Hippocampal mechanisms of memory and cognition

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The lamellar hypothesis revisited

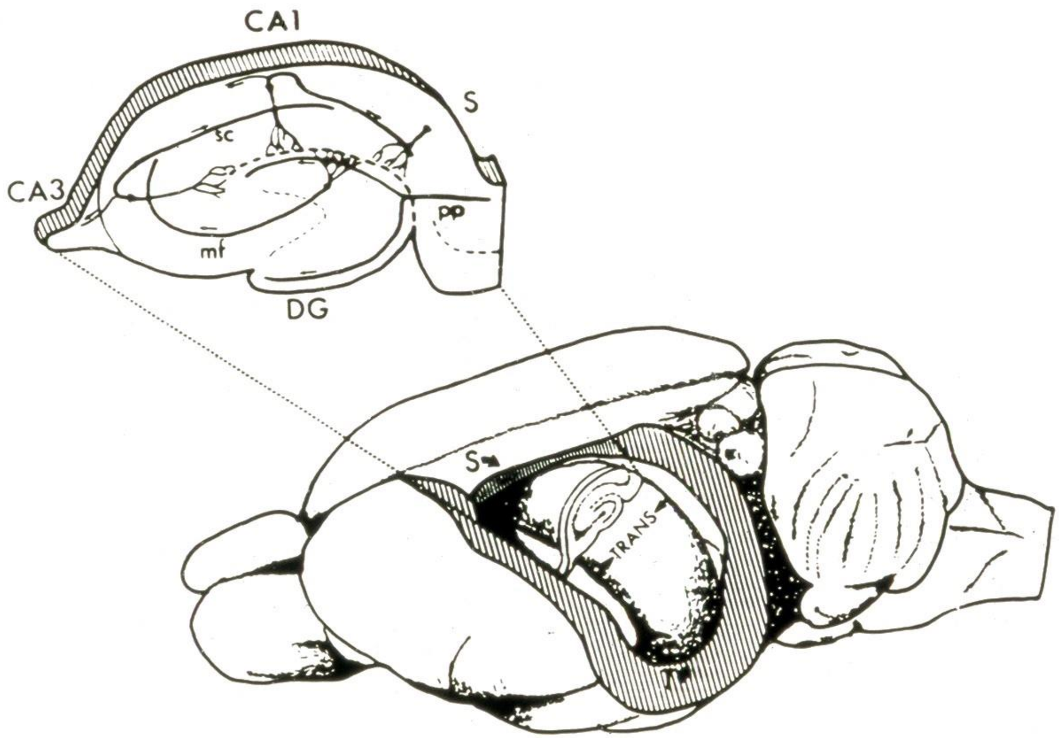


Fig. 2. The position of the hippocampal formation in the rat brain is shown in this drawing of a preparation in which the cortical surface overlying the hippocampus has been removed. The hippocampus is an elongated, C-shaped structure with the long or septotemporal axis running from the septal nuclei rostrally (S) to the temporal cortex (T) ventrocaudally. The short or transverse axis (TRANS) is oriented perpendicular to the septotemporal axis. The major fields of the hippocampal formation (except for the entorhinal cortex) are found in slices taken approximately midway along the septotemporal axis. The slice pictured at top left is a representation of the summary of the major neuronal elements and intrinsic connections of the hippocampal formation as originally illustrated by Andersen *et al.* (see text for details).
Abbreviations: DG, dentate gyrus; mf, mossy fibers; pp, perforant path; sc, Schaffer collaterals.

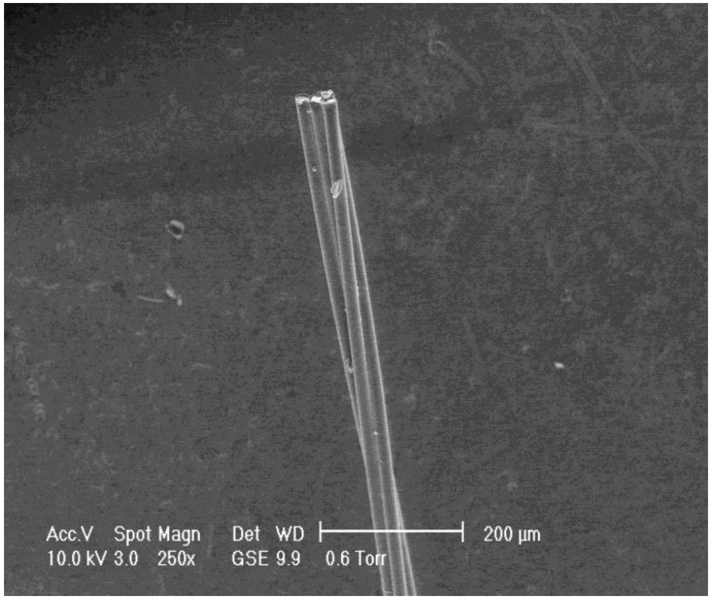
Source: Amaral, David G., and M. P. Witter. "The three-dimensional organization of the hippocampal formation: A review of anatomical data." Neuroscience 31, no. 3 (1989): 571-591.

From Amaral and Witter, 1989

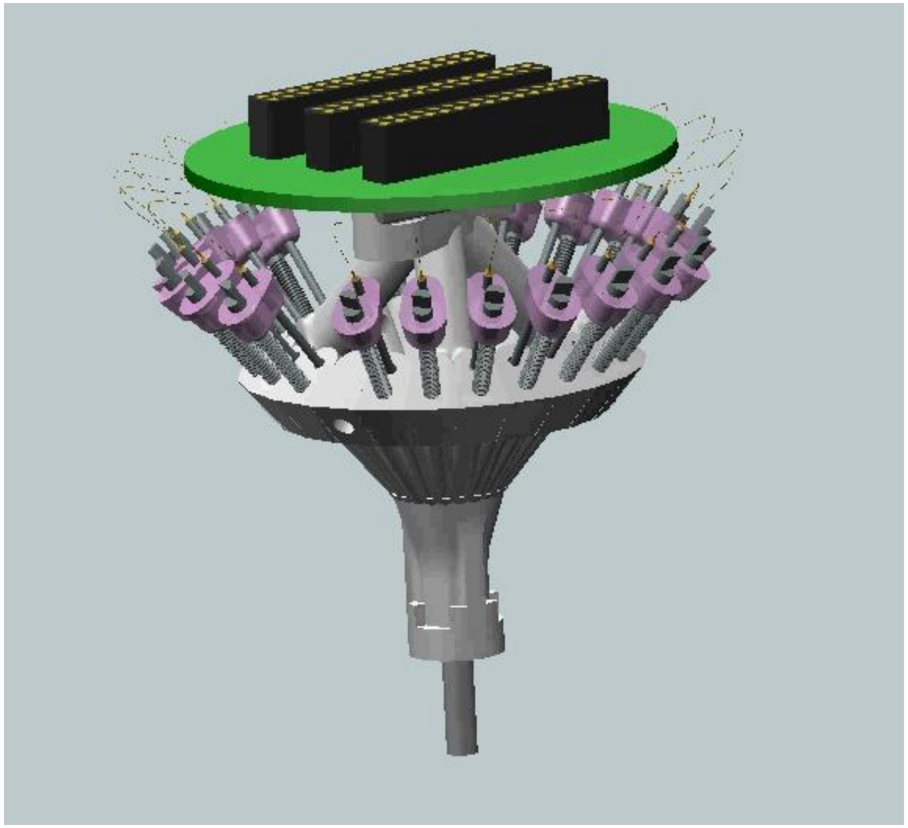
Hippocampus in spatial and episodic memory

- The hippocampus is involved in the formation of episodic memory as well as spatial memory used in navigation.
- Navigation - linkage of spatial locations
- Episodic memory - linkage of events
- Both may depend critically on temporal sequence encoding

Neural recording device

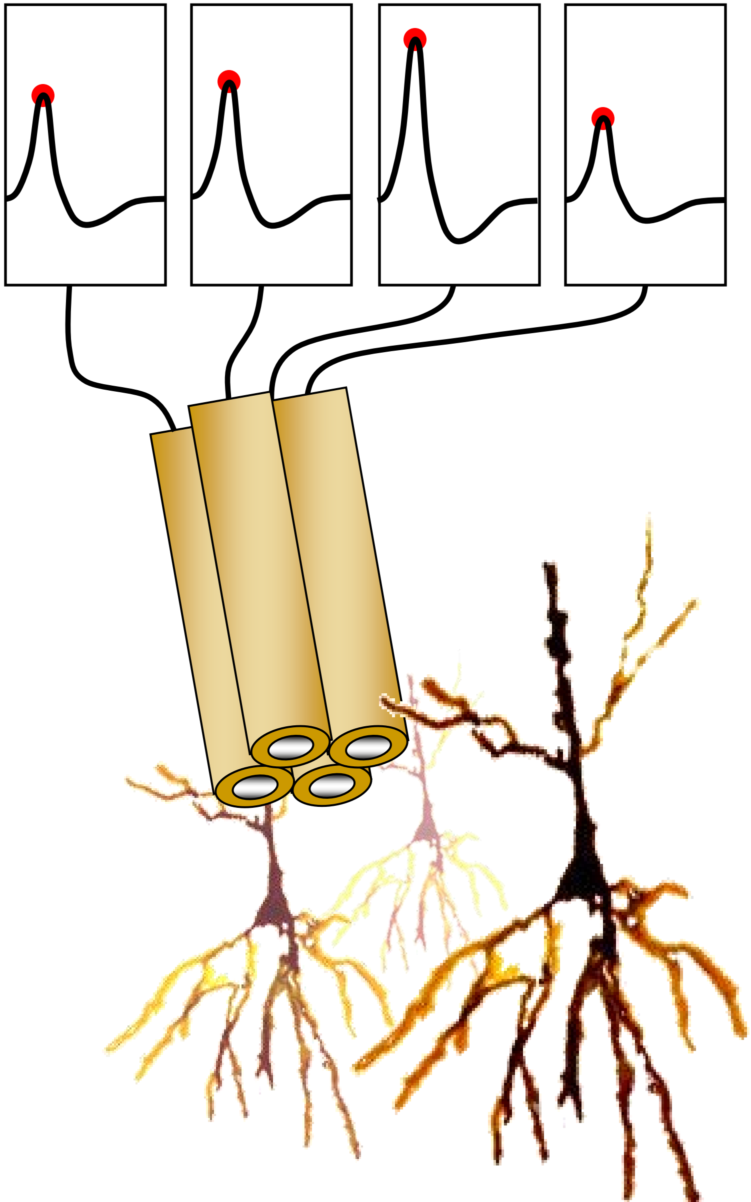


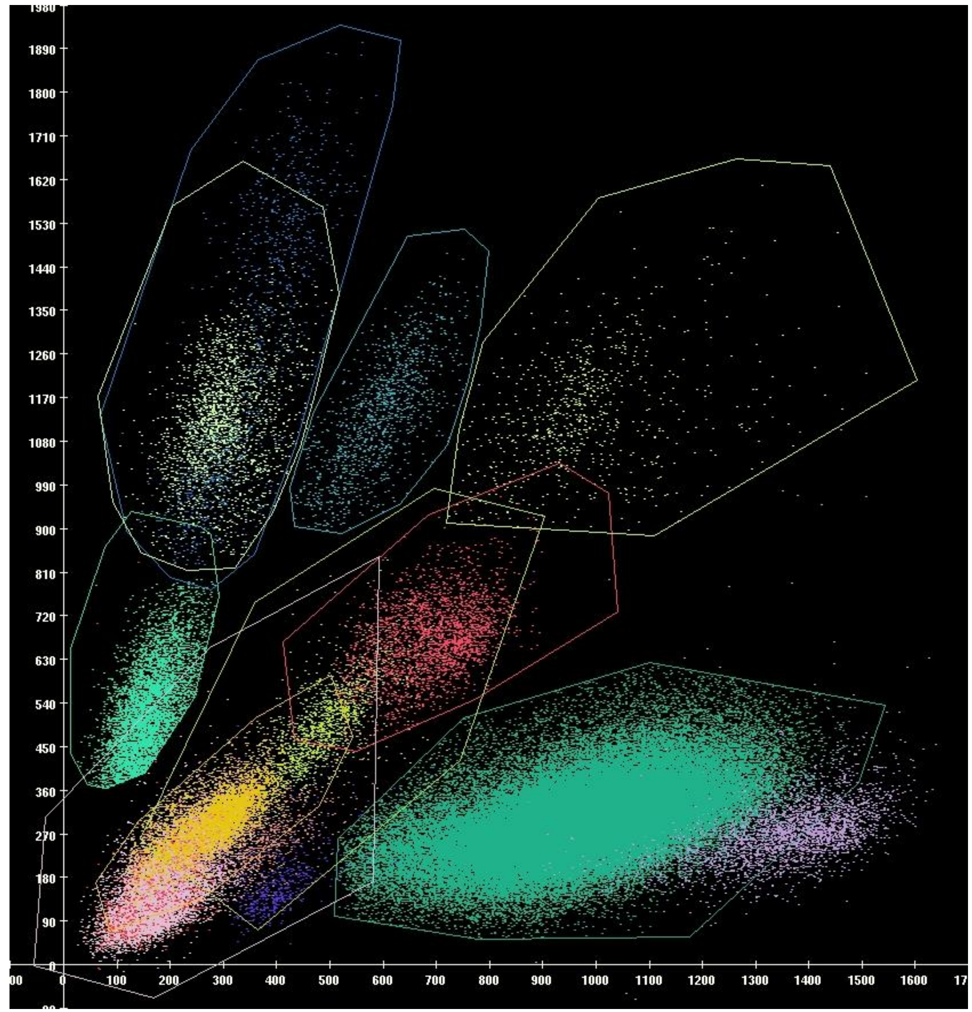
4-channel microwire electrode



Multiple electrode microdrive array

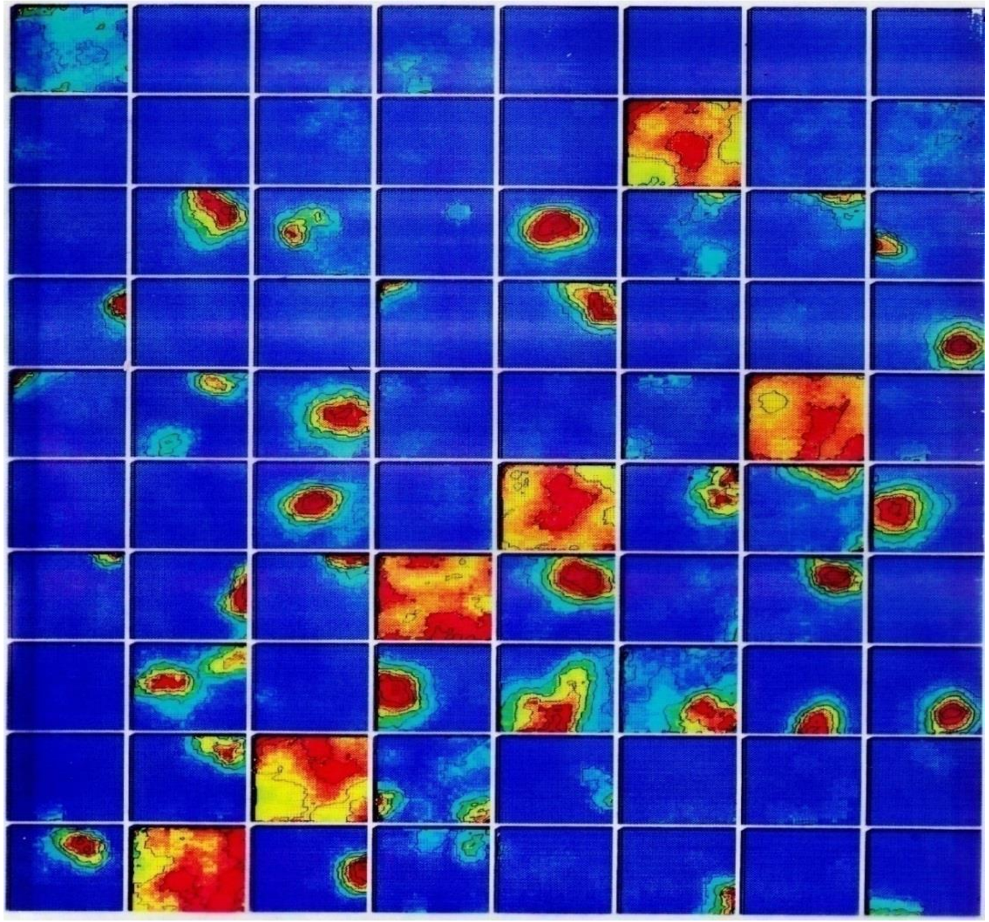
Spike amplitude clustering





Example of a Simple Spatial Environment

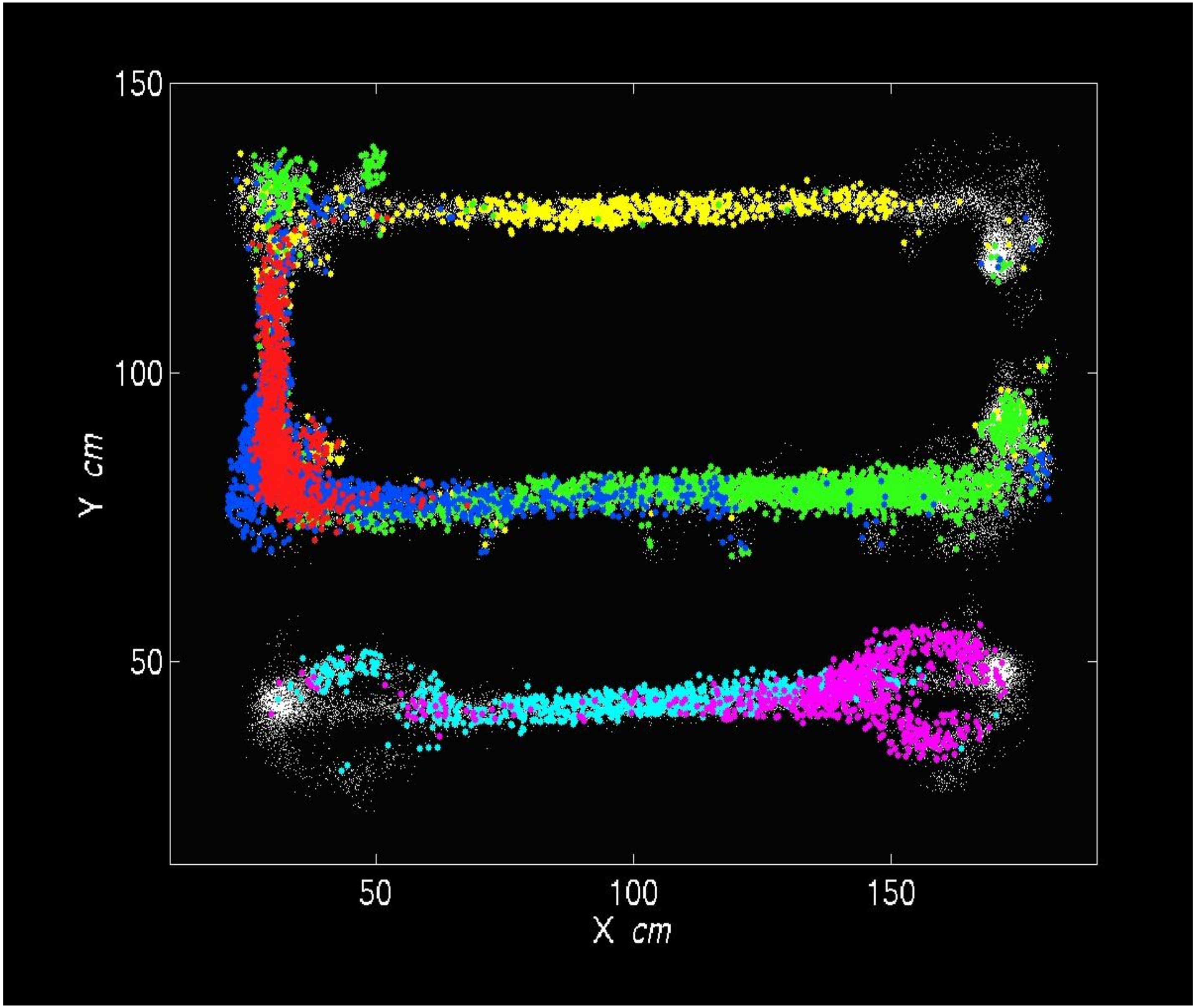
Ensemble Activity in Area CA1 During Spatial Exploration



