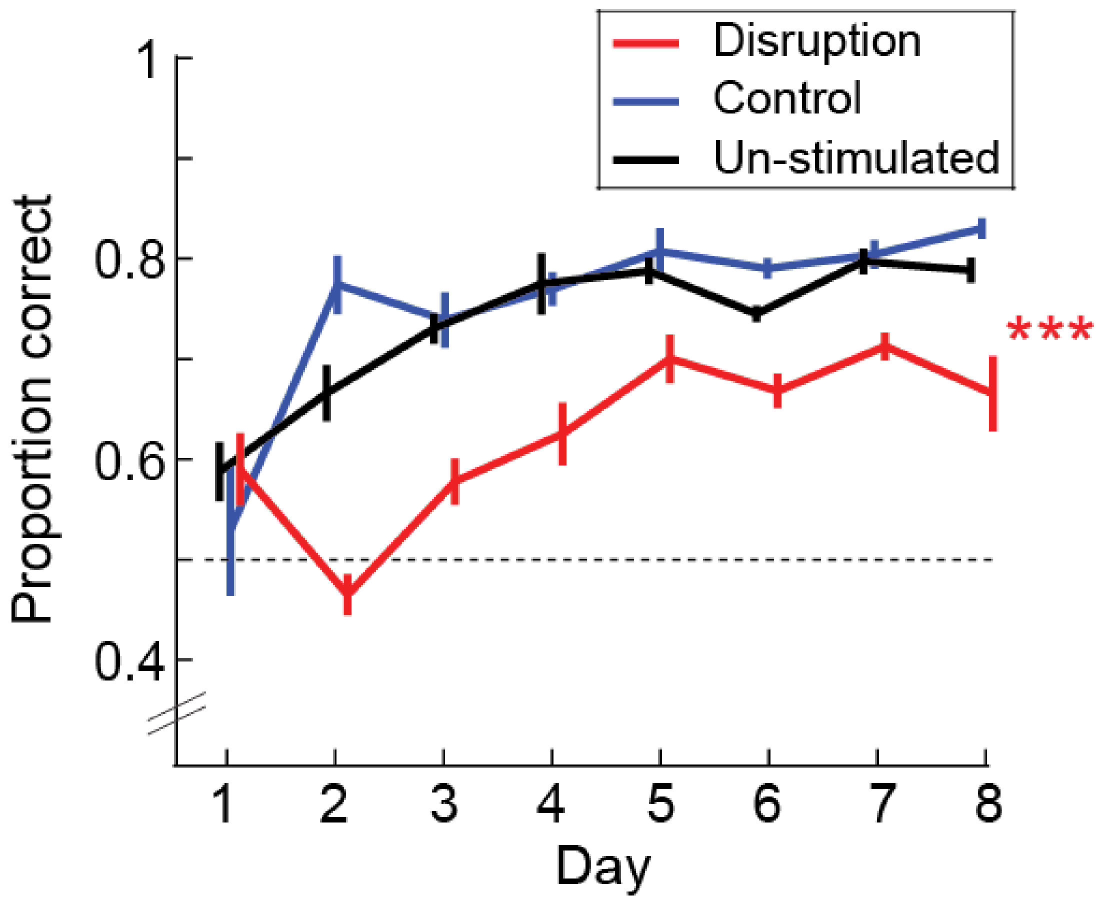
Outbound Trials



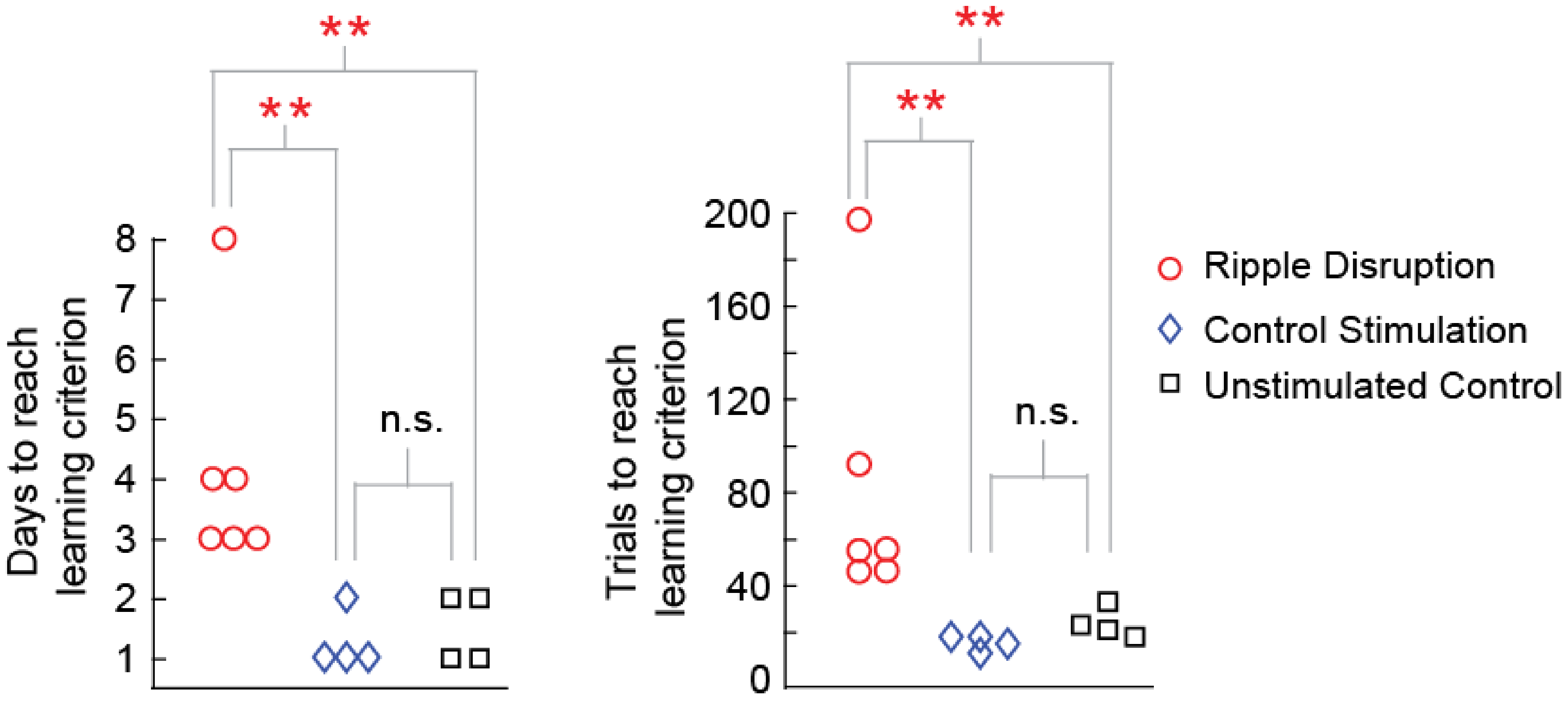




Learning – Outbound

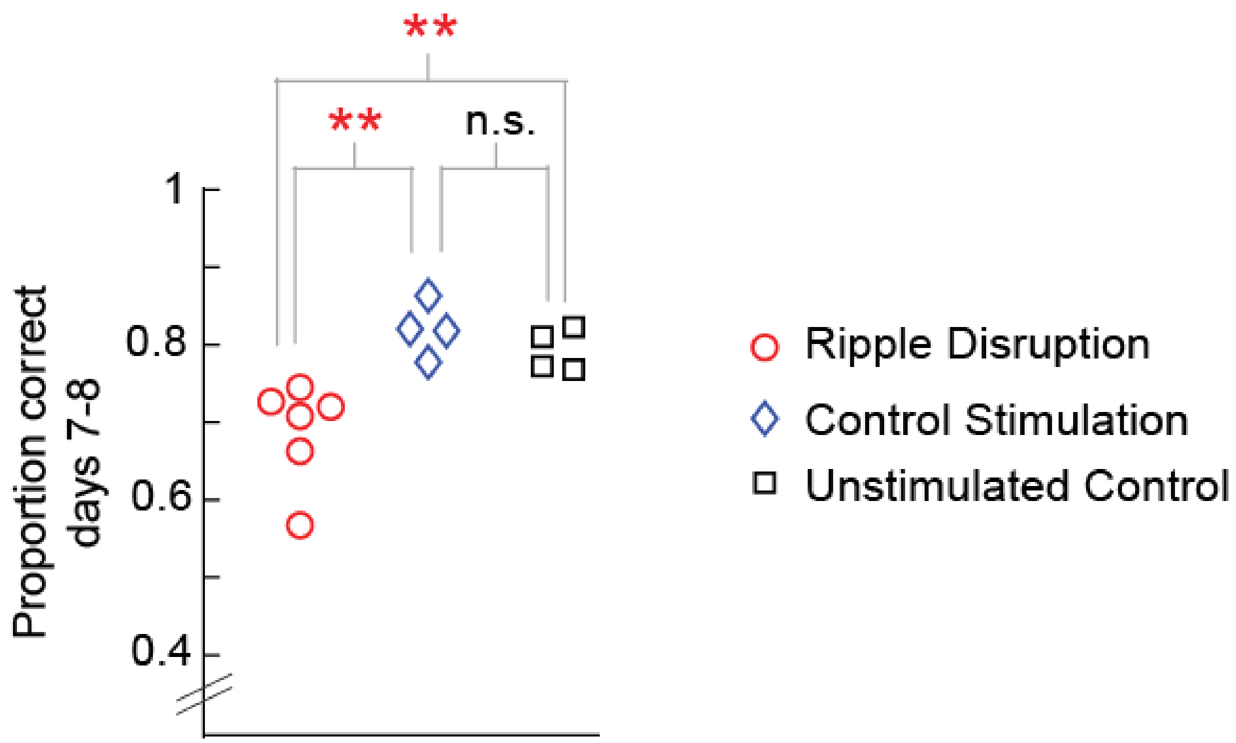


Learning – Outbound



Perfect separation between disruption and control groups ($p < 0.001$)

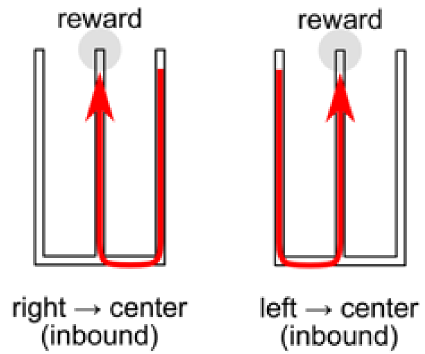
Learning – Final Two Days Outbound



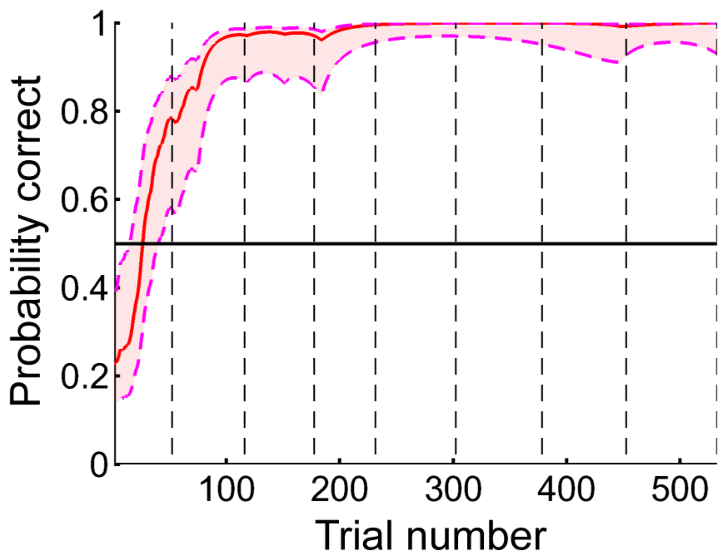
Perfect separation between disruption and control groups ($p < 0.001$)