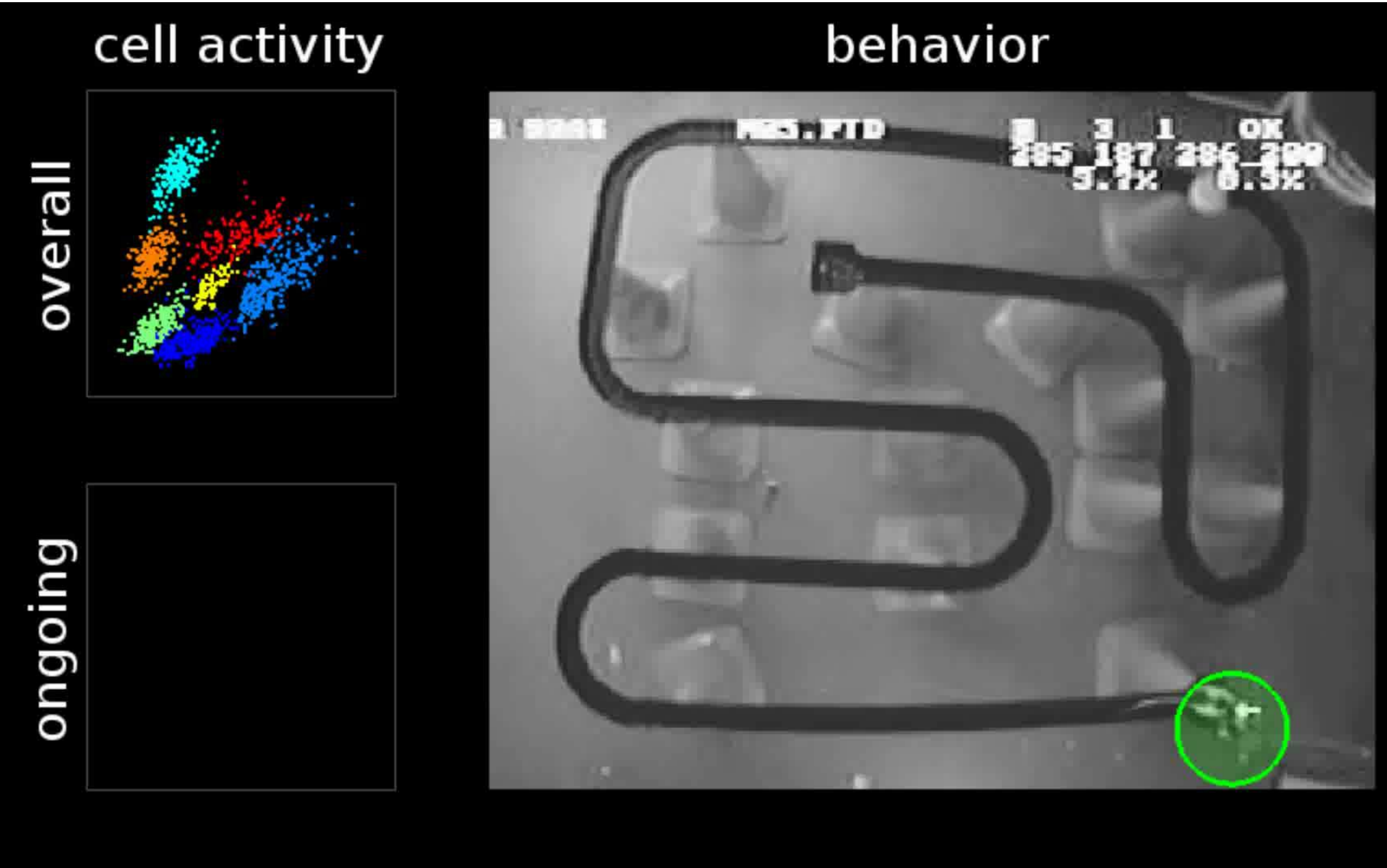
Source: Wilson, M. A., and B. L. McNaughton. "Dynamics of the Hippocampal Ensemble Code for Space (Vol 261, Pg 1055, 1993)." Science 264, no. 5155 (1994): 16.

Wilson and McNaughton, *Science*, 1993

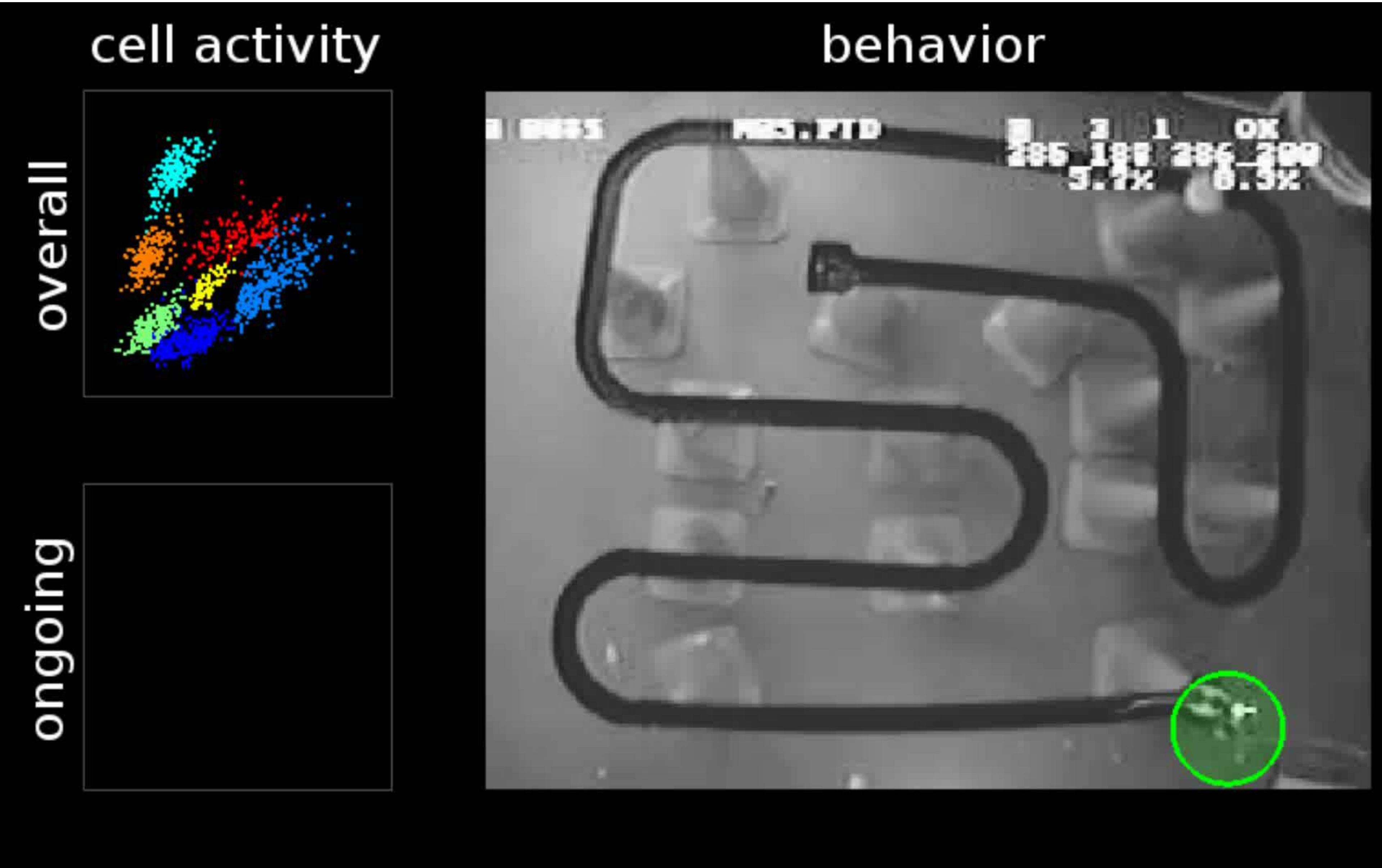
Place Fields on Linear Tracks



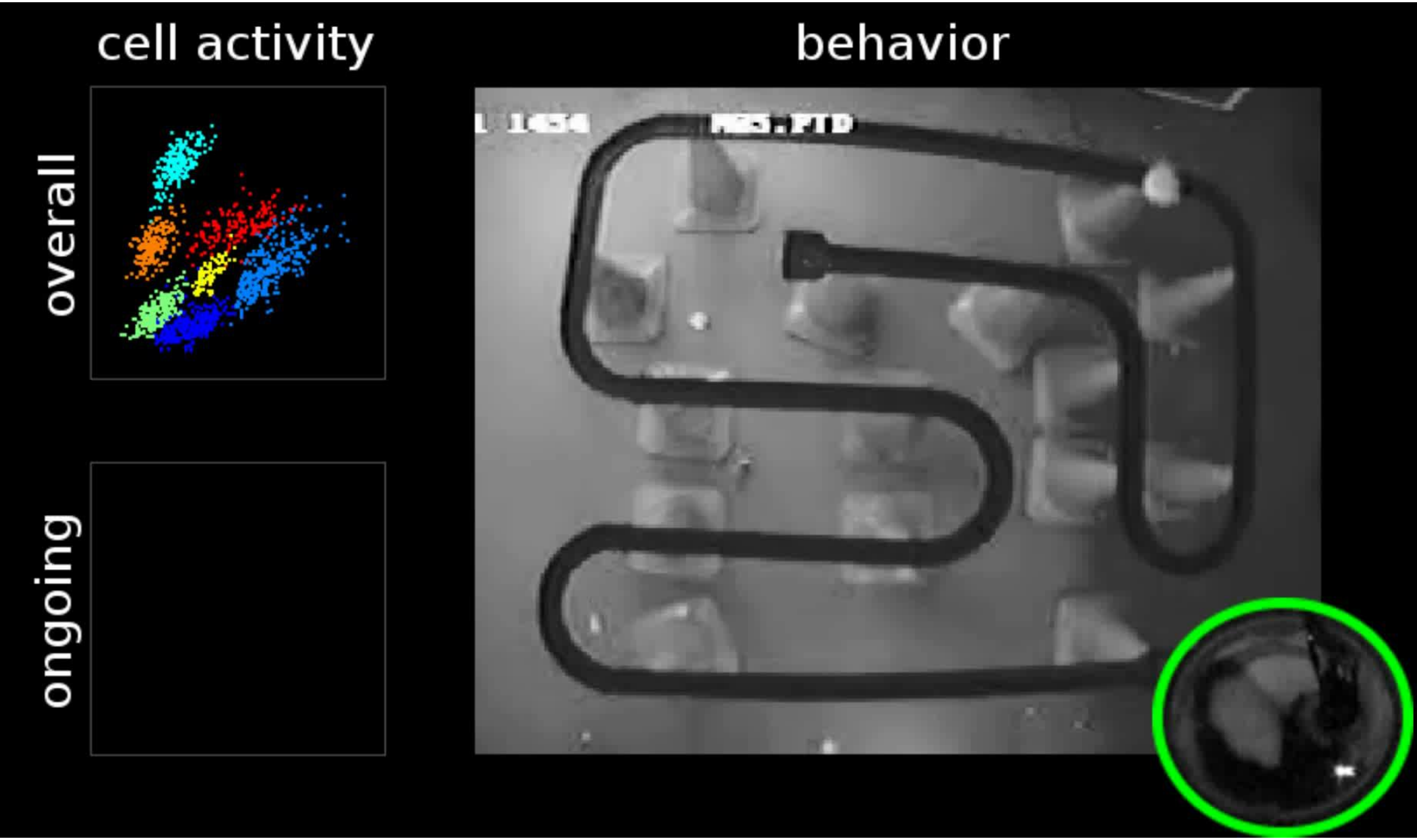
Hippocampal Place Cells



Hippocampal Ensemble Decoding



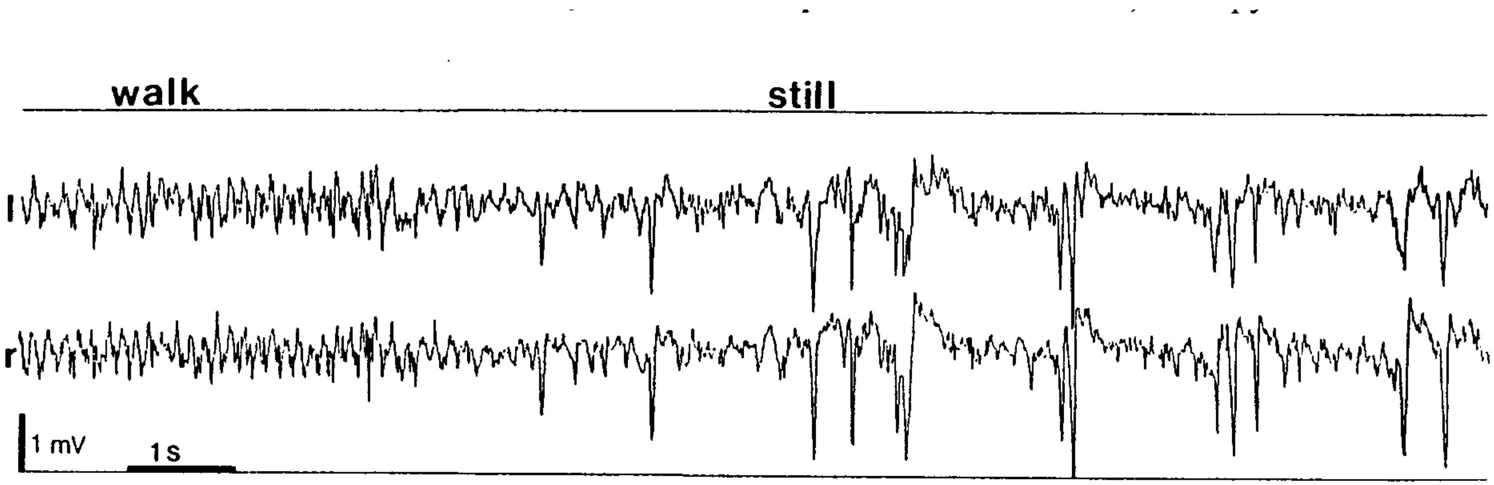
Decoding Sleep Reactivation



Hippocampus online and offline

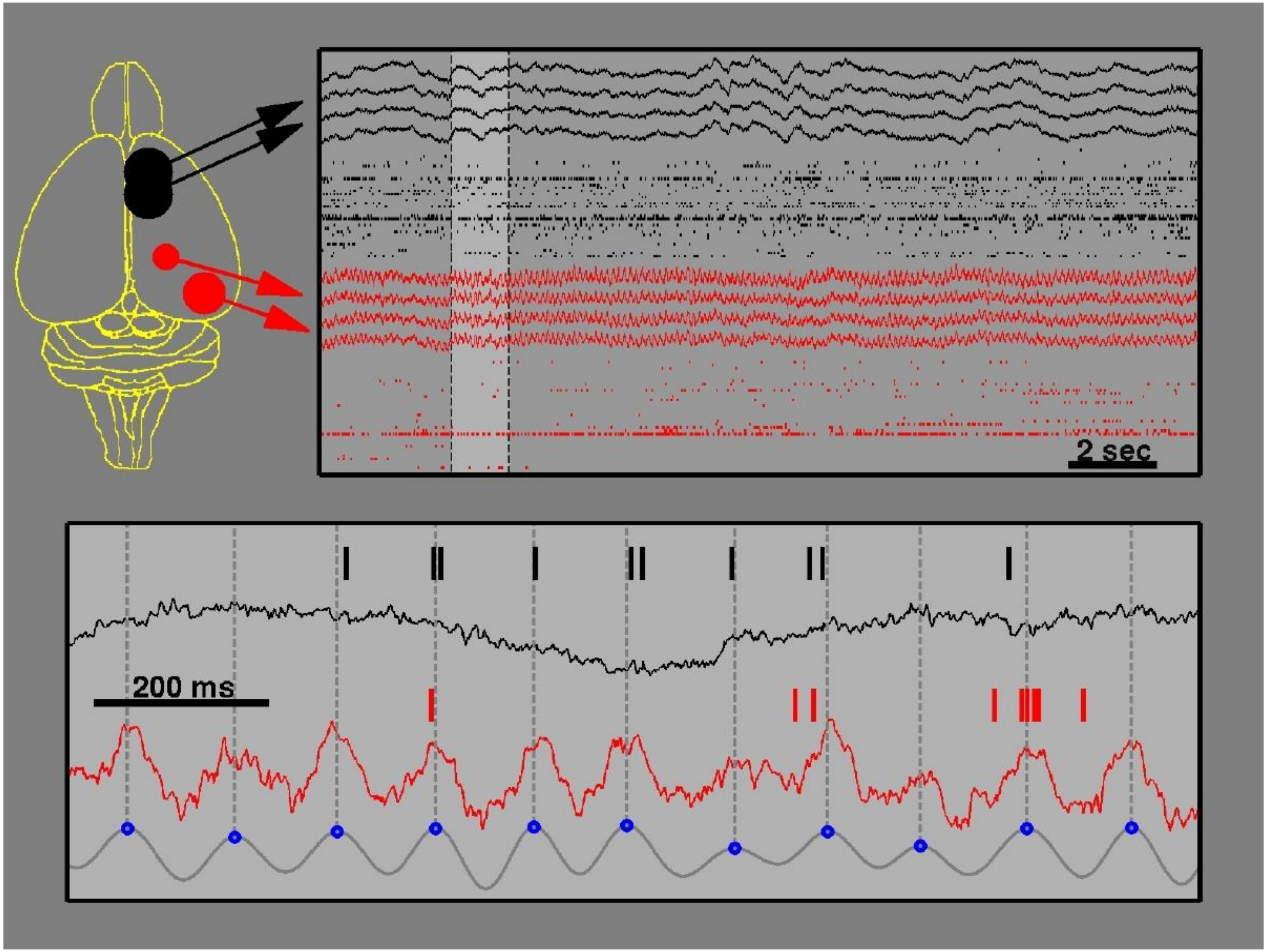
Theta rhythm

Sharp wave/ripples



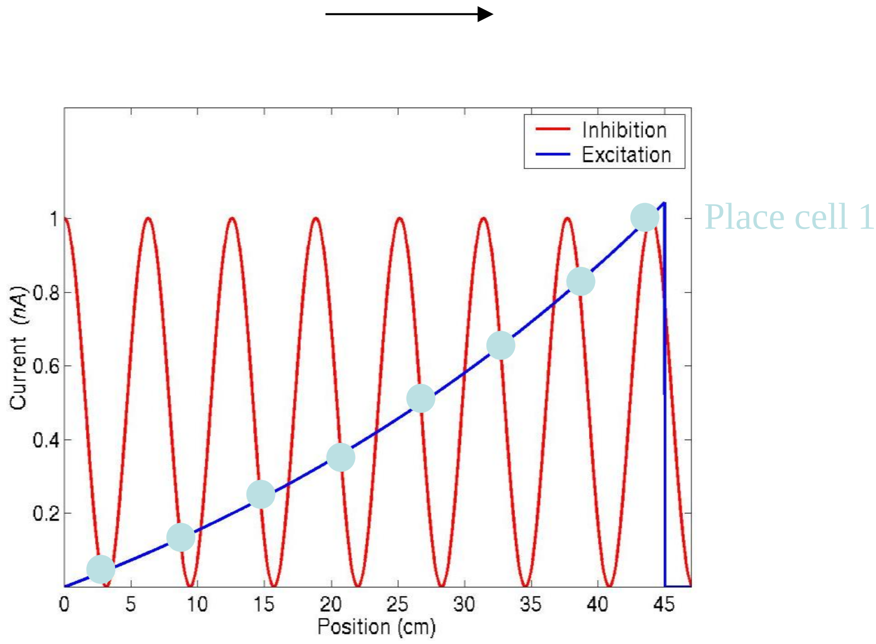
Source: Buzsáki, György. "Two-stage model of memory trace formation: A role for "noisy" brain states." Neuroscience 31, no. 3 (1989): 551-570.