Learning – Inbound

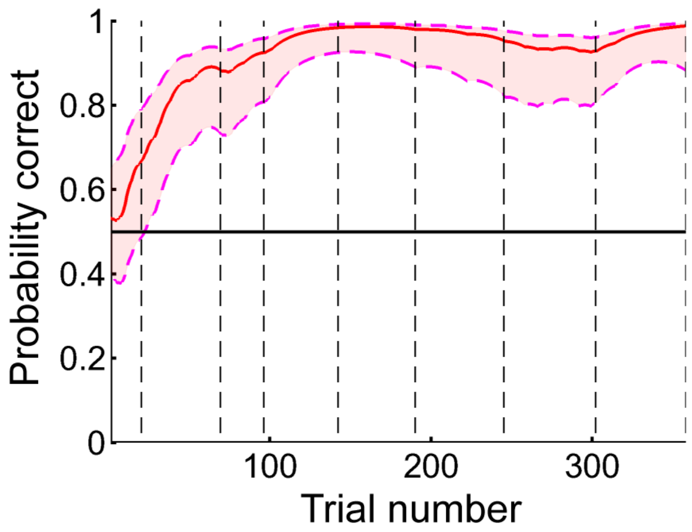
Inbound Trials



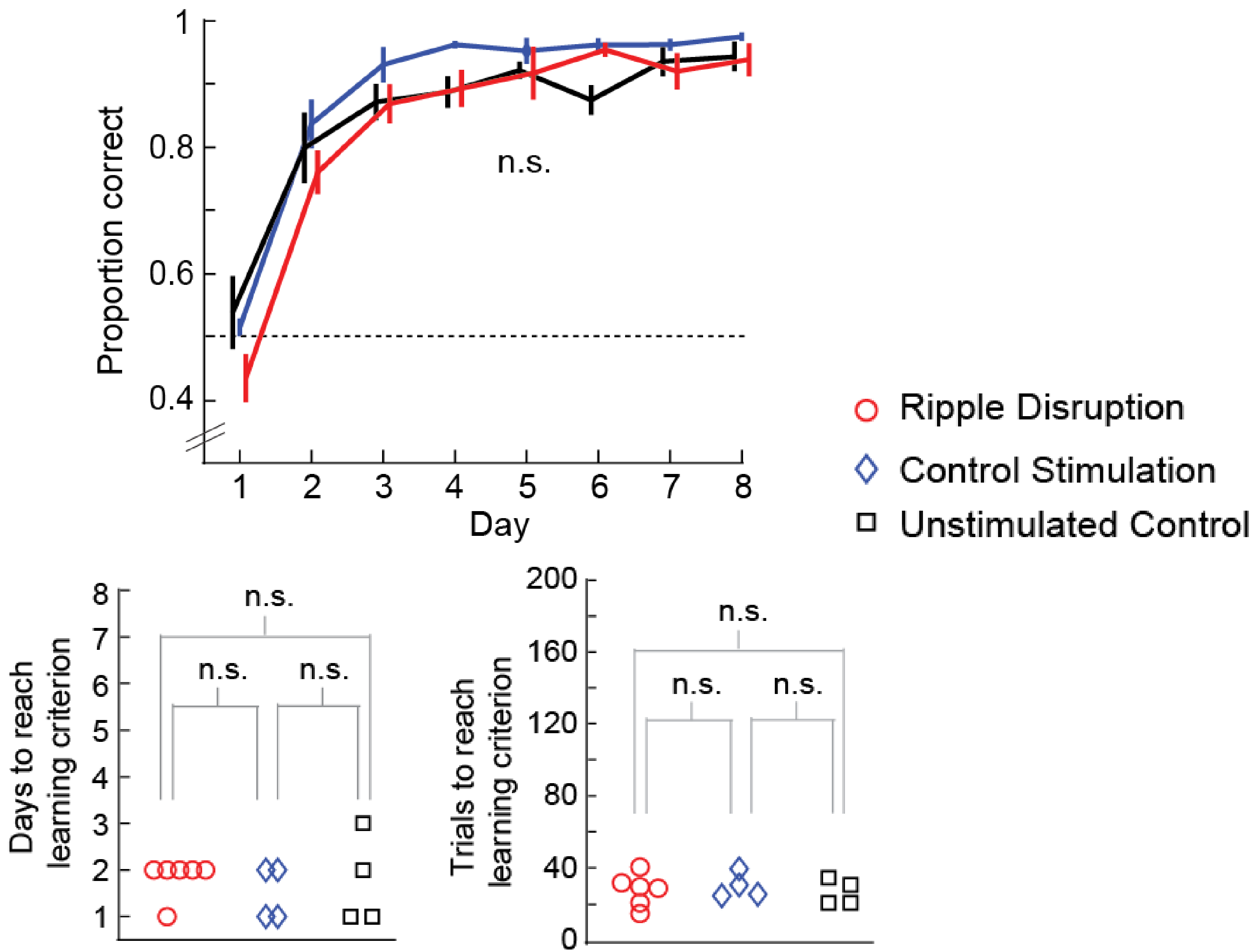
Control Stimulation



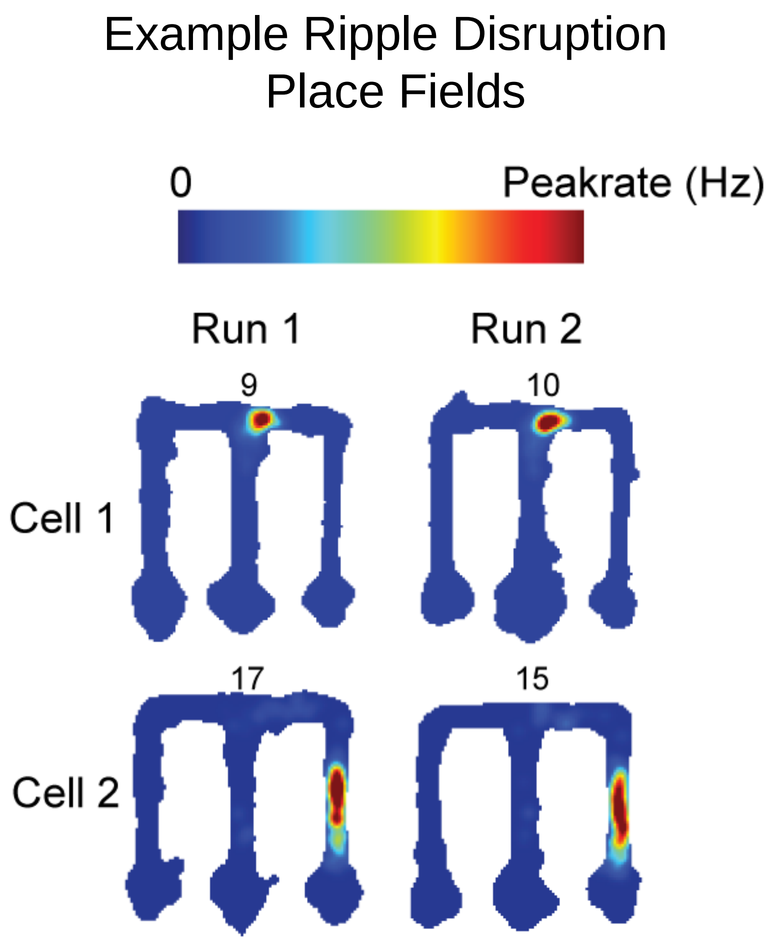
Ripple Disruption

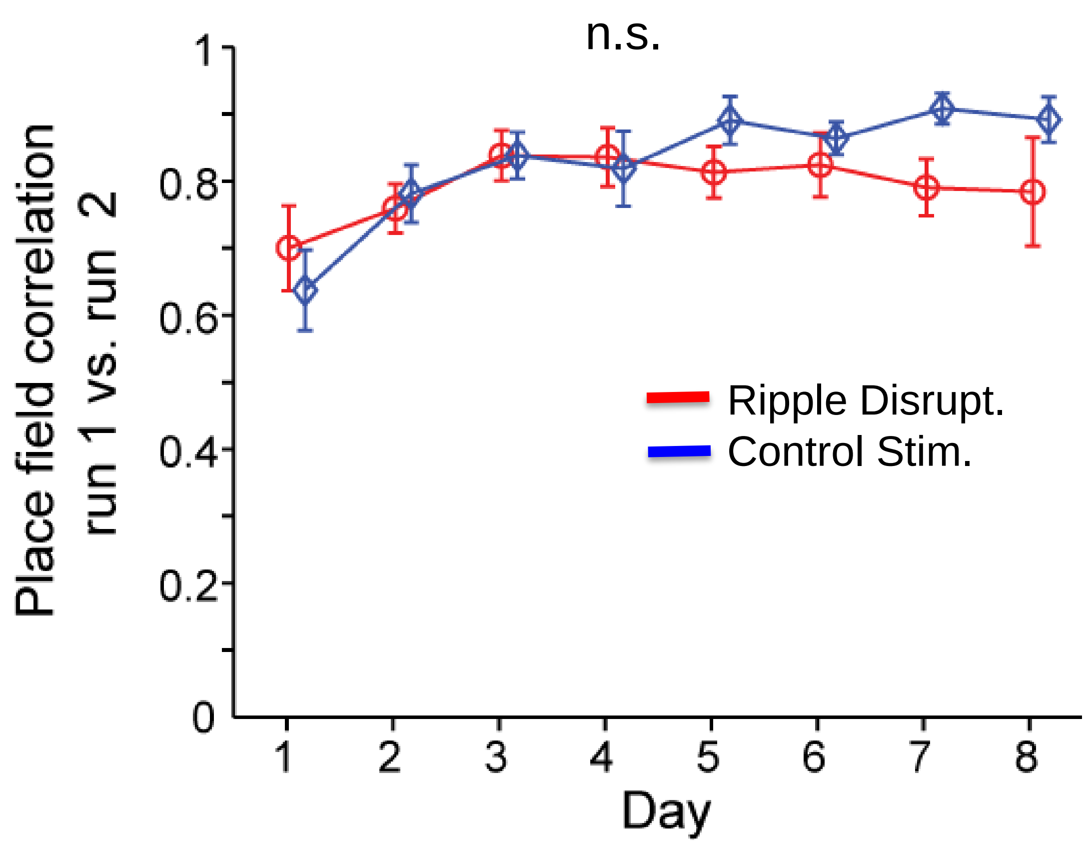


Learning – Inbound



Stable Place Fields Across Run Sessions





Conclusions – Awake ripple disruption

- We are able to specifically disrupt hippocampal ripples in the awake state during behavior.

- Ripple disruption during behavior in the W-task leads to an impairment in the outbound component of the task.

- Ripple disruption does not affect the inbound component of the task.

- Activity during awake ripples plays a role in learning.

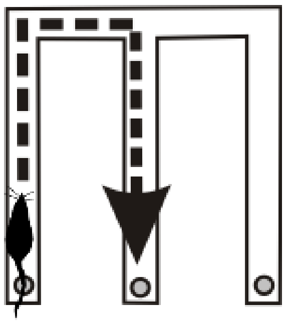
Questions

- Do awake SWRs contribute to memory-guided decision-making?

- How does memory replay during SWRs inform subsequent decisions?

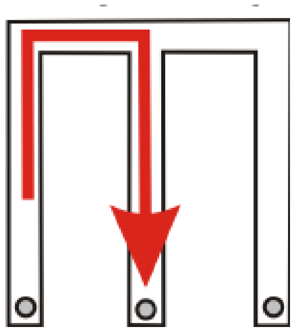
Why are Awake SWRs Important for Outbound Performance?

Inbound

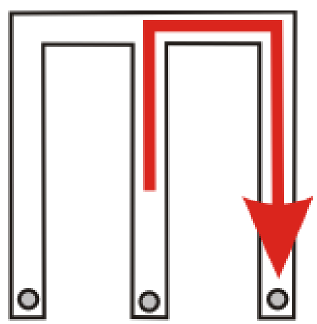


- Awake replay could be providing information about

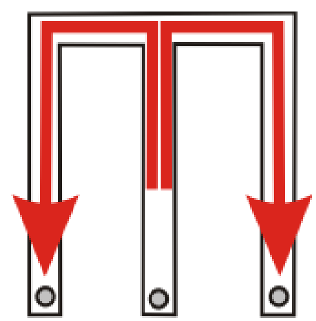
Past



Future



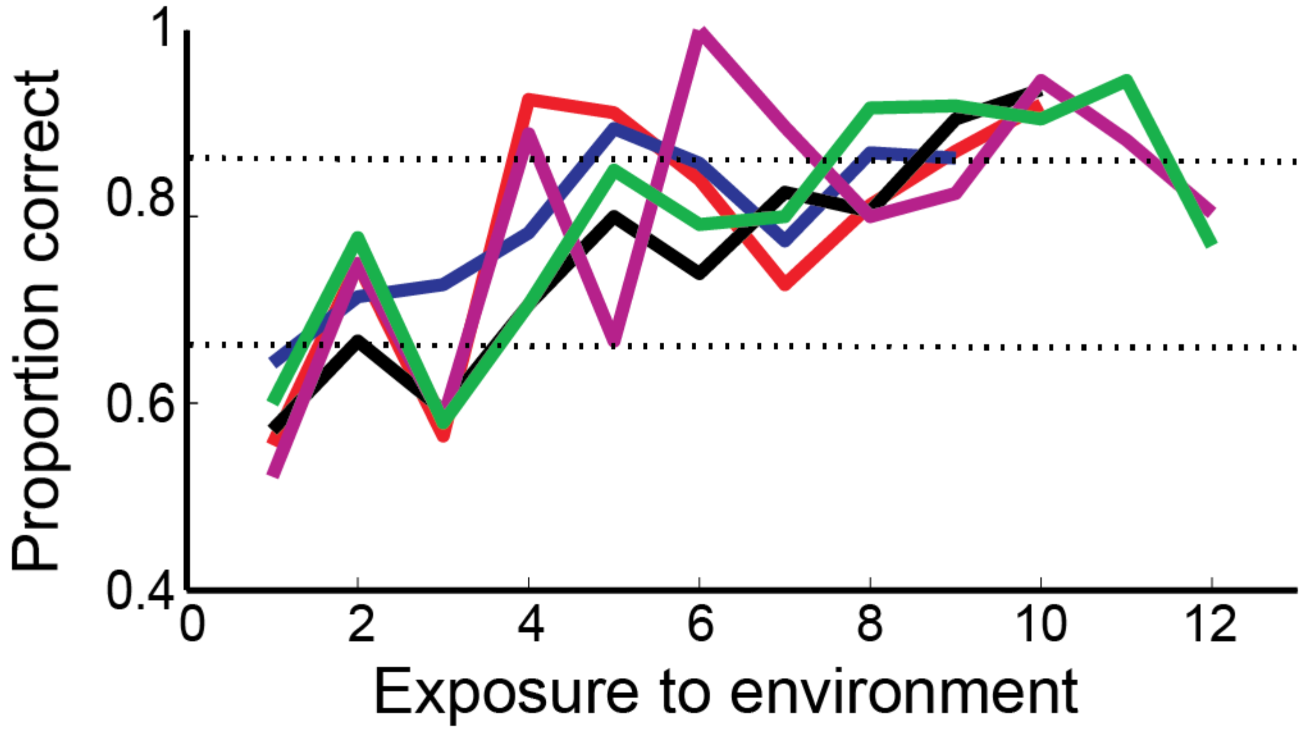
Future Options

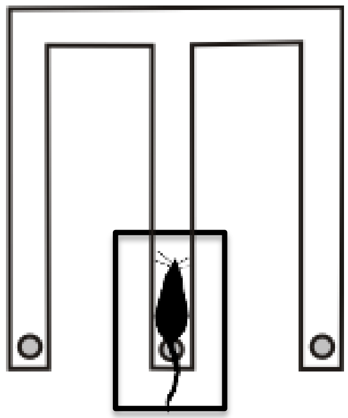


Annabelle Singer

Singer et. al., Neuron (2013)

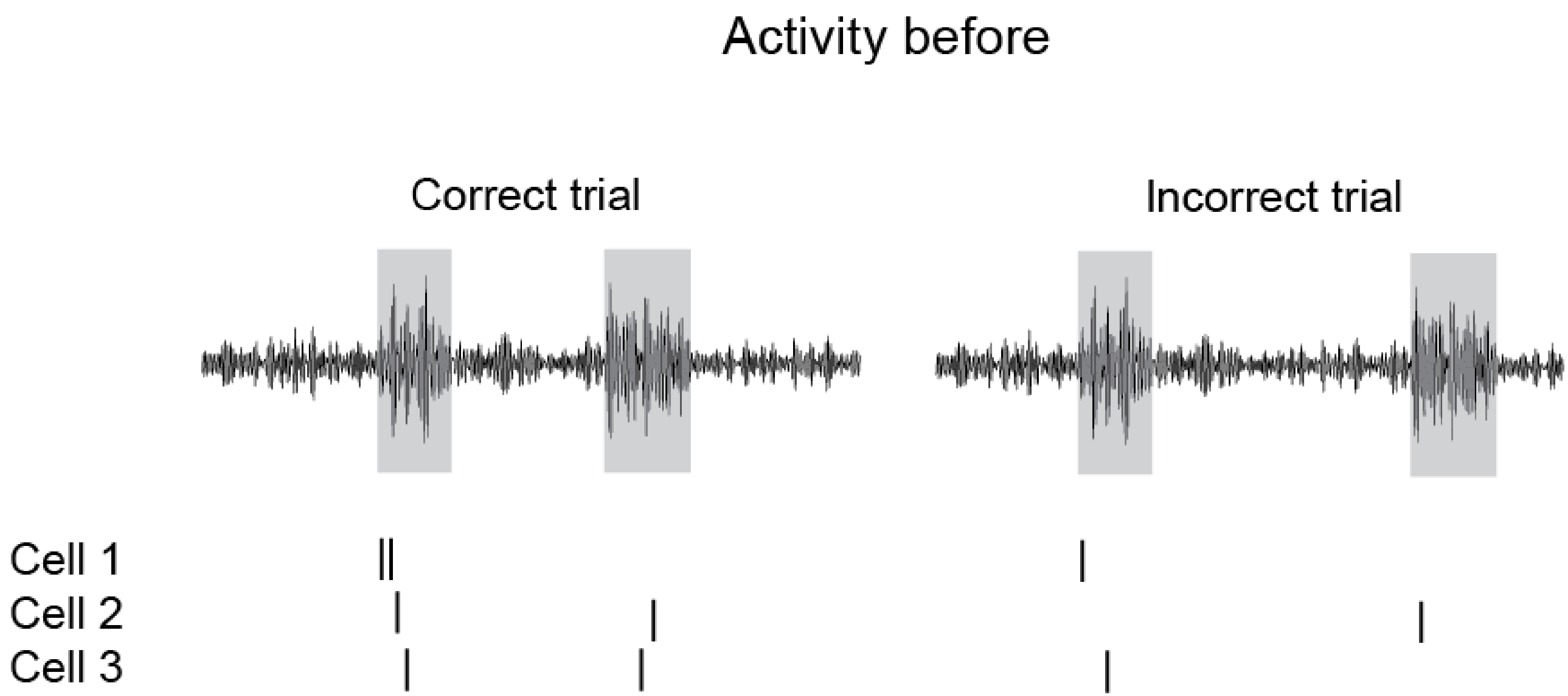
Behavior and SWRs on Outbound Trials





Examine SWRs when animal within 20 cm of center well

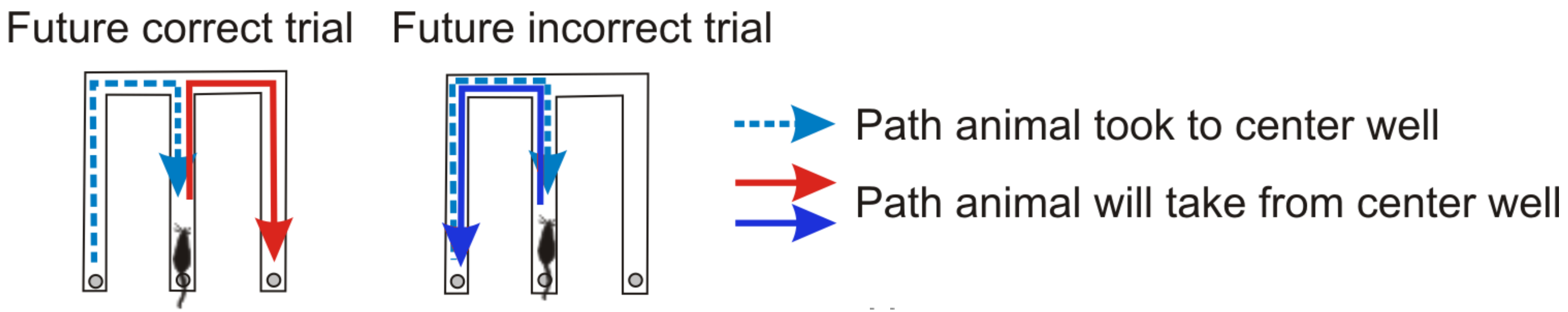
Analyzing Pair-wise Activity during SWRs