Buzsáki 1989

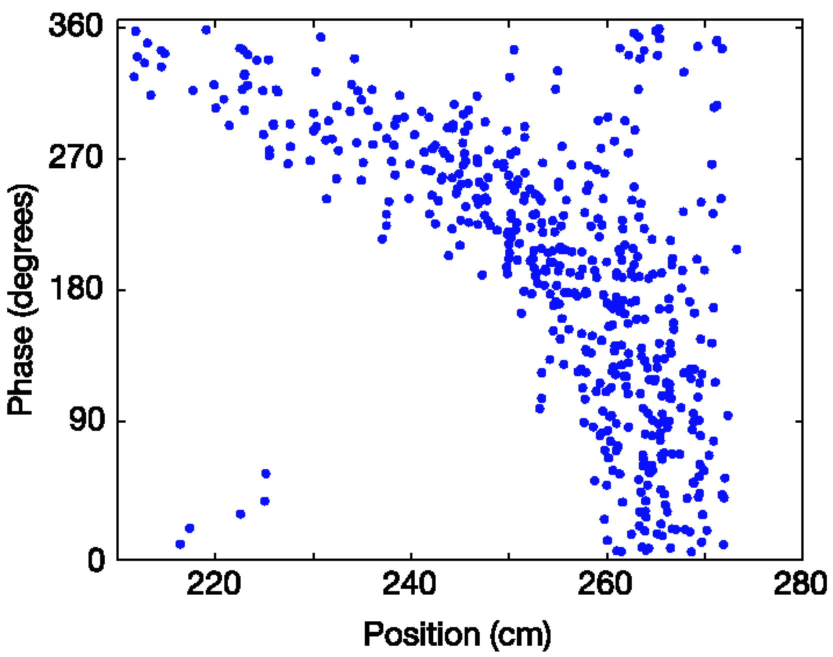

2 sec
200 ms

Interaction of asymmetric excitation with oscillatory variation in inhibition can translate one linear dimension (space) into another (time). Hippocampal phase precession may be a demonstration of that process.

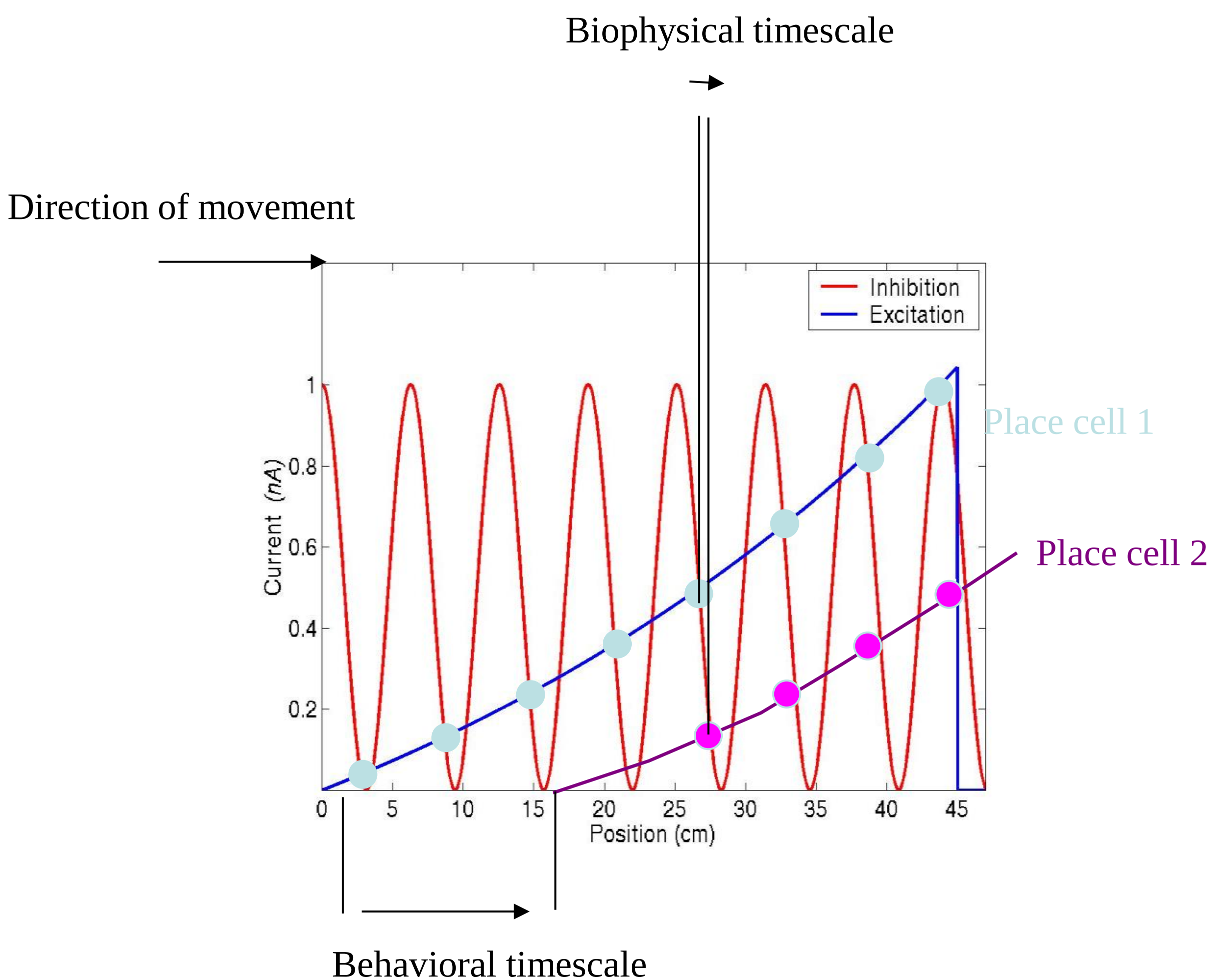
Direction of movement



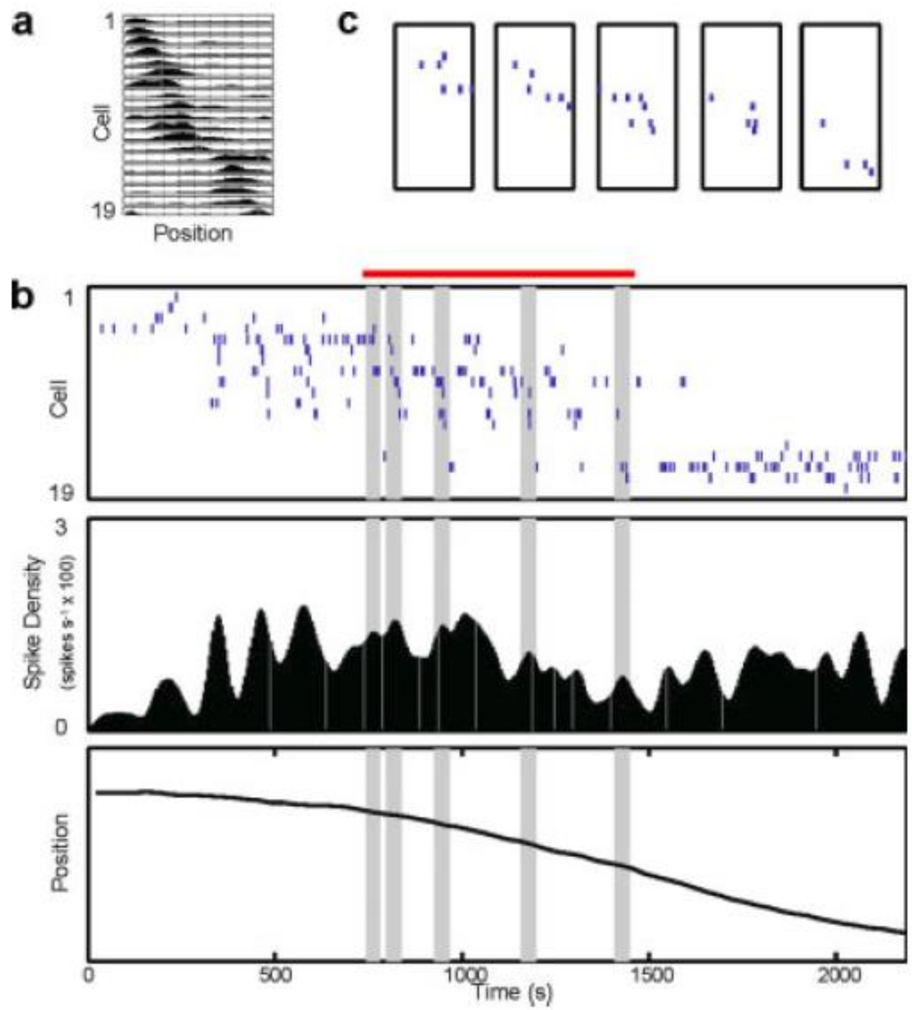
Direction of movement



Overlapping asymmetric place fields with oscillatory variation in excitability translate behavioral time relationships to biophysical timescales with preserved temporal order



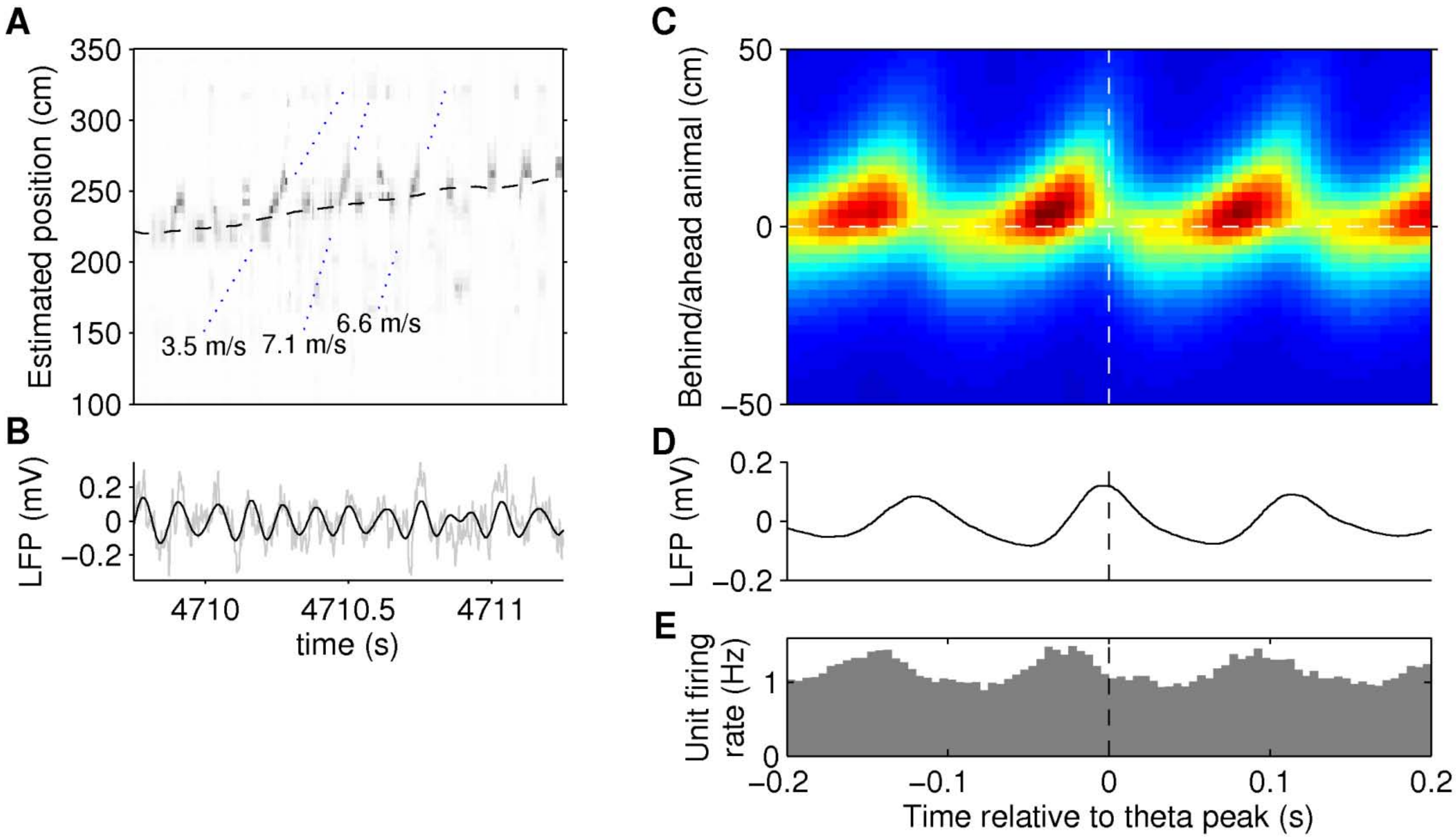
Hippocampal theta sequences



Source: Foster, David J., and Matthew A. Wilson. "Hippocampal theta sequences. "Hippocampus 17, no. 11 (2007): 1093-1099.

Foster and Wilson, 2007

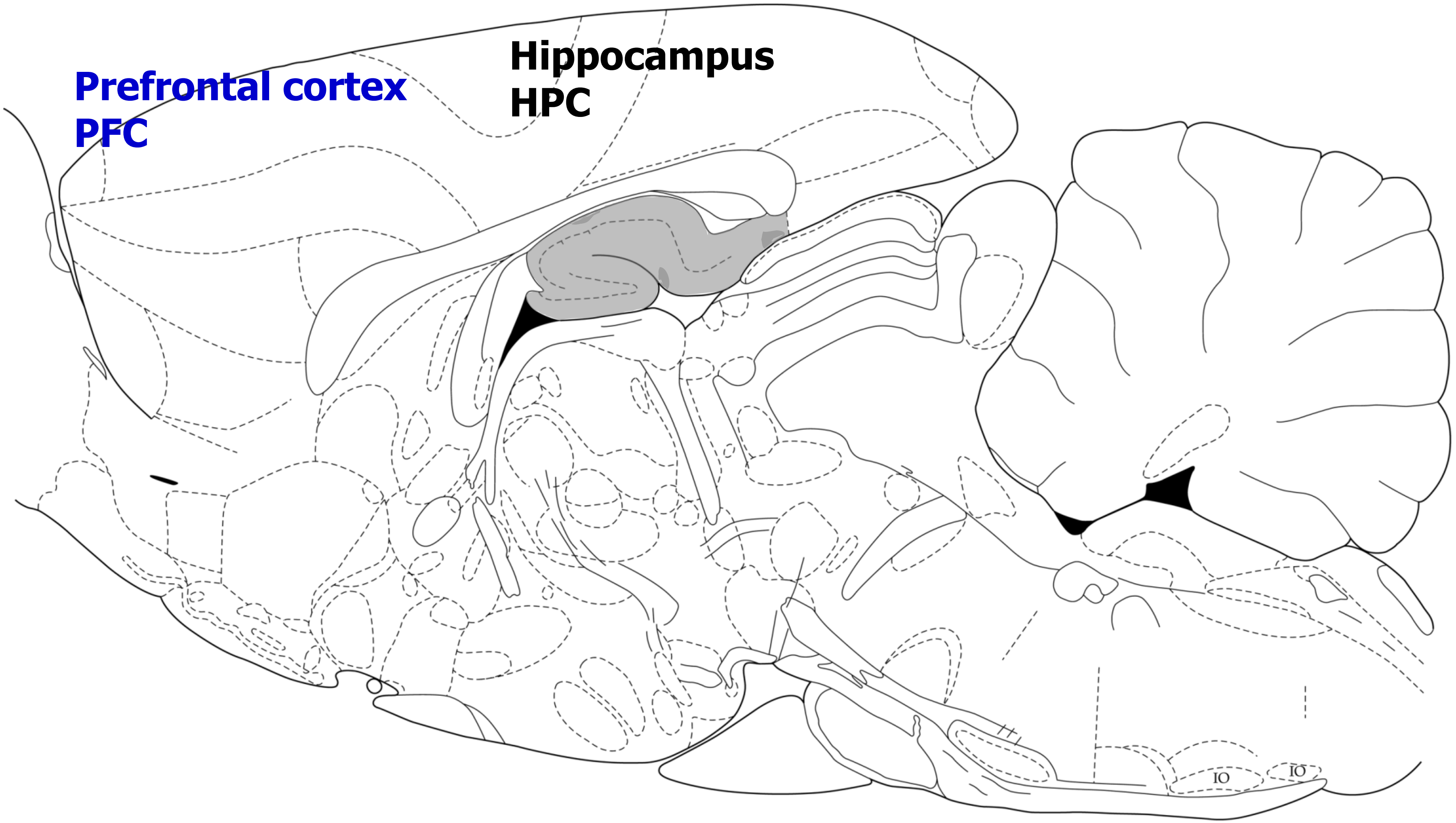
Hippocampal spatial representations are encoded as sequences during behavior



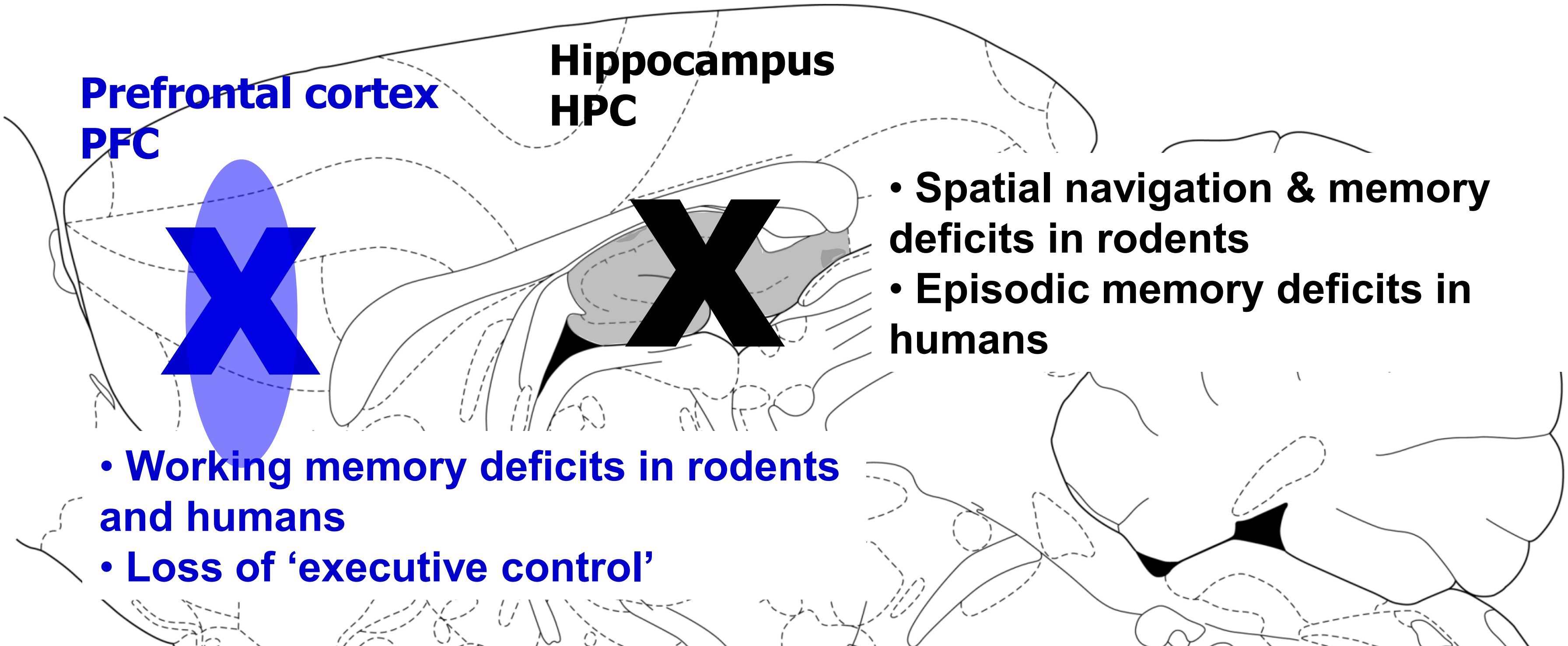
Source: Davidson, Thomas J., Fabian Kloosterman, and Matthew A. Wilson. "Hippocampal replay of extended experience." Neuron 63, no. 4 (2009): 497-507.