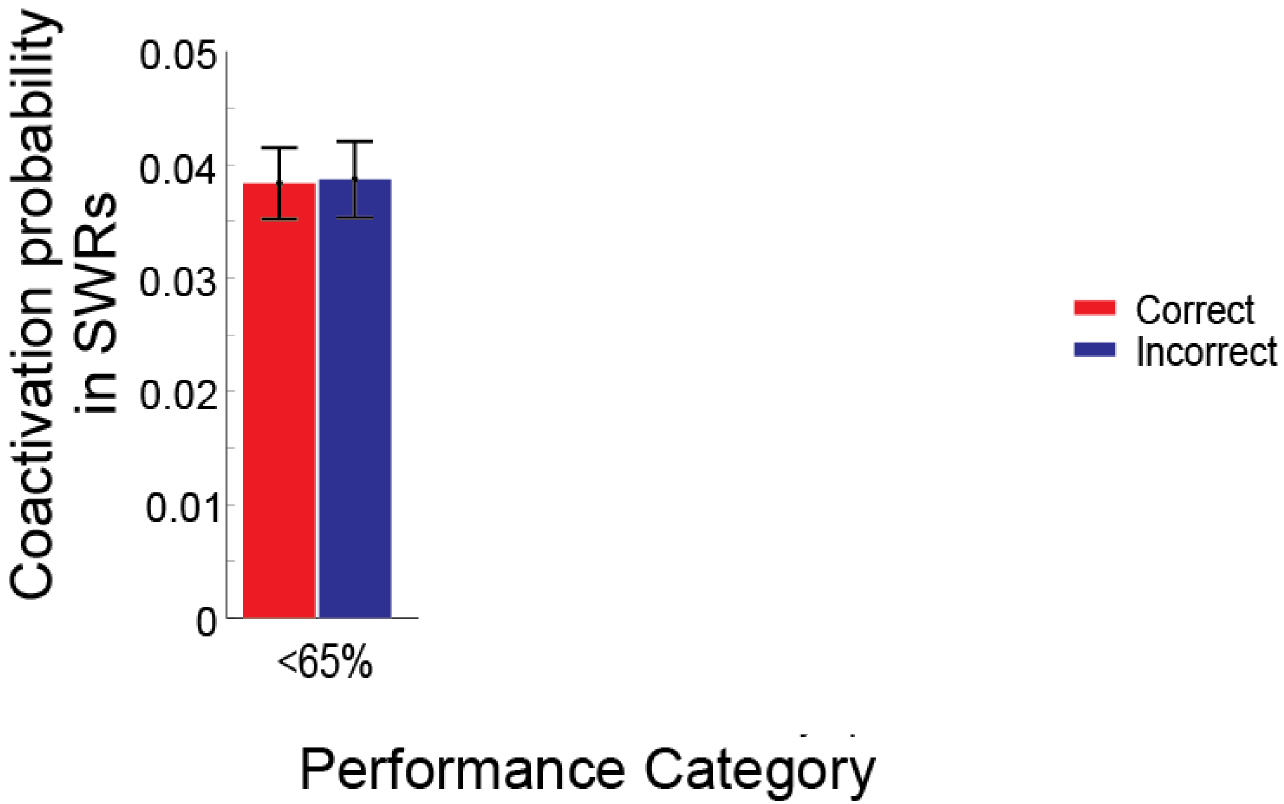


For each cell pair, compute, across all SWRs and trials

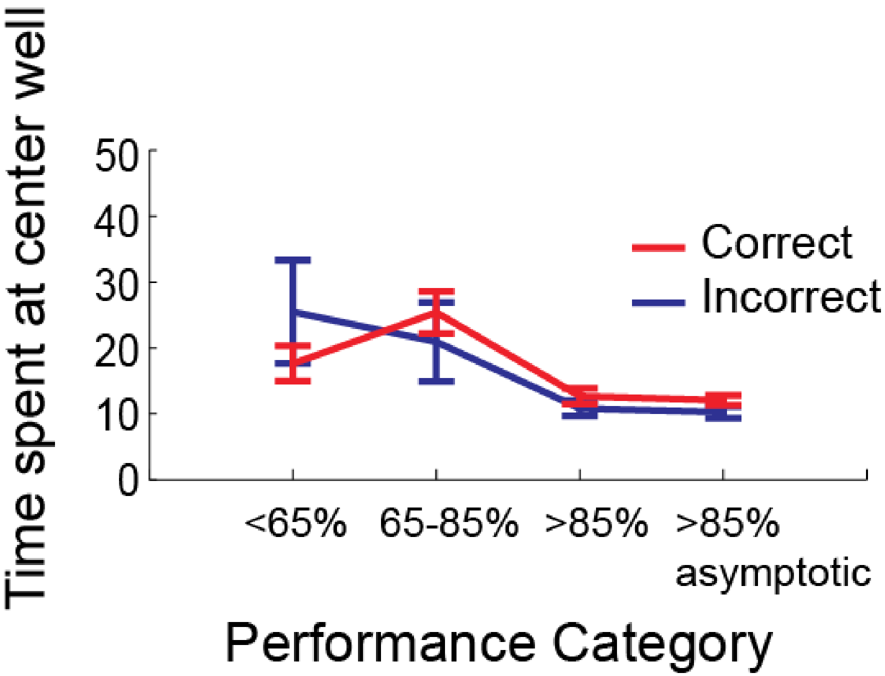
$$\hat{p}_{correct} = \frac{n\_coactive_{correct}}{N\_SWRs_{correct}} \quad \& \quad \hat{p}_{incorrect} = \frac{n\_coactive_{incorrect}}{N\_SWRs_{incorrect}}$$

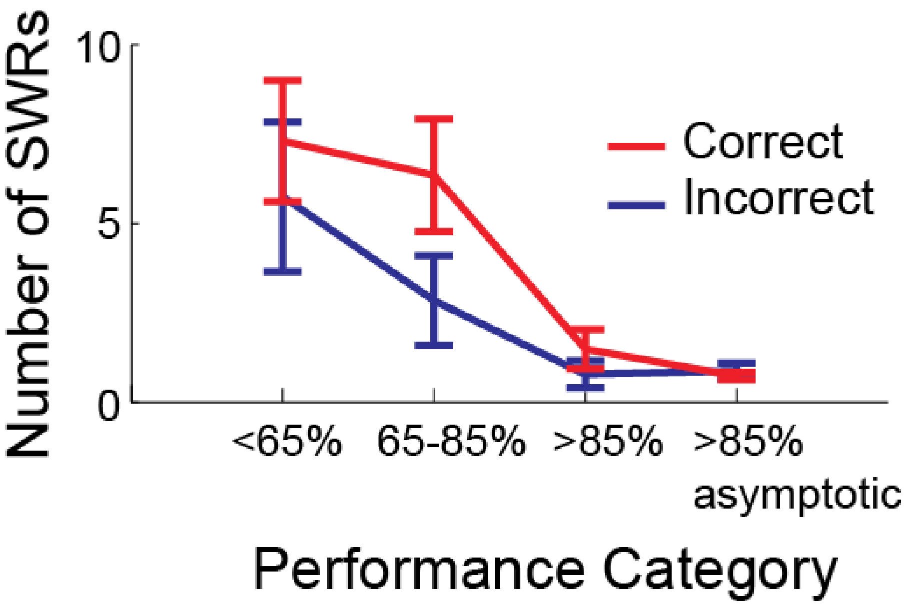
Greater Coordinated Activity on Correct Trials





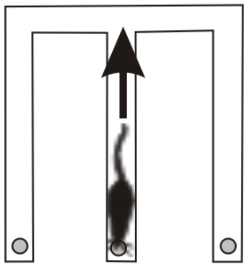
Similar Times and Numbers of SWRs Before Decisions



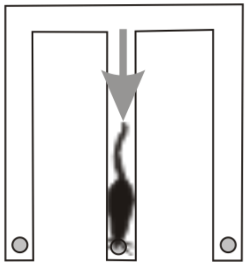


Bias Toward Outbound Trajectories on Correct Trials

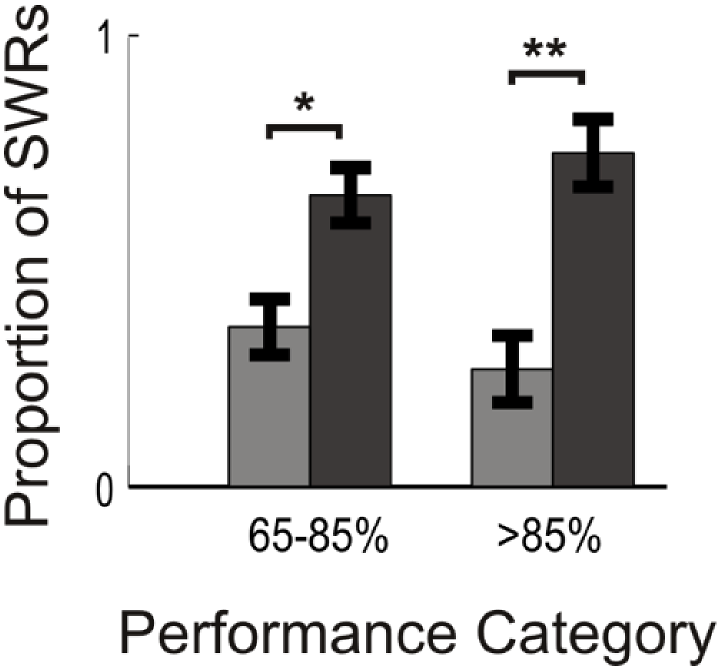
Pattern of activity during SWRs more consistent with



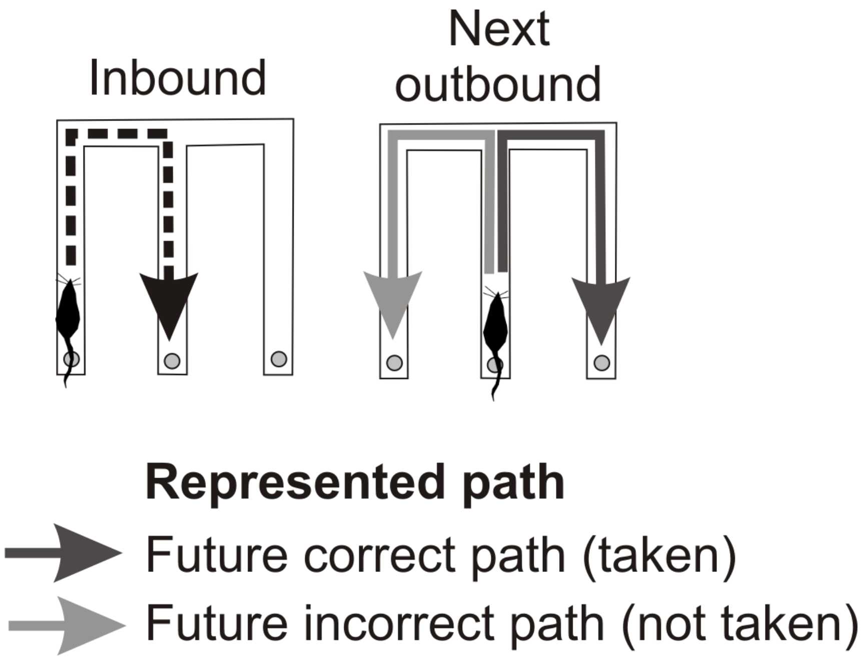
Outbound direction and future possible paths

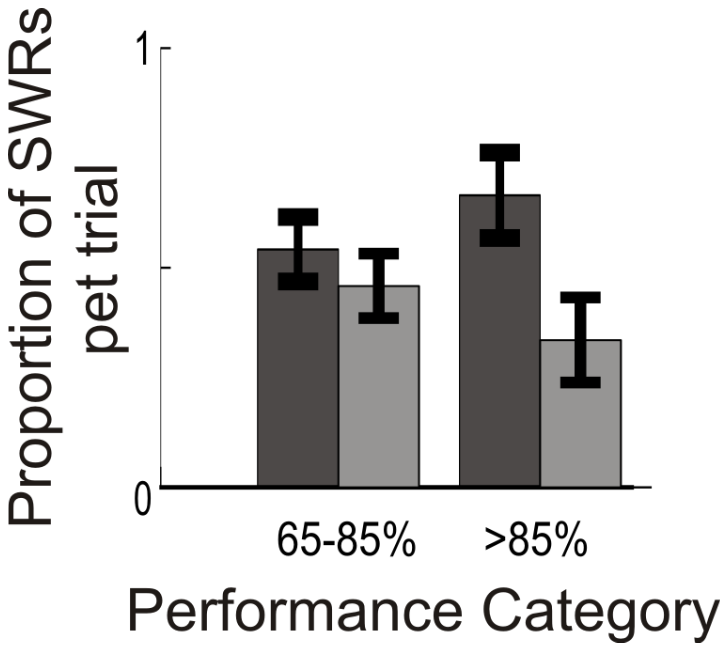


Inbound direction and past paths



No Bias Toward Correct Outbound Trajectories





Consistent with Karlsson and Frank (2009), Davidson et. al. (2009), Gupta et. al. (2010)

Conclusions – SWRs and Decision Making

- There is greater coordinated reactivation during SWRs preceding correct trials during learning.