Davidson, Kloosterman, and Wilson, *Neuron*, 2009

HPC-PFC: functionally connected



HPC-PFC: functionally connected



- Spatial navigation & memory deficits in rodents
- Episodic memory deficits in humans

- Working memory deficits in rodents and humans
- Loss of 'executive control'

The hippocampus: **encoding and recognising spatial context**

The prefrontal cortex: **integrating the cues of current context (held on-line in working memory) to control appropriate behaviour**

HPC-PFC: **functionally** connected during spatial working memory tasks

Hippocampus

Prefrontal c
PFC

• Working r
and human
• Loss of 'e

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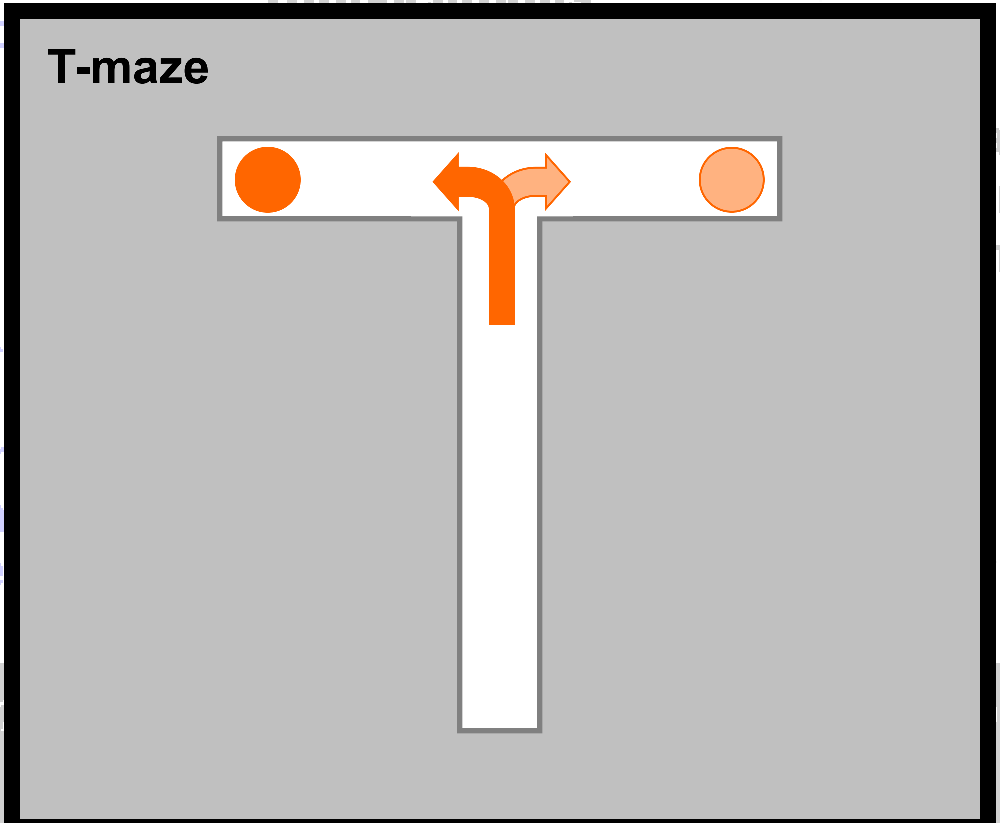
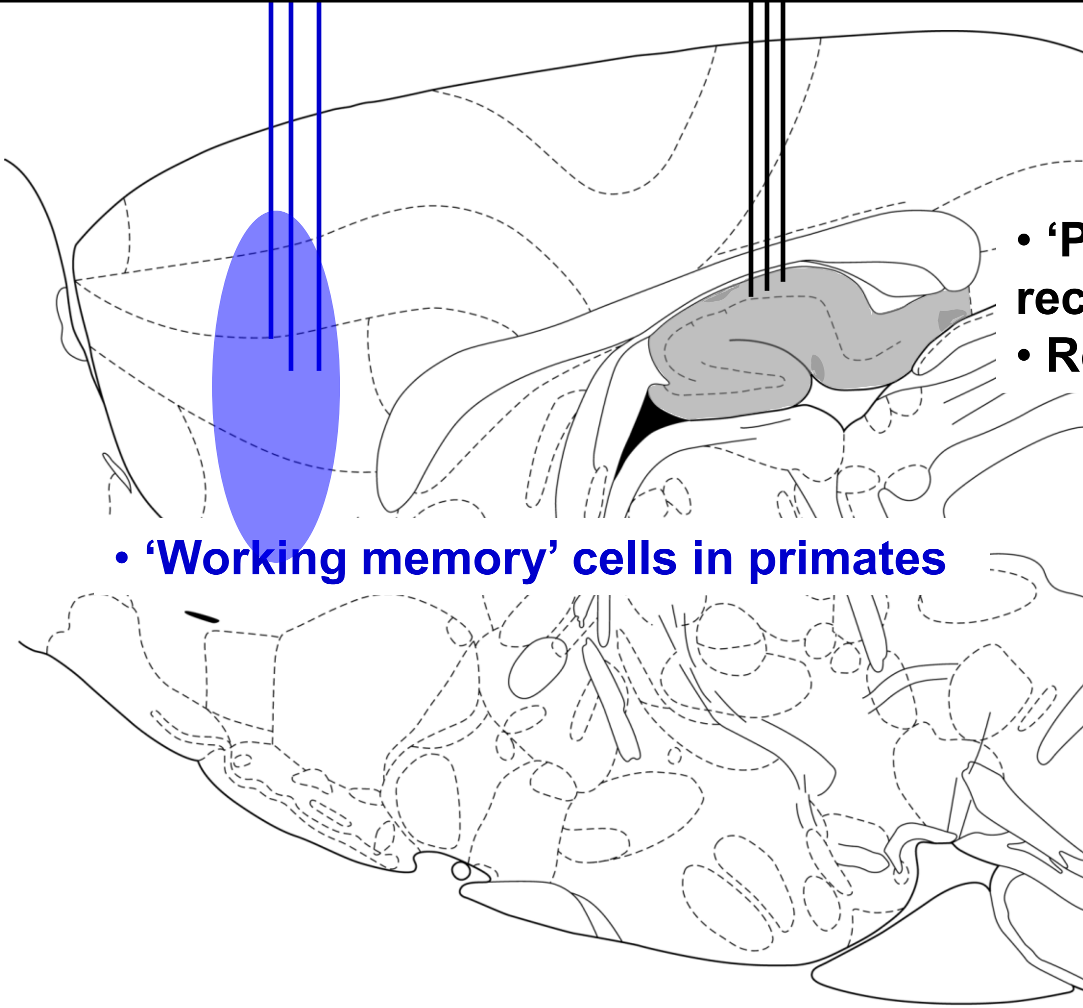
nts
nory deficits in



The hippocam atial context

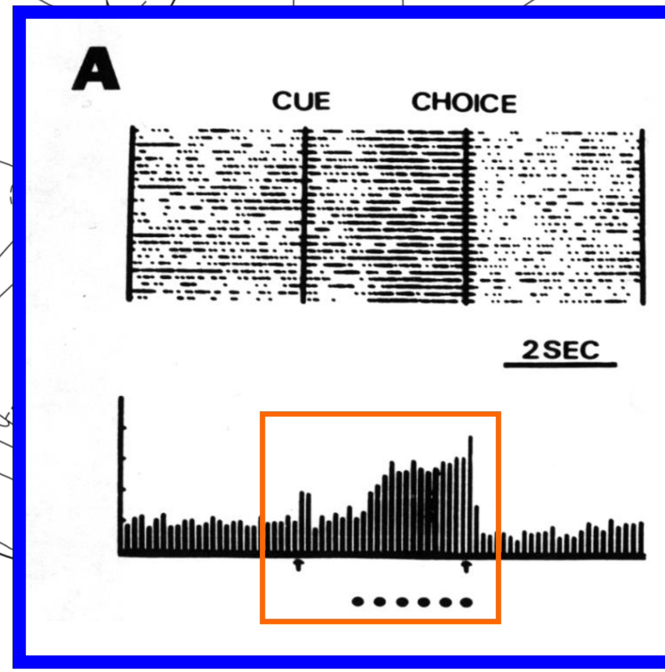
The prefrontal cortex: integrating the cues of current context (held on-line in working memory) to control appropriate behaviour

HPC-PFC: individual electrophysiologies



- ‘Place cells’: neurons with spatial receptive fields (‘place fields’)
- Rodents, primates, humans

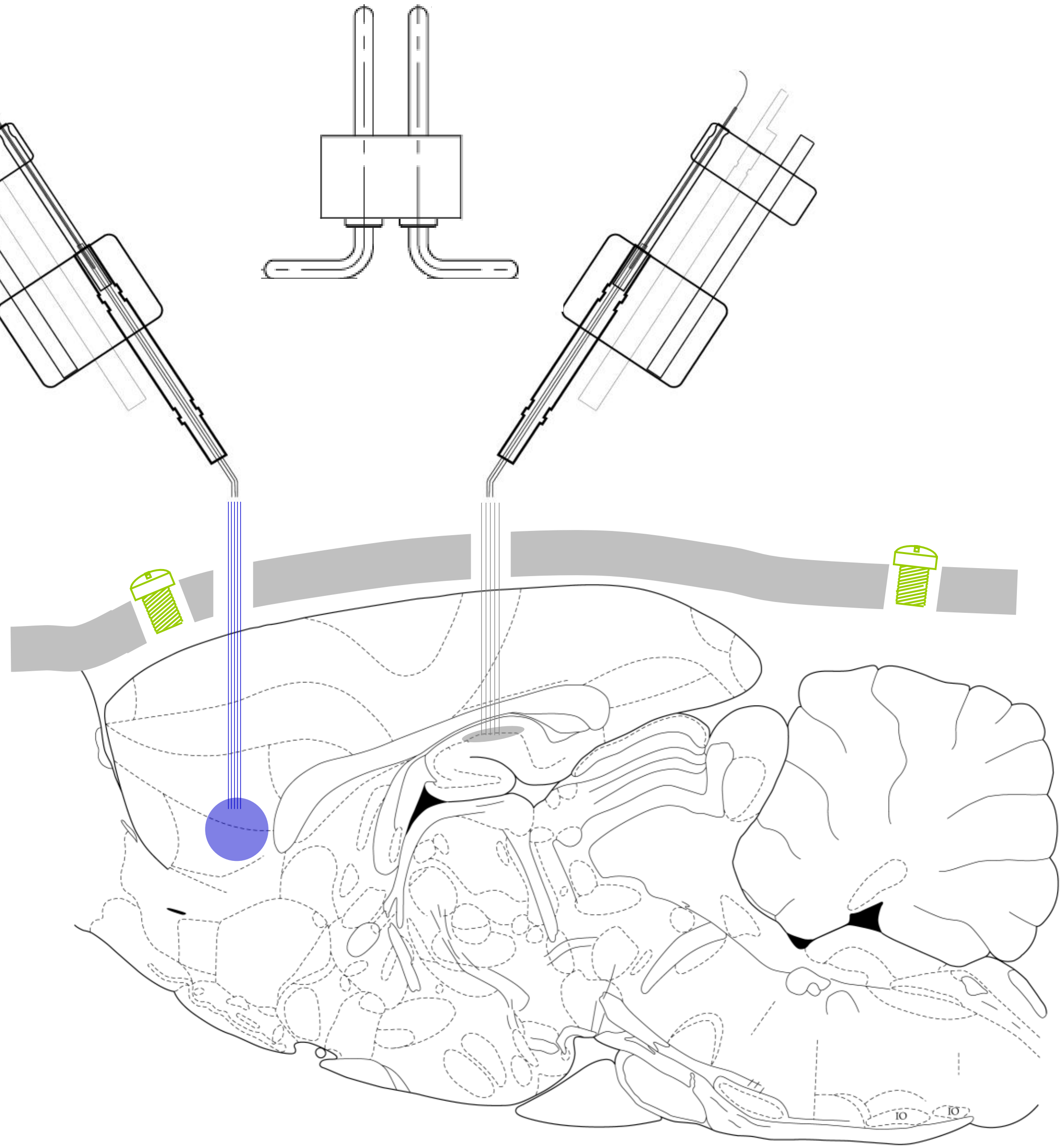
- ‘Working memory’ cells in primates

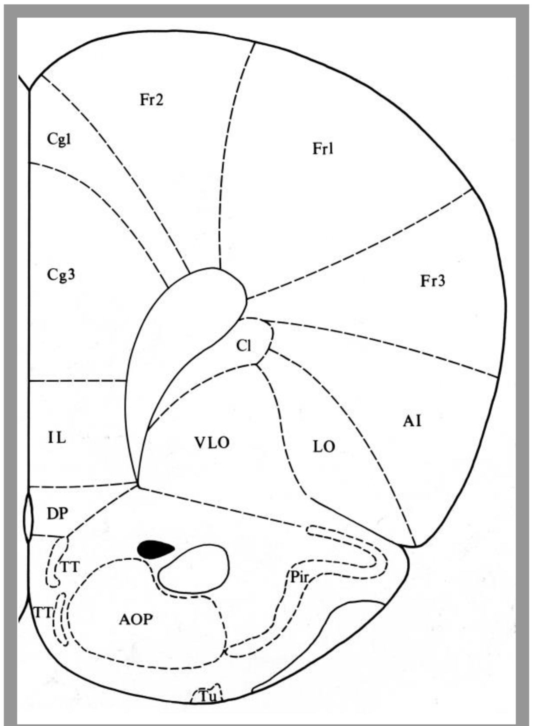


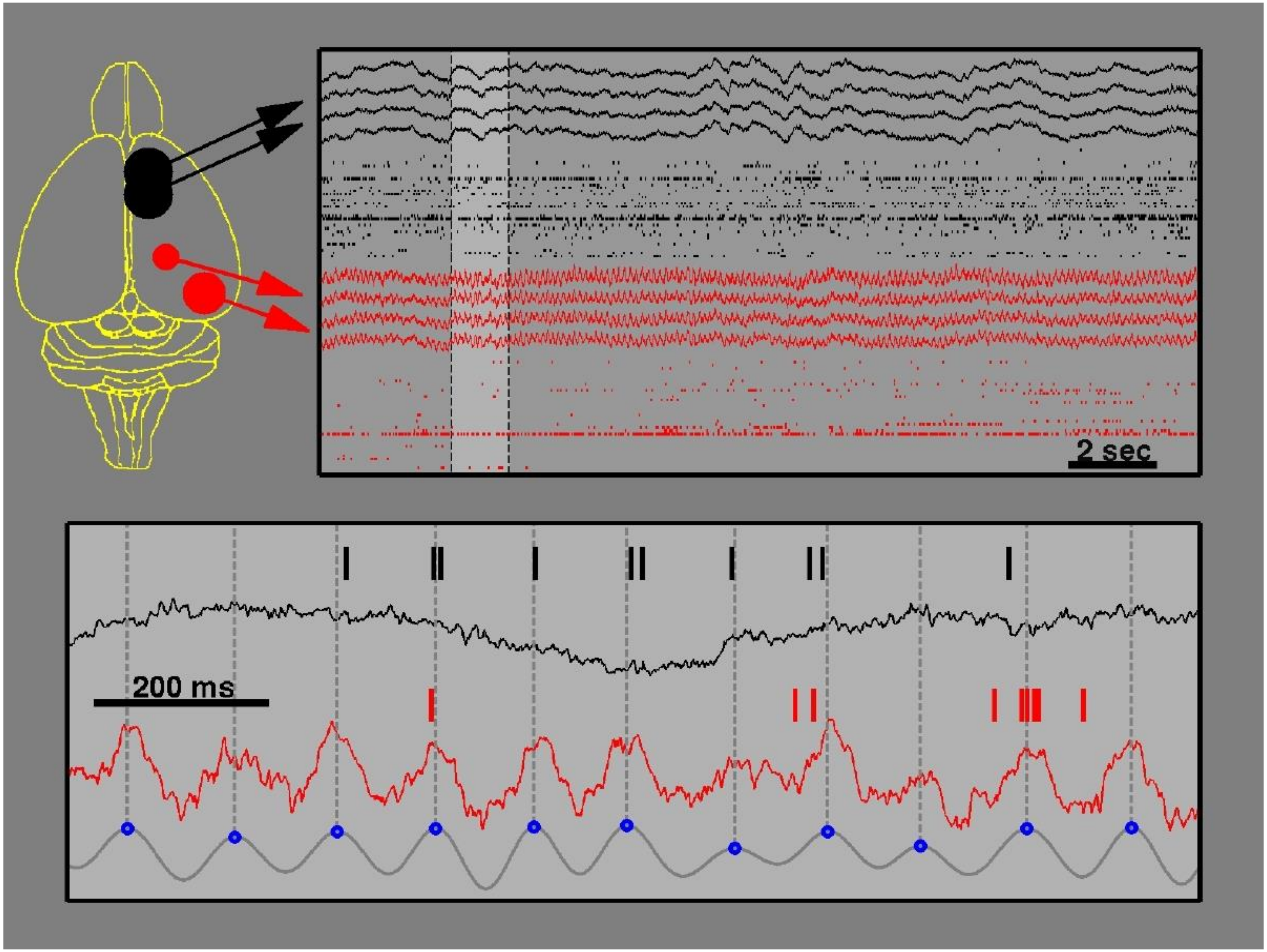
from Niki (1974) *Brain Res*. **70**, 346-349

Source: Niki, Hiroaki. "Differential activity of prefrontal units during right and left delayed response trials." Brain research 70, no. 2 (1974): 346-349.

Multiple units from multiple electrodes in multiple sites



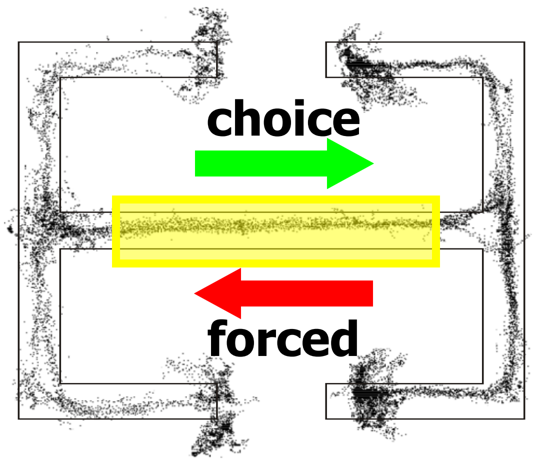




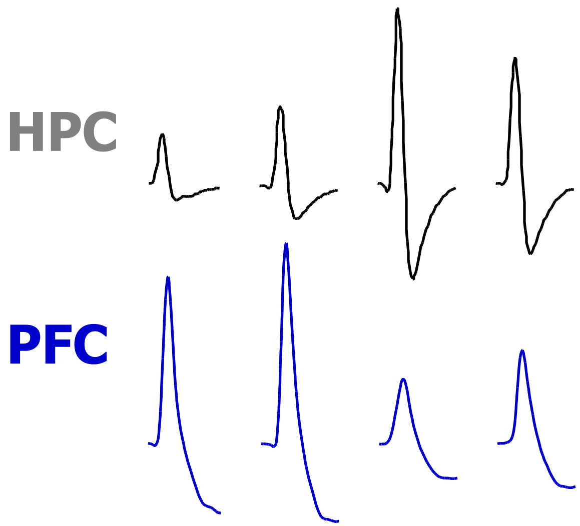
2 sec
200 ms

Data

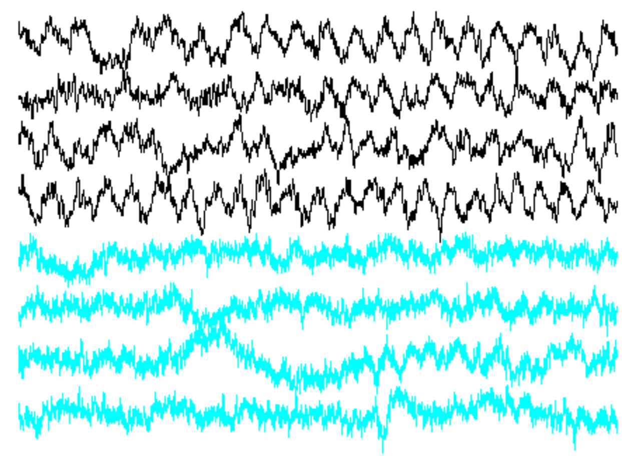
Behaviour & Position



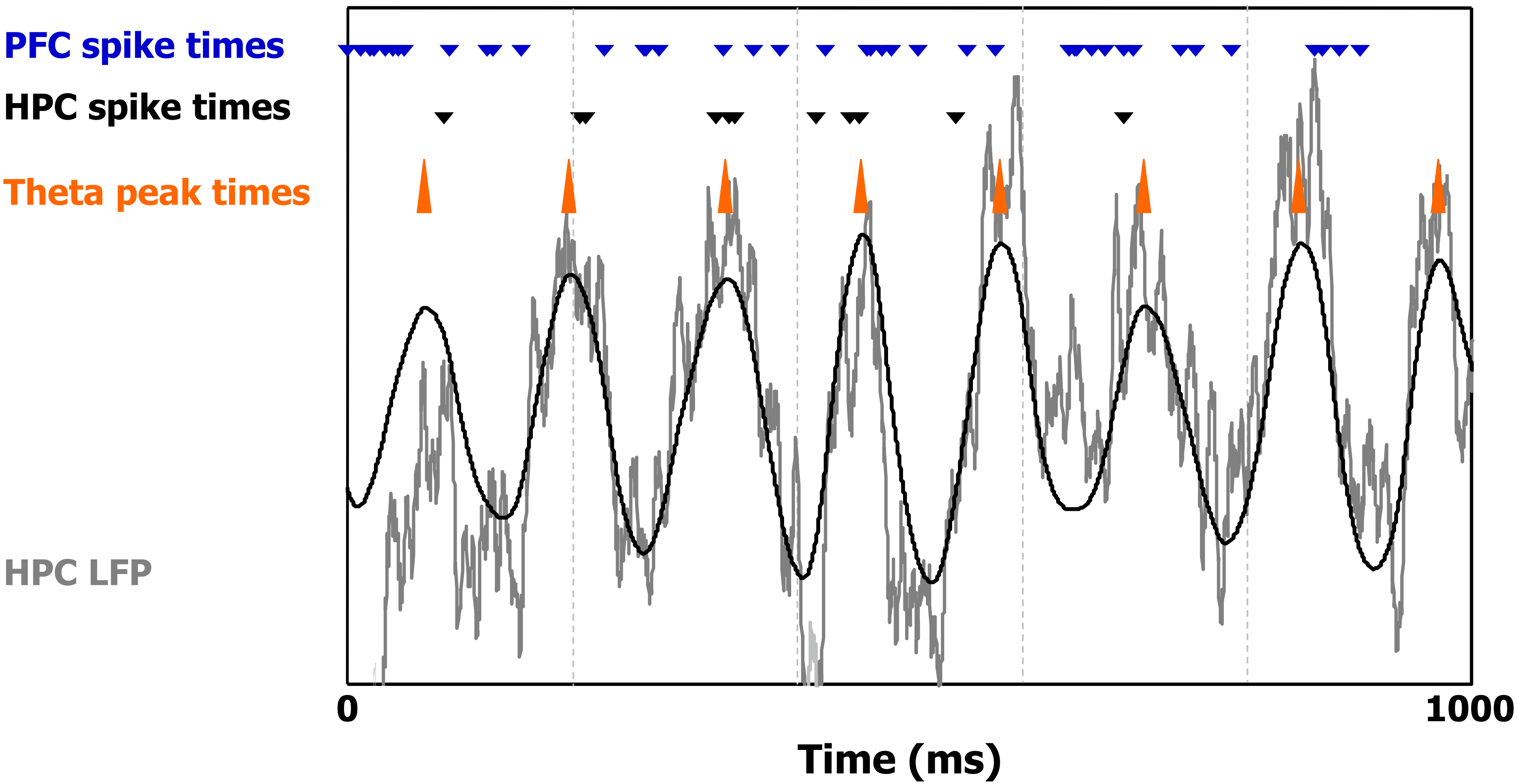
Extracellular Action Potentials (spikes)