- This reactivation tends to activate both possible outbound paths

- These results suggest that awake reactivation provides information about future possibilities to other brain regions.

Hypothesis

Different patterns of hippocampal activity support different types of memory:

Awake replay – remote memory retrieval, planning and consolidation

Sleep replay – consolidation of memories.

Place field activity – learning and associations related to current location.

Lab members and collaborators

Lab Members

Emily Anderson
Jason Chung
P. Walter German
Irene Grossrubatscher
Sheri Harris
Shantanu Jadhav
Kenny Kay
Mattias Karlsson
Daniel Liu
Gideon Rothschild
Demetris Roumis
Marielena Sosa
Jai Yu

Former Lab Members

Margaret Carr
Sen Cheng
Yuri Dabaghian
Caleb Kemere
Steve Kim
Annabelle Singer

Collaborators

Stanford

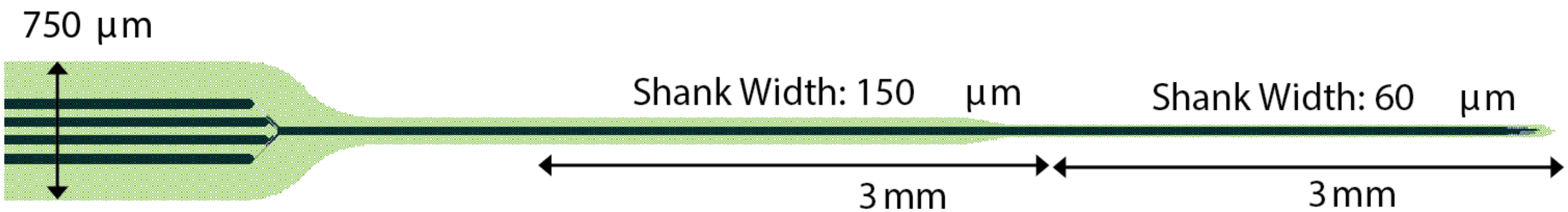
Karl Deisseroth

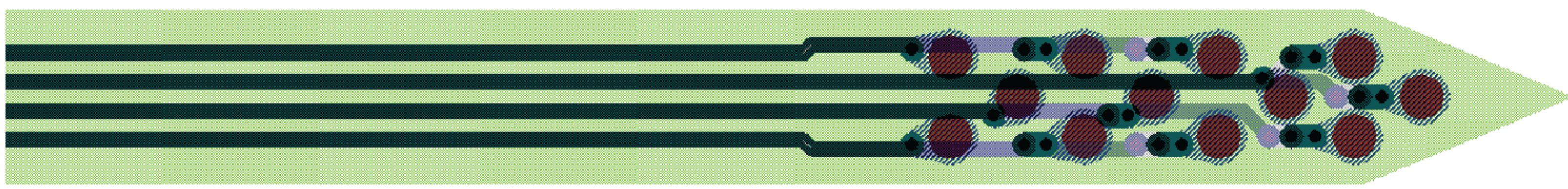
LLNL

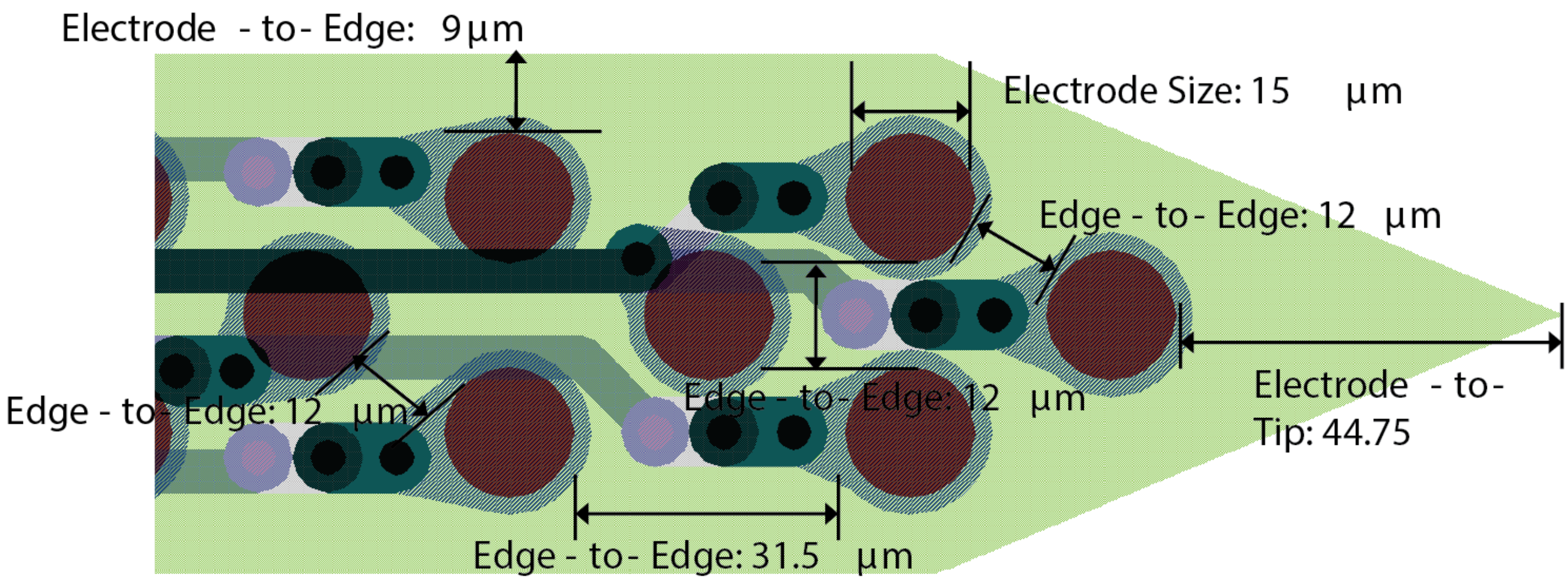
Vanessa Tolosa
Kedar Shah

Funding: McKnight Foundation, John Merck Fund, NIH

New High Density Recording Probes







Vanessa Tolosa, LLNL