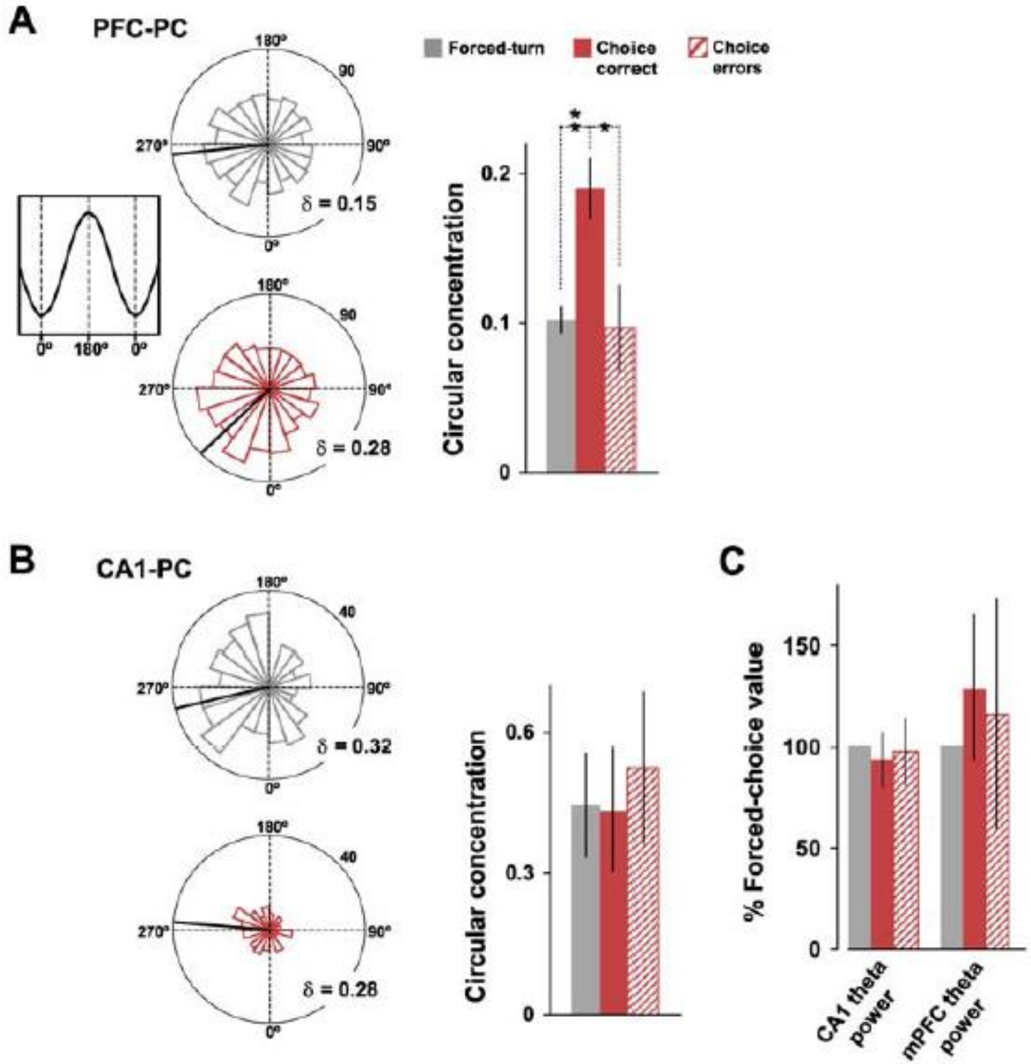
Local Field Potentials (LFP)



Interactions: spikes vs. LFP



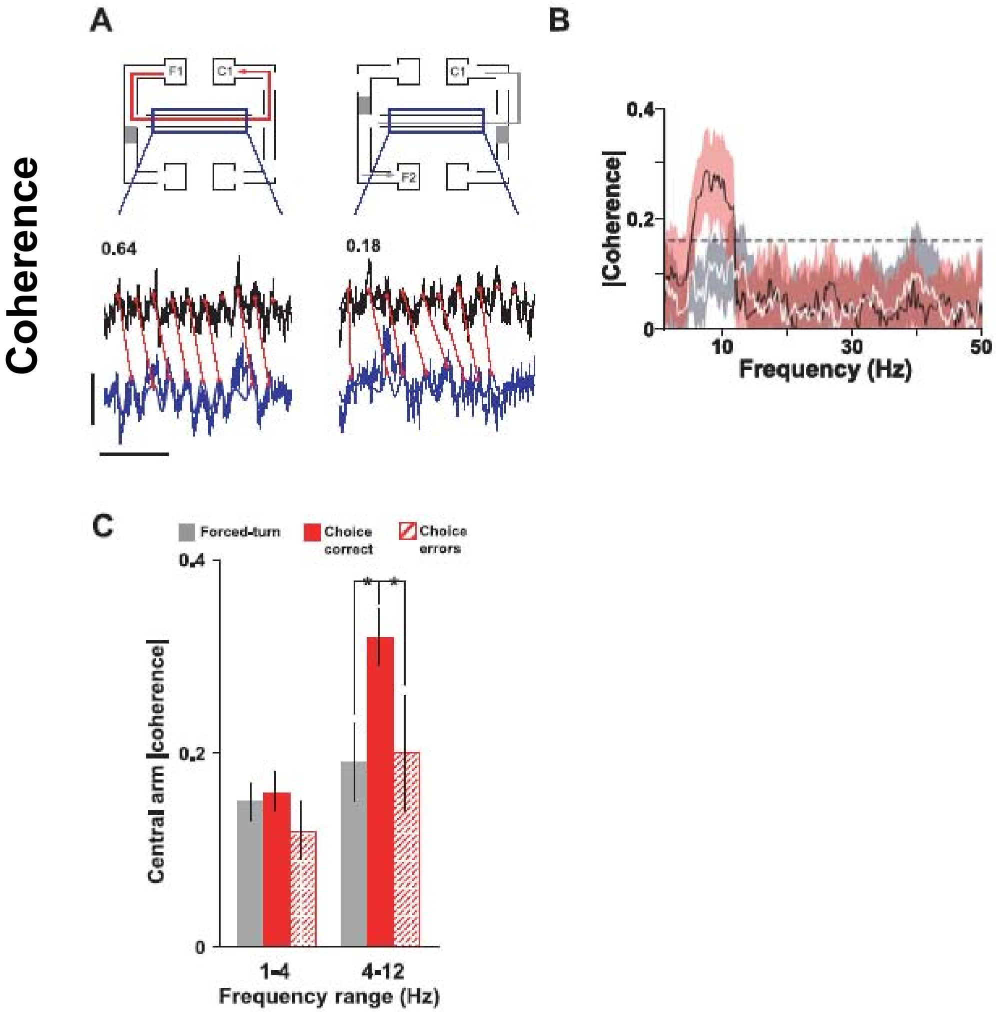
Enhanced theta-phase locking during ‘ correct choice’



Jones, Matthew W., and Matthew A. Wilson. "Theta rhythms coordinate hippocampal–prefrontal interactions in a spatial memory task." PLoS biol 3, no. 12 (2005): e402. https://doi.org/10.1371/journal.pbio.0030402.

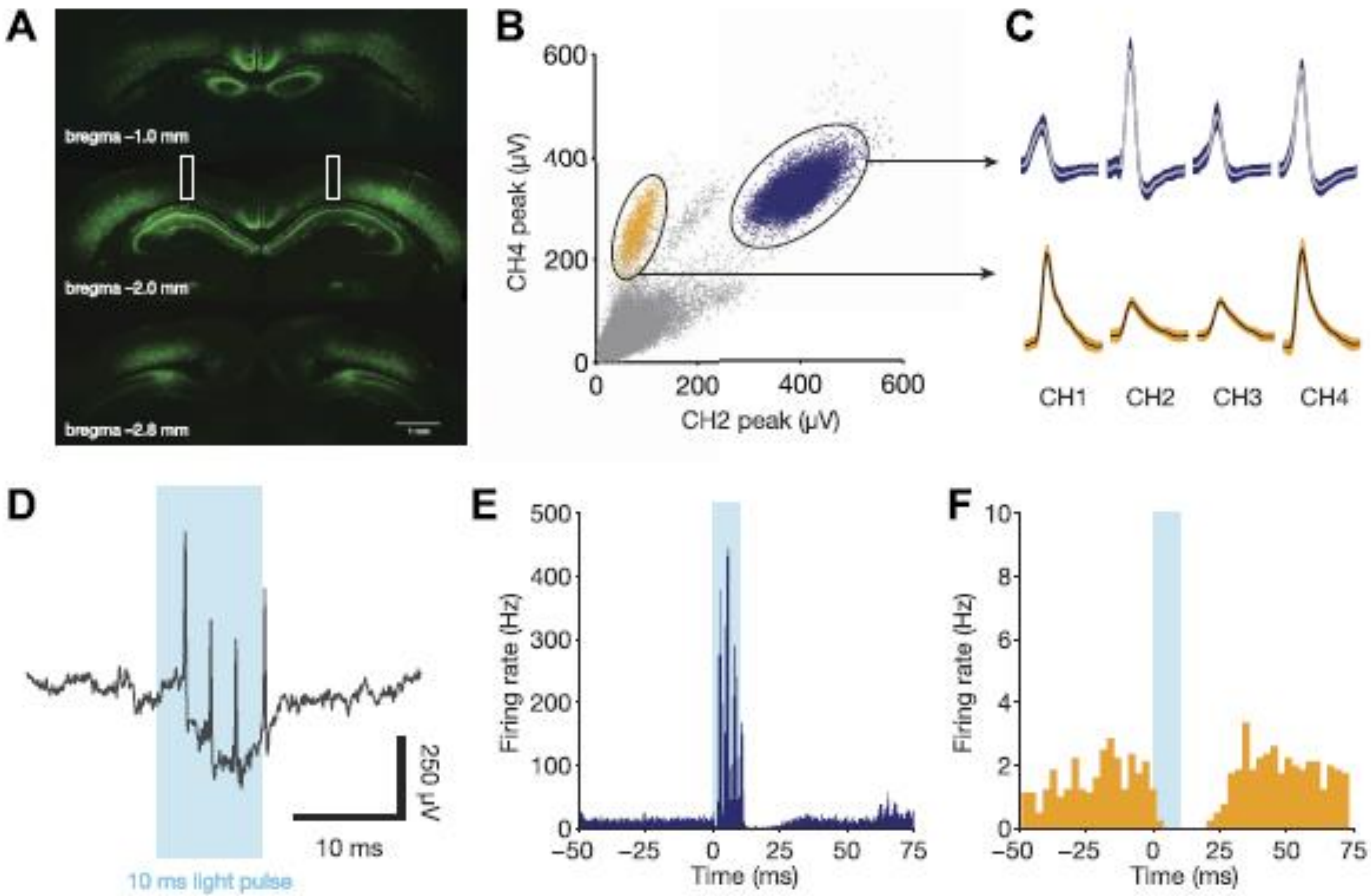
Jones and Wilson, *PLoS Biol.*, 2005

LFP *vs.* LFP: Coherence

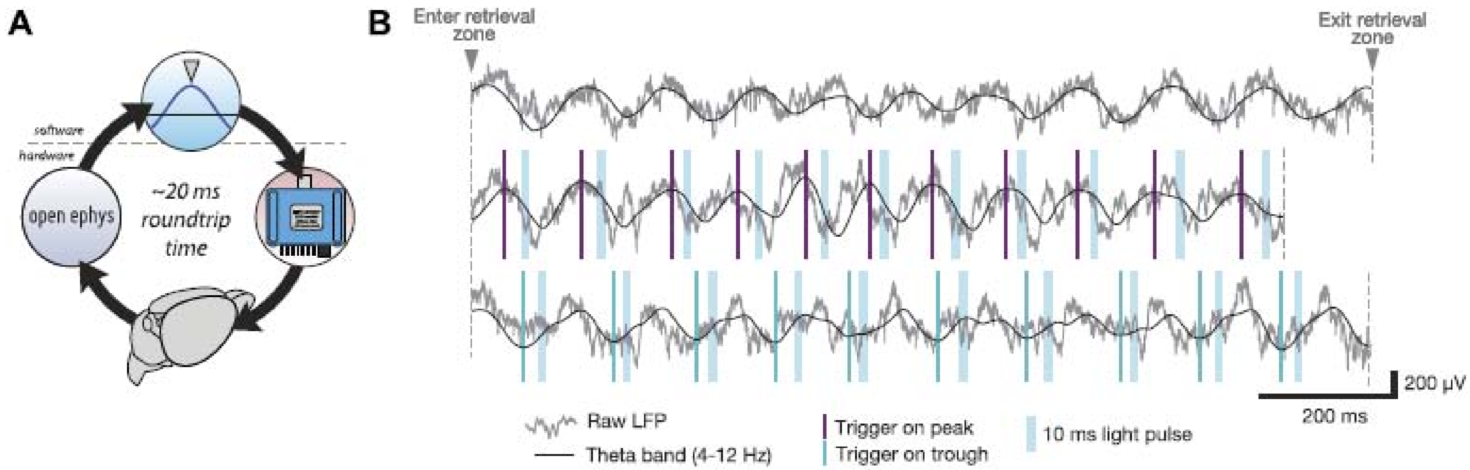


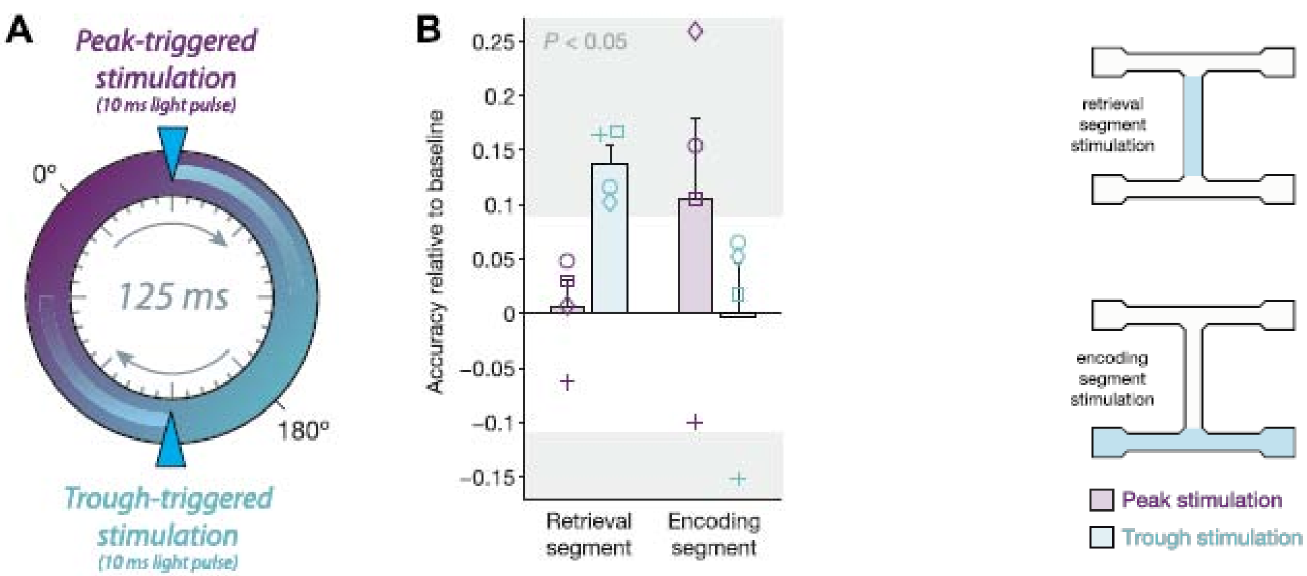
Jones, Matthew W., and Matthew A. Wilson. "Theta rhythms coordinate hippocampal–prefrontal interactions in a spatial memory task." PLoS biol 3, no. 12 (2005): e402. https://doi.org/10.1371/journal.pbio.0030402.

Optogenetic manipulation of hippocampal inhibitory cells



Source: Siegle, Joshua H., and Matthew A. Wilson. "Enhancement of encoding and retrieval functions through theta phase-specific manipulation of hippocampus." Elife 3 (2014): e03061





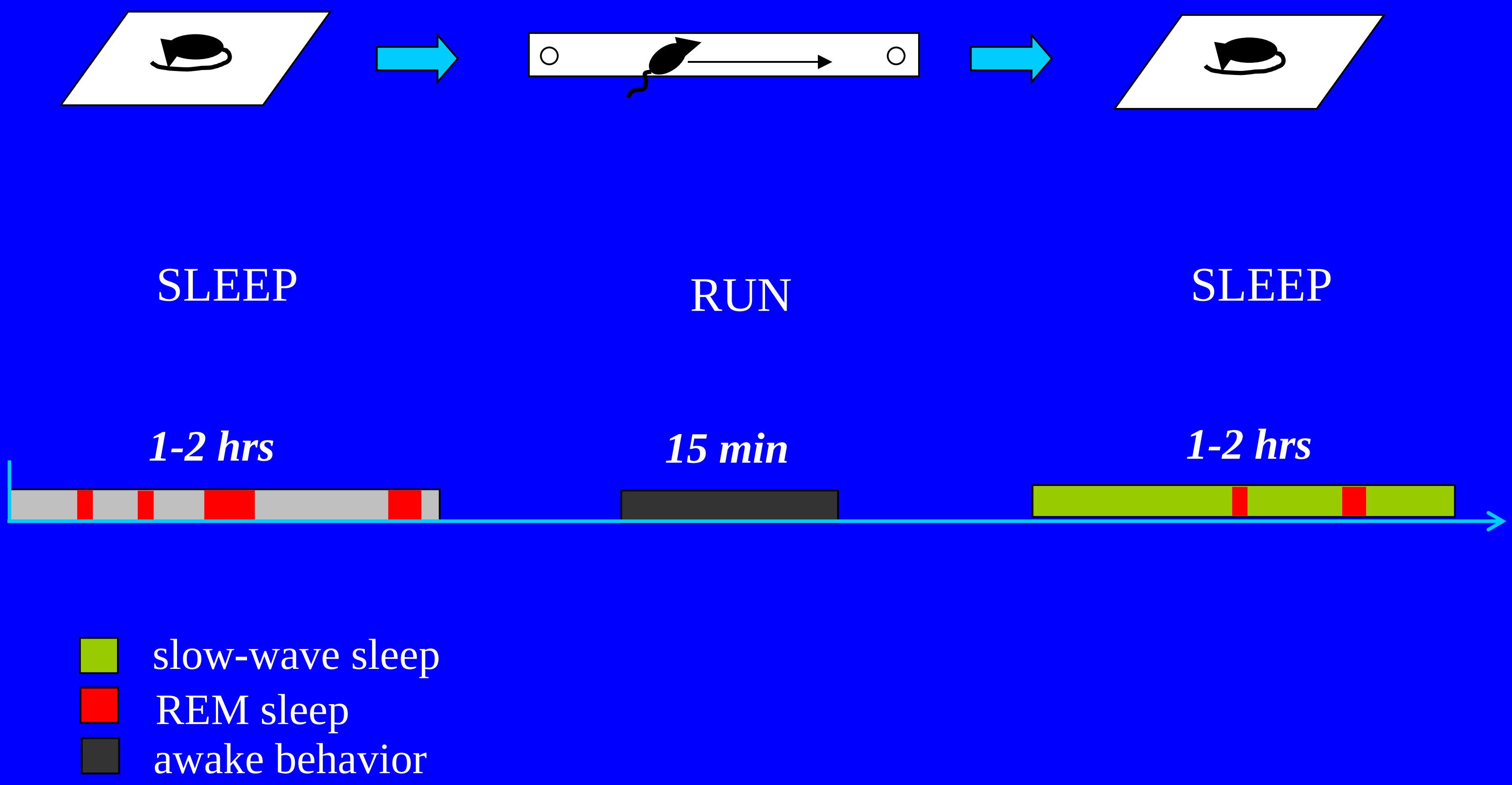
Source: Siegle, Joshua H., and Matthew A. Wilson. "Enhancement of encoding and retrieval functions through theta phase-specific manipulation of hippocampus." Elife 3 (2014): e03061

Siegle and Wilson, *eLIFE*, 2014

Role of Sleep in Memory

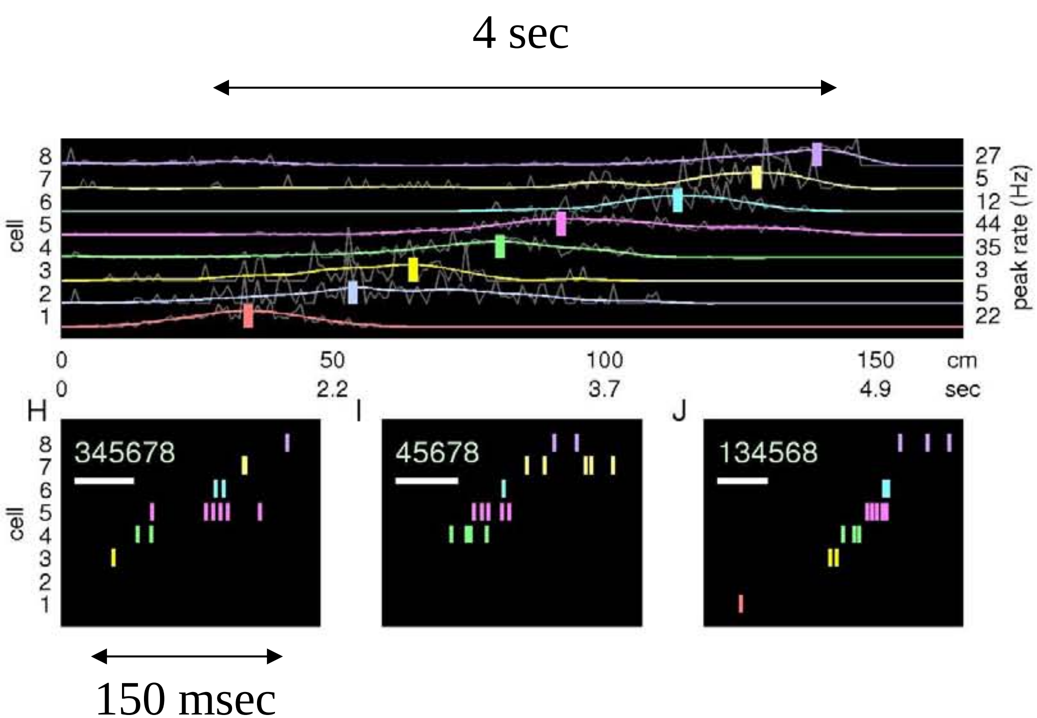
- Sleep allows examination of memory independent of behavior.
- The formation of lasting memories may involve the communication of information between brain areas during sleep.
- Broadly identify two stages of non-REM sleep –(NREM) and rapid eye movement sleep (REM).

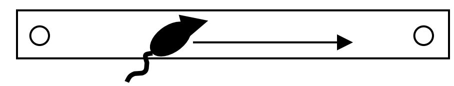
Experimental design



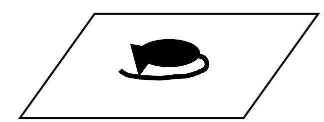
Source: Miller, Earl K., and Matthew A. Wilson. "All my circuits: using multiple electrodes to understand functioning neural networks." Neuron 60, no. 3 (2008): 483-488.

Compressed Run sequences are expressed in hippocampus during nREM sleep





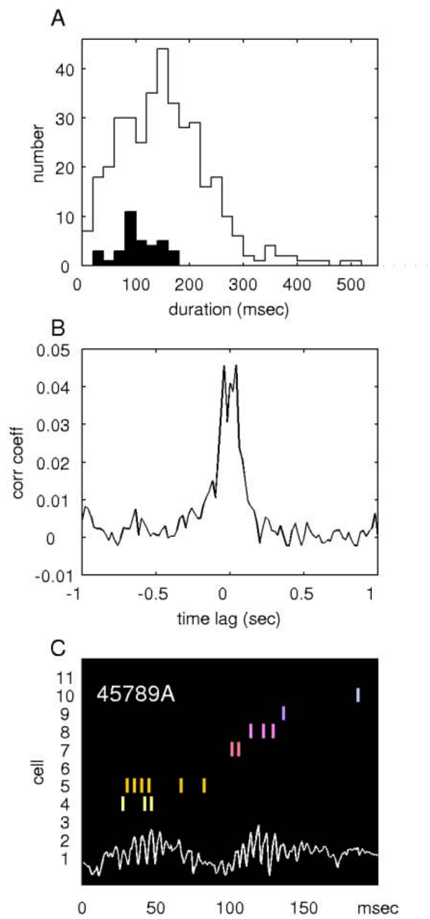
Run



Sleep

Lee and Wilson, *Neuron*, 2002

Sequences are re-expressed during CA1 ripple events



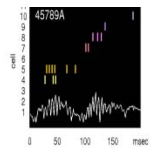
Duration of low probability sequences

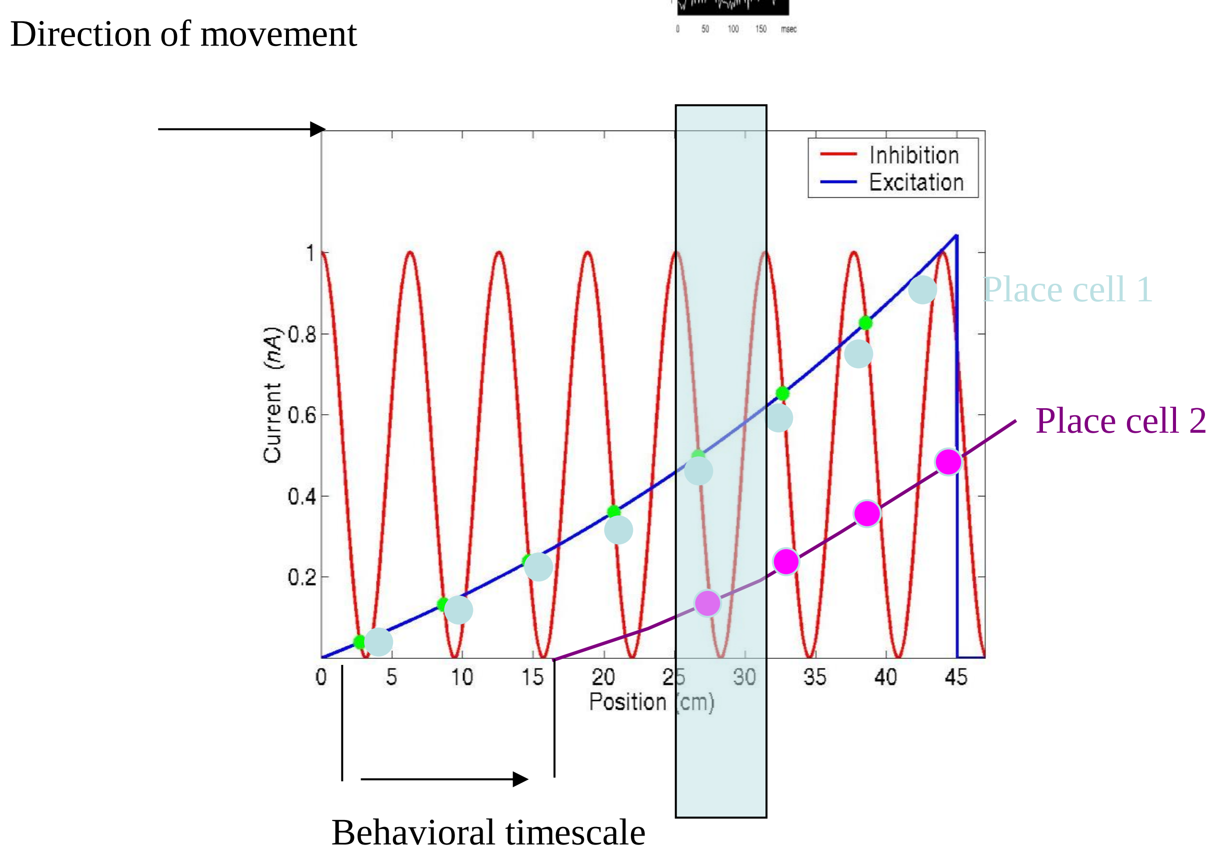
Correlation of low probability sequences and ripples

Example of a low probability sequence and a ripple event

Source: Lee, Albert K., and Matthew A. Wilson. "Memory of sequential experience in the hippocampus during slow wave sleep." Neuron 36, no. 6 (2002): 1183-1194.

Overlapping asymmetric place fields with oscillatory variation in excitability translate behavioral time relationships to biophysical timescales with preserved temporal order





Are there signatures of memory reactivation in the neocortex during hippocampal reactivation

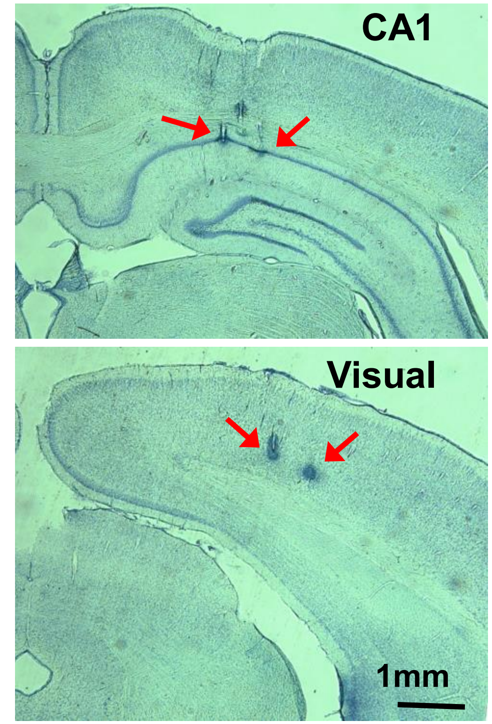
- Simultaneously record in the hippocampus and primary and secondary visual cortex during spatial behavior.
- Look for reactivation in both structures during sleep.

A

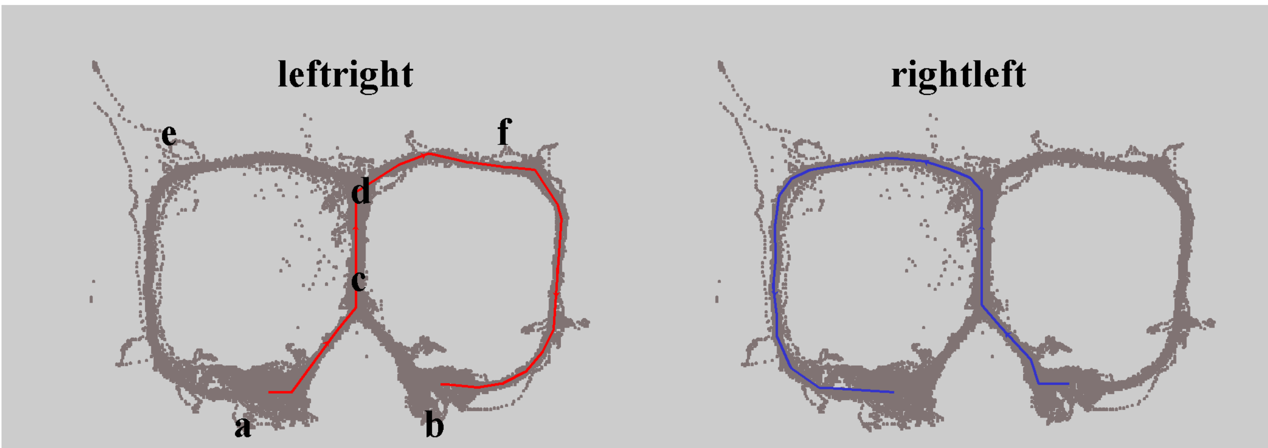
Experimental Design:

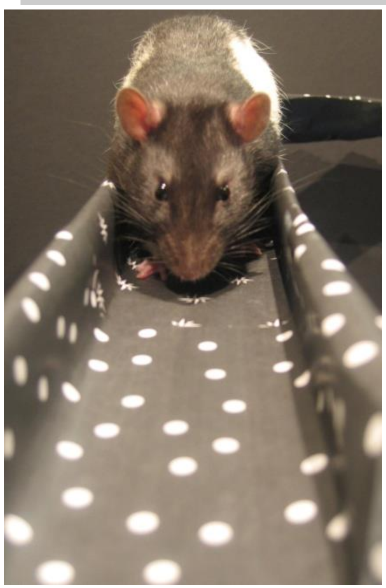
PRE (1-2hrs) — RUN (20-40mins) — POST (1-2hrs)

C



B

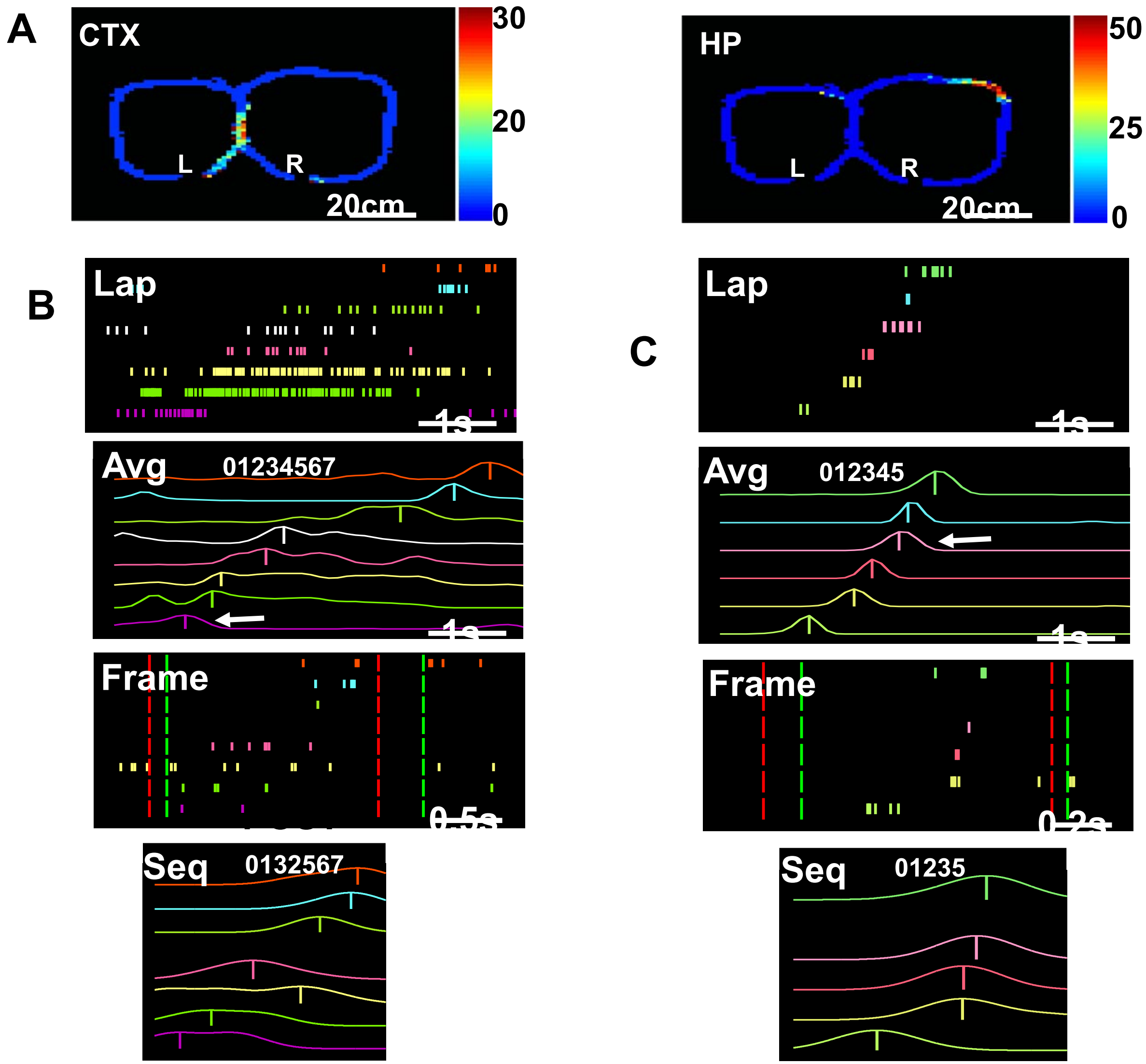




1. Intra-maze local cues, no prominent distal cues
2. Well trained animals: alternation task
3. Recording sites: visual cortex (Occ1, Occ2) and CA1
4. Sleep states (SWS, REM, Wake, Int) classified using EMG and hippocampal EEG

Source: i, Daoyun, and Matthew A. Wilson. "Coordinated memory replay in the visual cortex and hippocampus during sleep." Nature neuroscience 10, no. 1 (2007): 100-107.

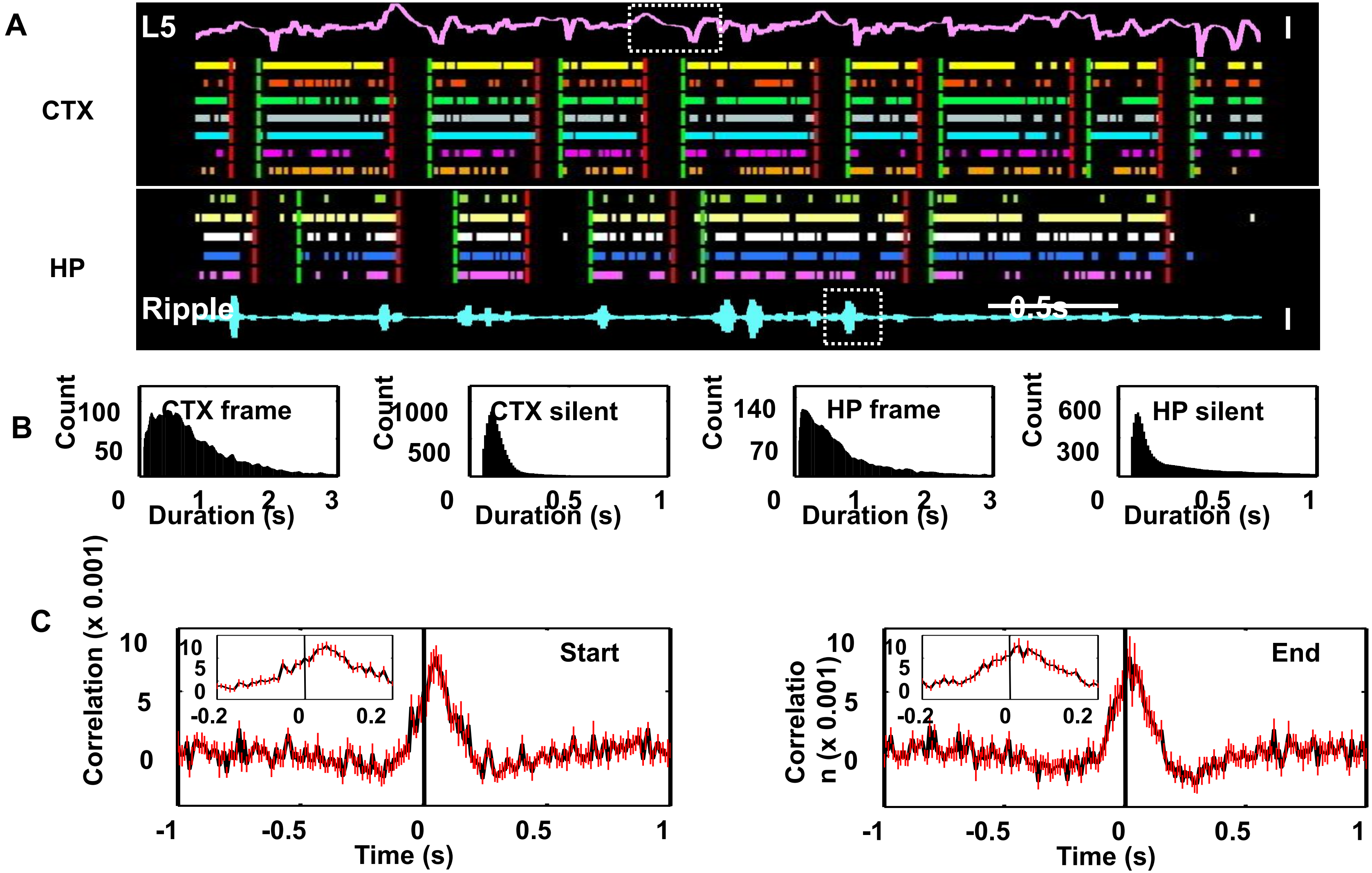
Sequence memory reactivation in hippocampus and visual cortex



Source: i, Daoyun, and Matthew A. Wilson. "Coordinated memory replay in the visual cortex and hippocampus during sleep." Nature neuroscience 10, no. 1 (2007): 100-107.

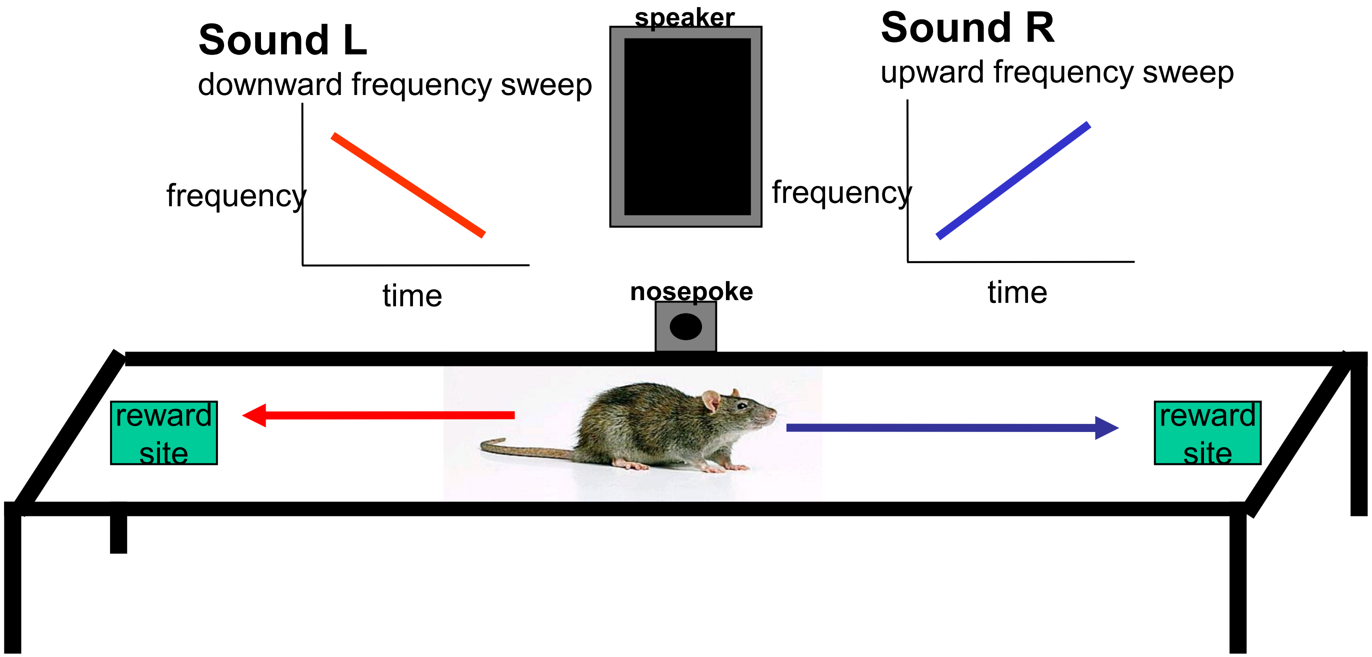
Ji and Wilson, *Nature Neuroscience*, 2007

Reactivation occurs during activity frames correlated with the slow oscillation



Source: i, Daoyun, and Matthew A. Wilson. "Coordinated memory replay in the visual cortex and hippocampus during sleep." Nature neuroscience 10, no. 1 (2007): 100-107.

Can we influence memory reactivation during sleep?

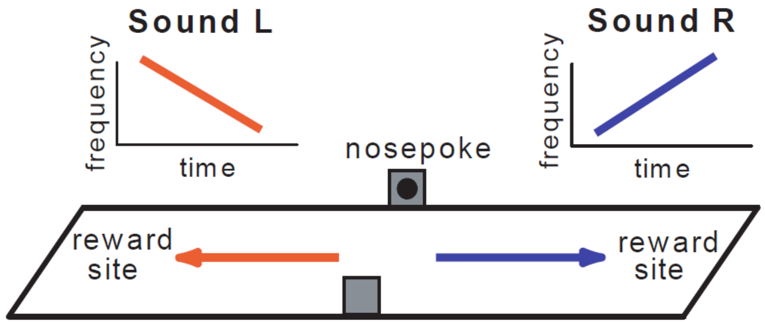


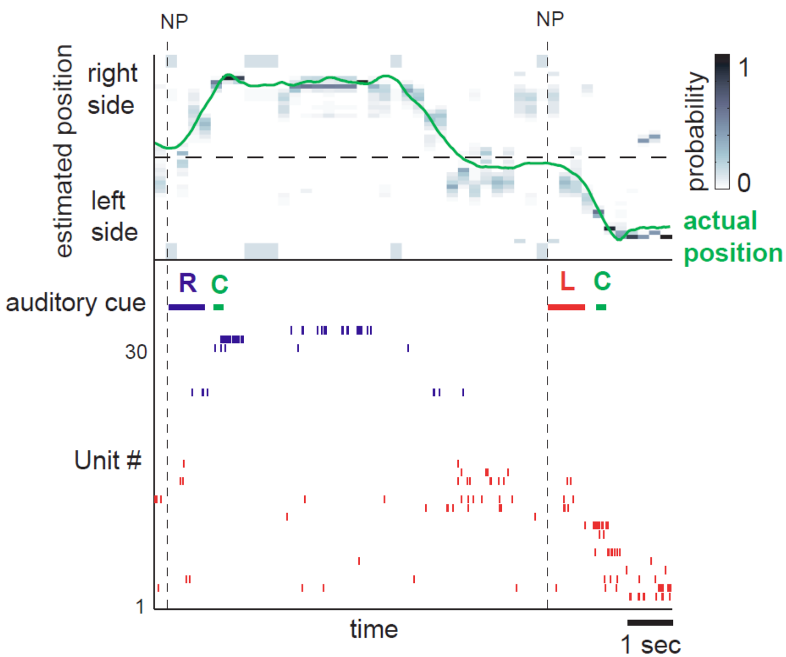
For 2-2.5 hours

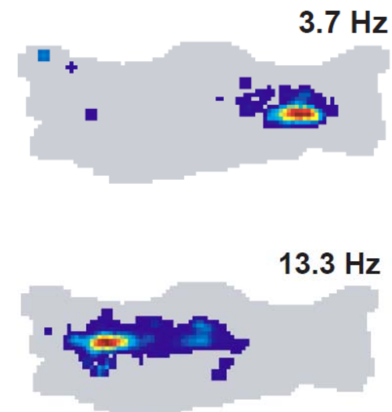
Sound L
Sound R
control sounds

Source: L Bendor, Daniel, and Matthew A. Wilson. "Biasing the content of Hippocampal replay during sleep." Nature neuroscience 15, no. 10 (2012): 14391444

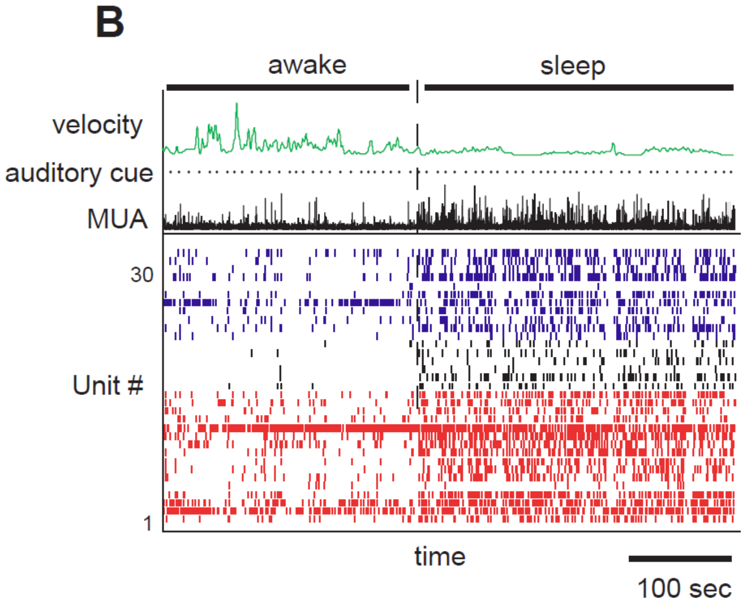
Behavioral task design







Source: L Bendor, Daniel, and Matthew A. Wilson. "Biasing the content of Hippocampal replay during sleep." Nature neuroscience 15, no. 10 (2012): 14391444

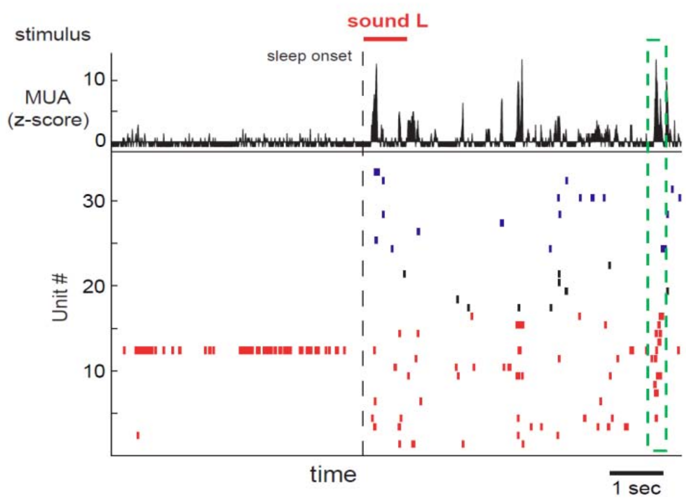


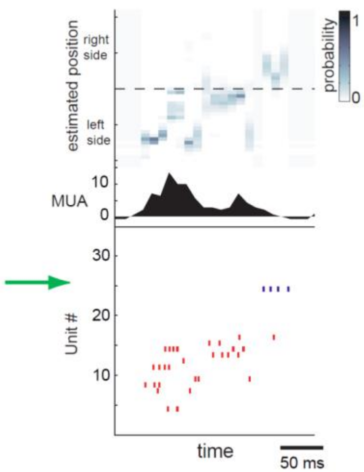
Do task-related sounds bias the content of future replay?

Hypothesis:

Sound R- place cells with **right-sided** place fields are more active during replay

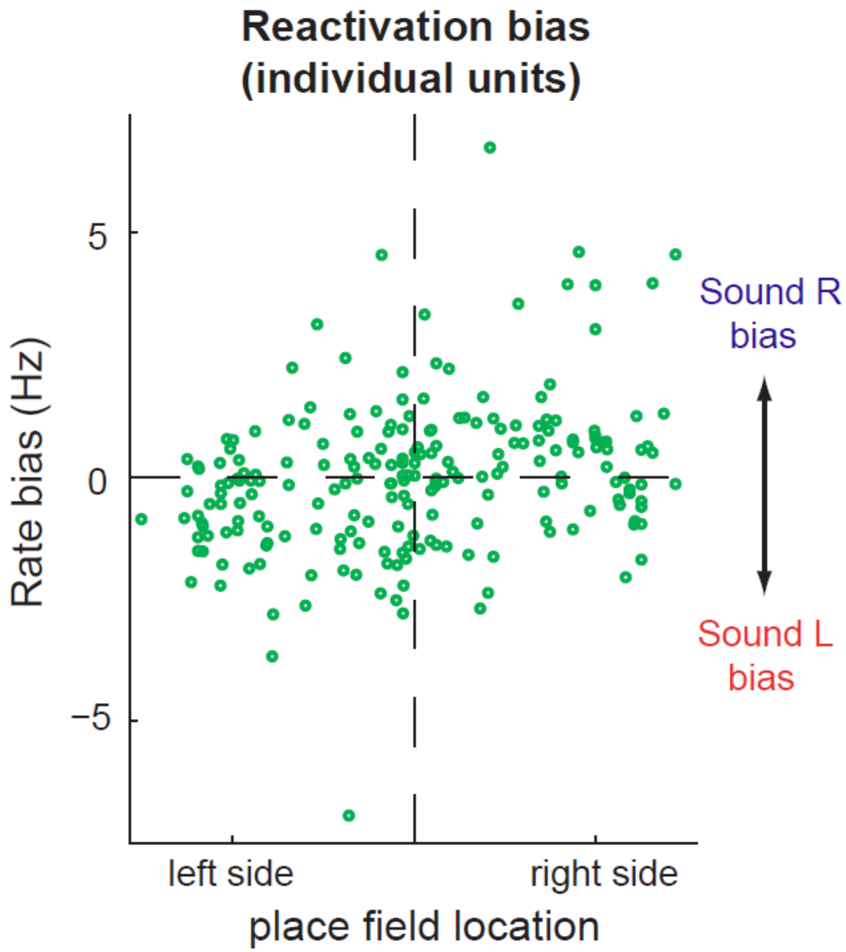
Sound L- place cells with **left-sided** place fields are more active during replay

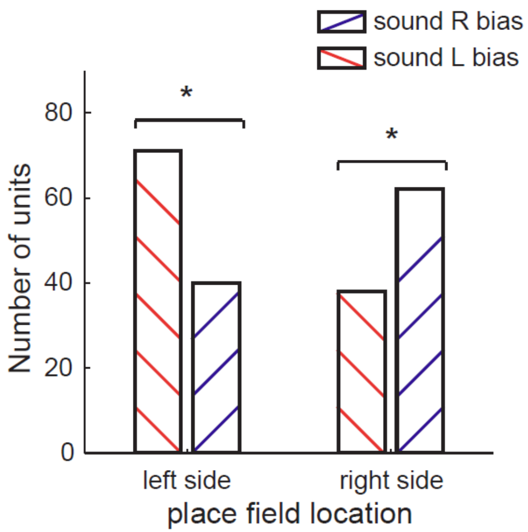


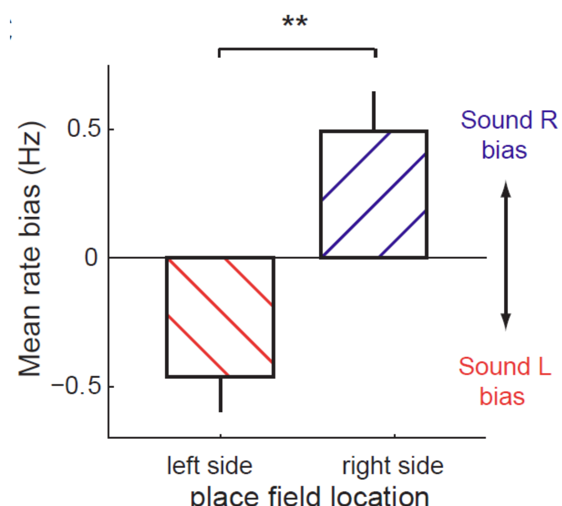


Source: L Bendor, Daniel, and Matthew A. Wilson. "Biasing the content of Hippocampal replay during sleep." Nature neuroscience 15, no. 10 (2012): 14391444

Bias observed in individual place cell responses

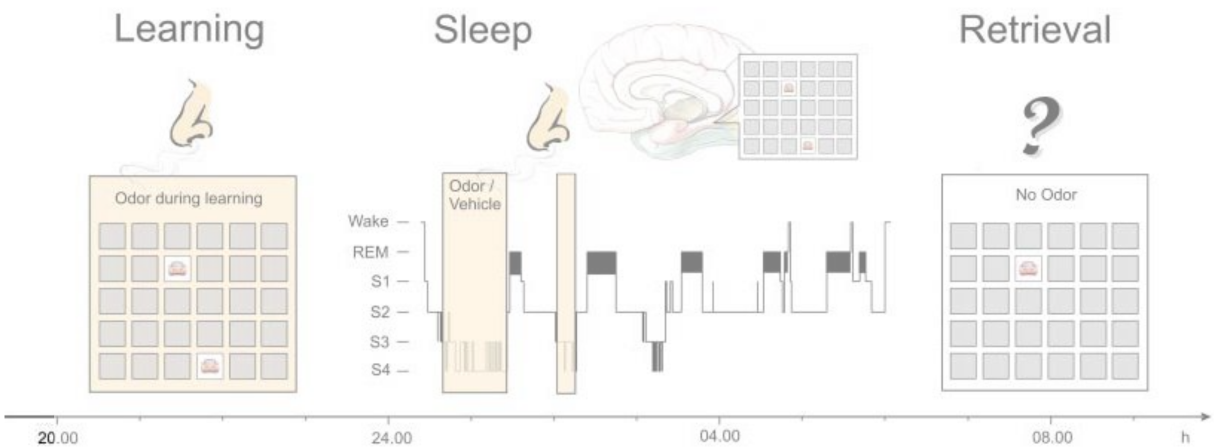


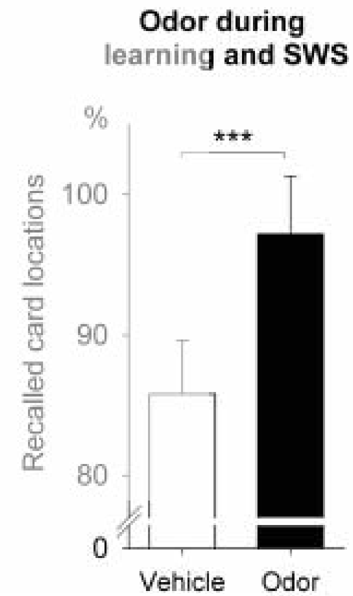




Source: L Bendor, Daniel, and Matthew A. Wilson. "Biasing the content of Hippocampal replay during sleep." Nature neuroscience 15, no. 10 (2012): 14391444

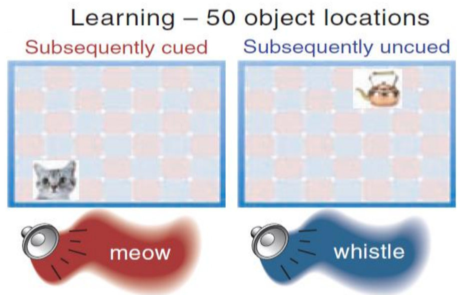
Bendor and Wilson, *Nature Neuroscience*, 2012

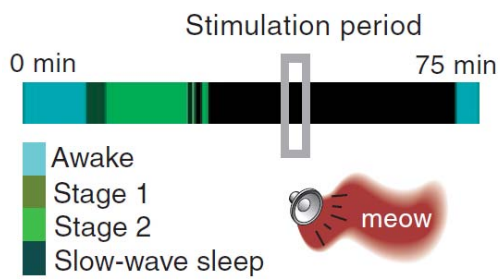


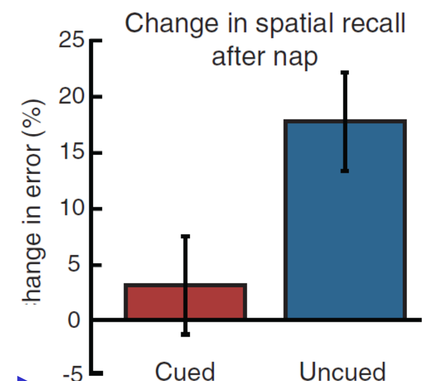


Rasch et al. 2007

Nap – 25 sound cues







Rudoy et al. 2009

stimulation

Bias pre-replay brain state

Cortex

Hippocampus

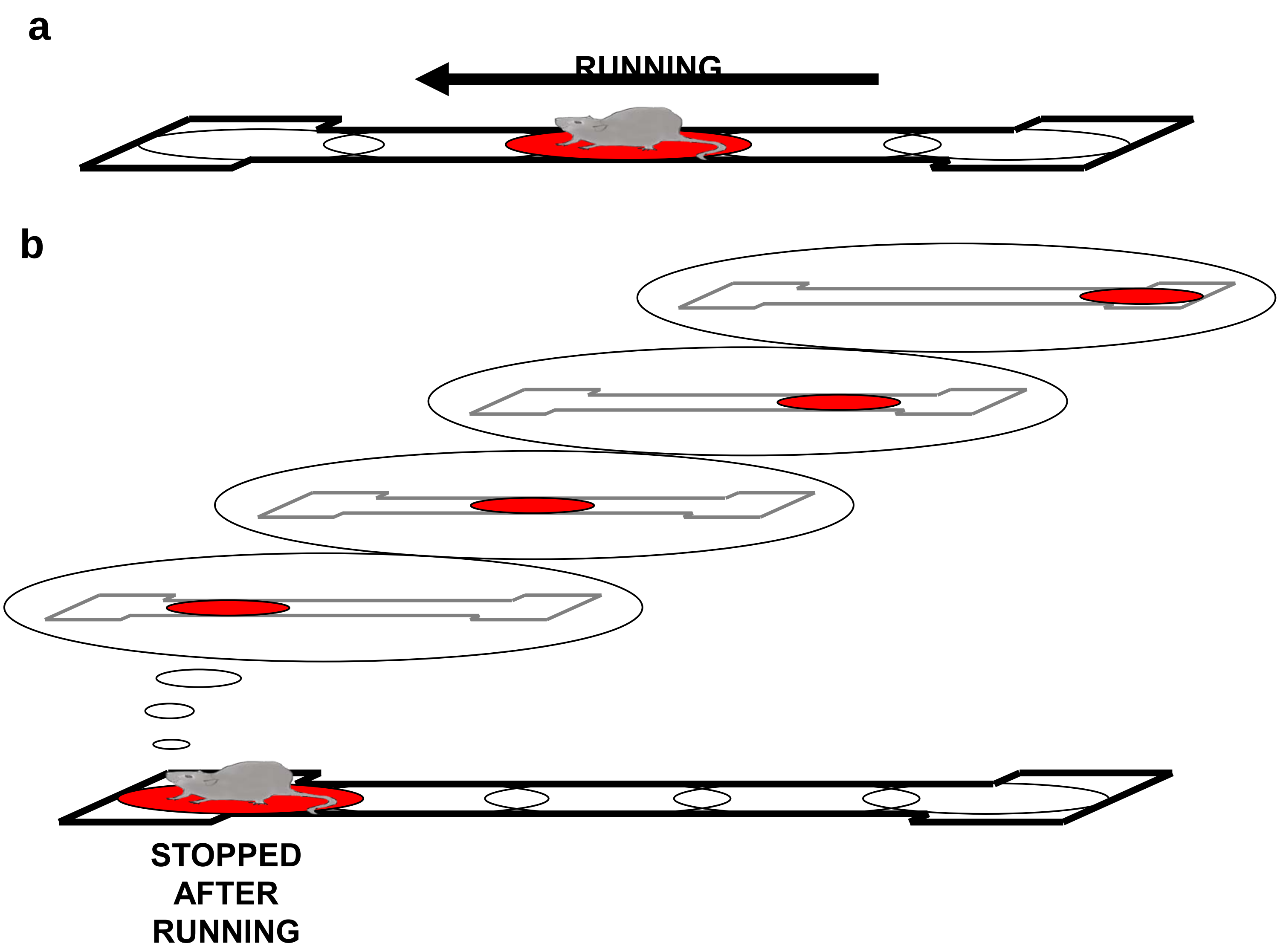
Bias which memories are transferred

Source: Rasch, Björn, Christian Büchel, Steffen Gais, and Jan Born. "Odor cues during slow-wave sleep prompt declarative memory consolidation." Science 315, no. 5817 (2007): 1426-1429.

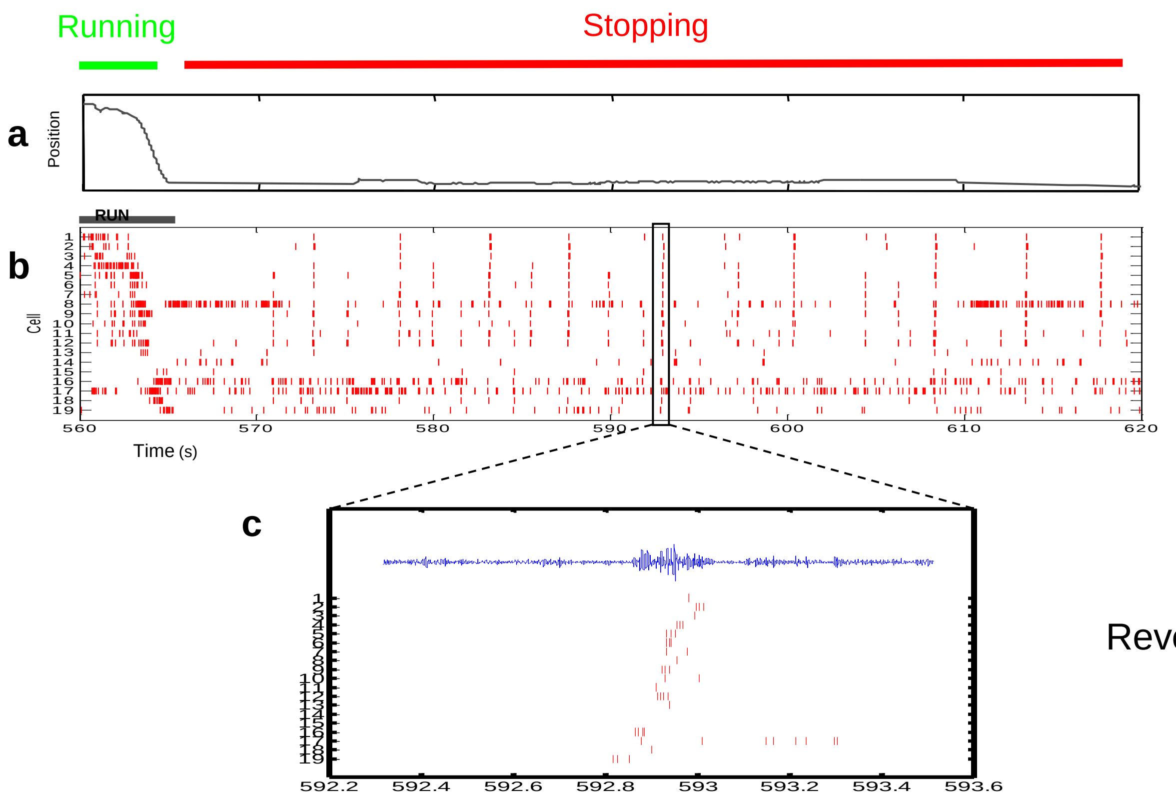
Hippocampal activity during quiet wakefulness

- During awake behavior, there are periods of quiet wakefulness that have EEG that is similar to NREM consisting of brief bursts of activity modulated by high frequency “ripple” oscillations.
- Is there structure to the patterns of multiple single neuron activity during this state?

Does sequence reactivation occur during quiet wakefulness?



Memory of recent experience replayed in reverse-time order



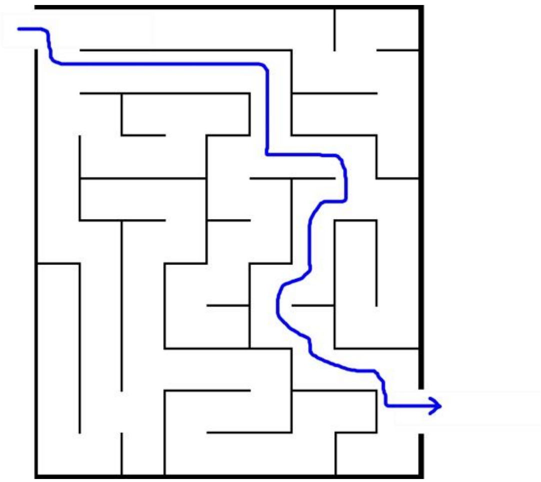
Position vs. time

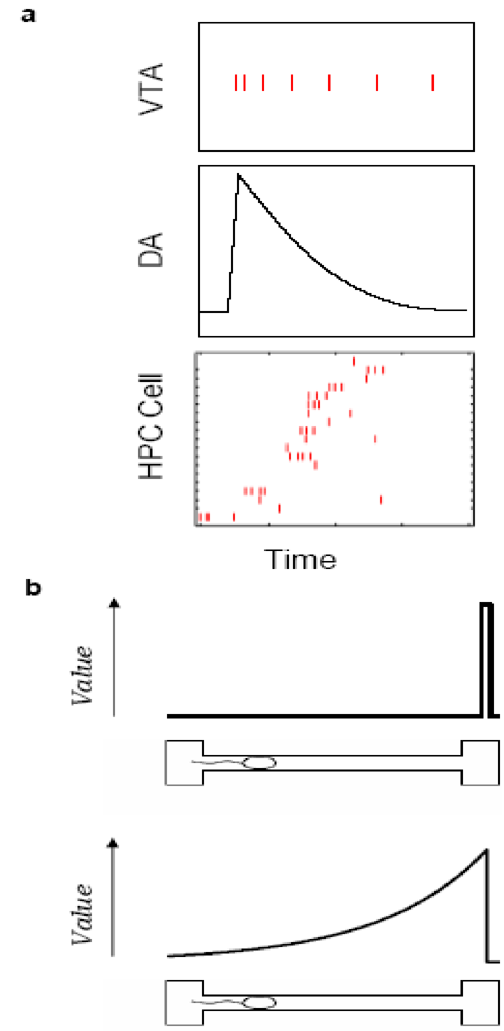
Hippocampal place-cell activity vs. time

Reverse-time sequence replay during hippocampal ripples

Foster and Wilson, *Nature*, 2006

Learning sequences of actions



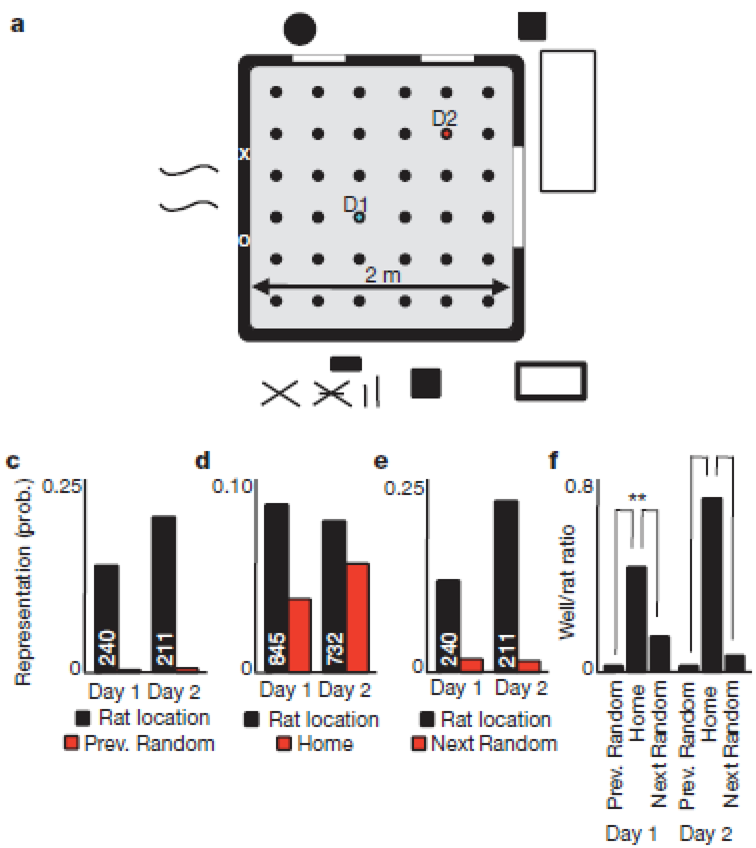


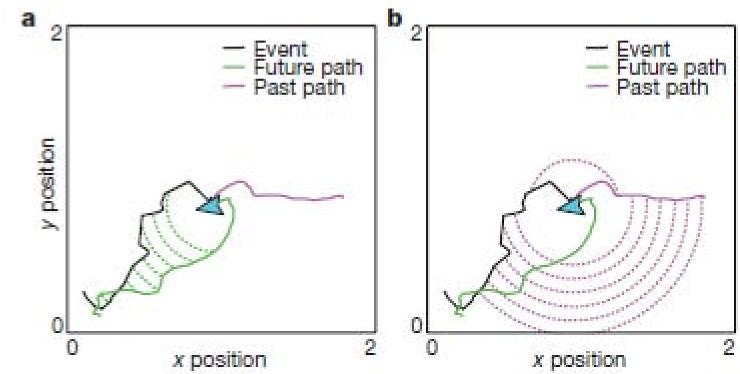
Temporal credit assignment

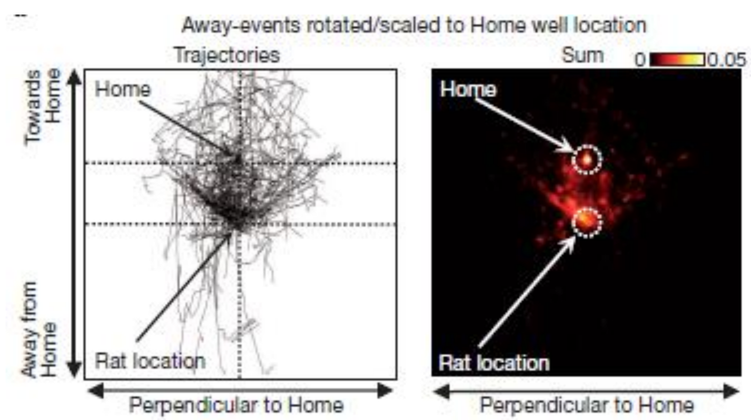
Dopamine unit activity could differentially weight the content of hippocampal sequences, propagating value information from the rewarded location backwards along the incoming trajectory.

Foster and Wilson, Nature 440: 680-683, 2006

Hippocampal place-cell sequences depict future paths to remembered goals
Brad E. Pfeiffer & David J. Foster
Nature, 2013

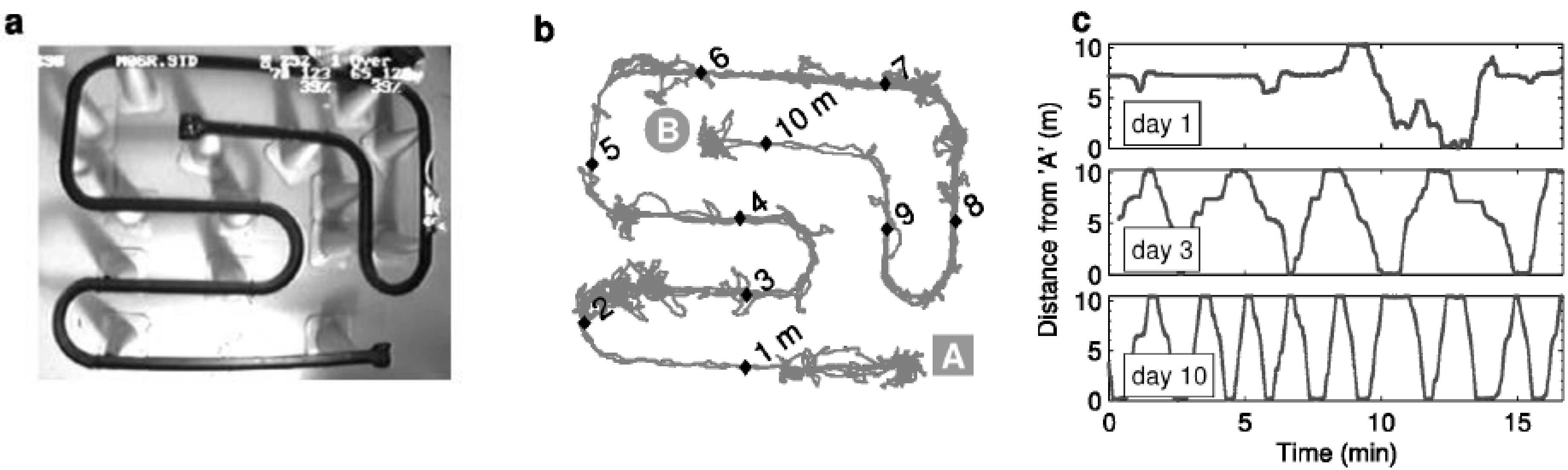






Source: Pfeiffer, Brad E., and David J. Foster. "Hippocampal place-cell sequences depict future paths to remembered goals." Nature 497, no. 7447 (2013): 74-79.

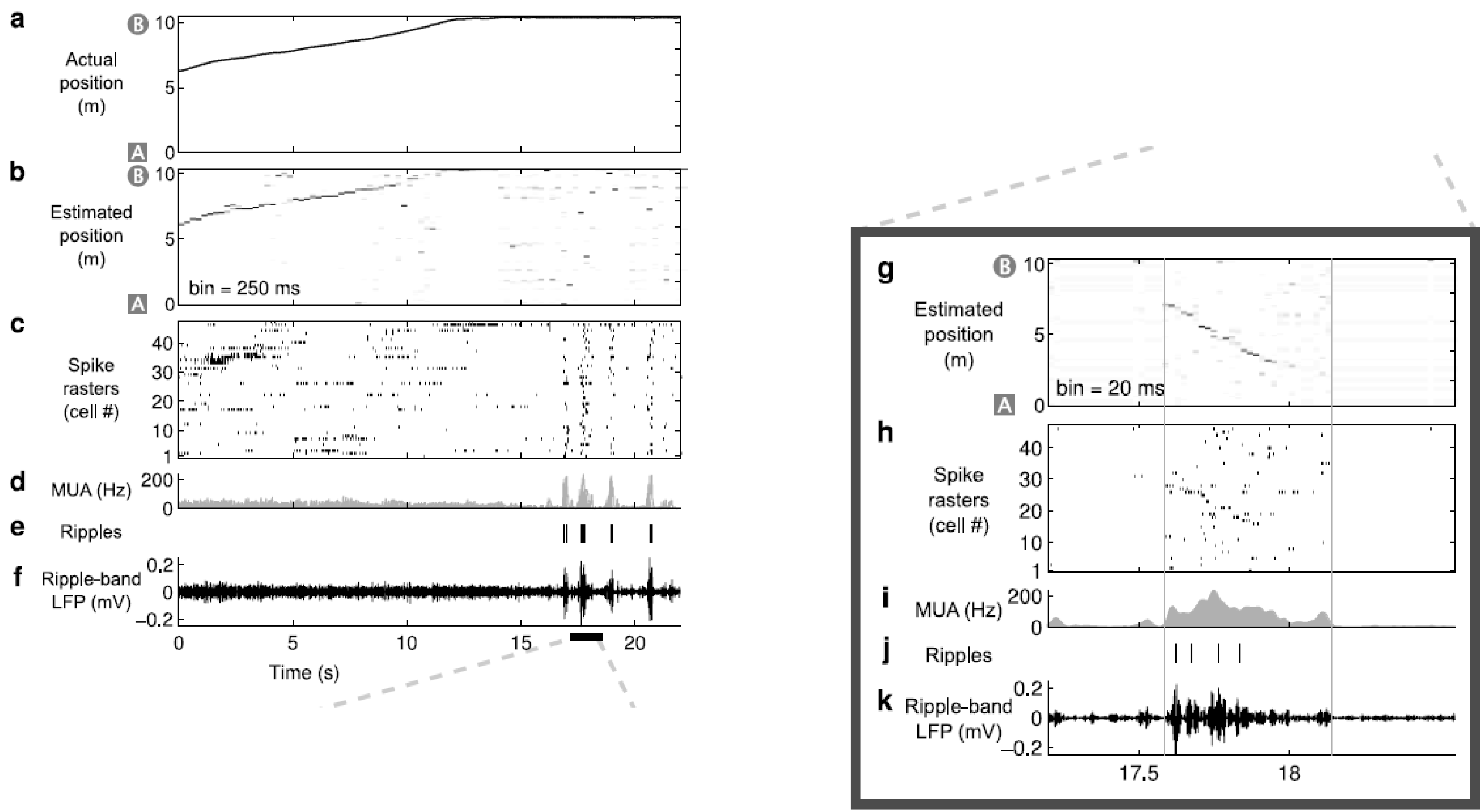
Long behavioral sequences on a 10m track



Source: Davidson, Thomas J., Fabian Kloosterman, and Matthew A. Wilson. "Hippocampal replay of extended experience." Neuron 63, no. 4 (2009): 497-507.

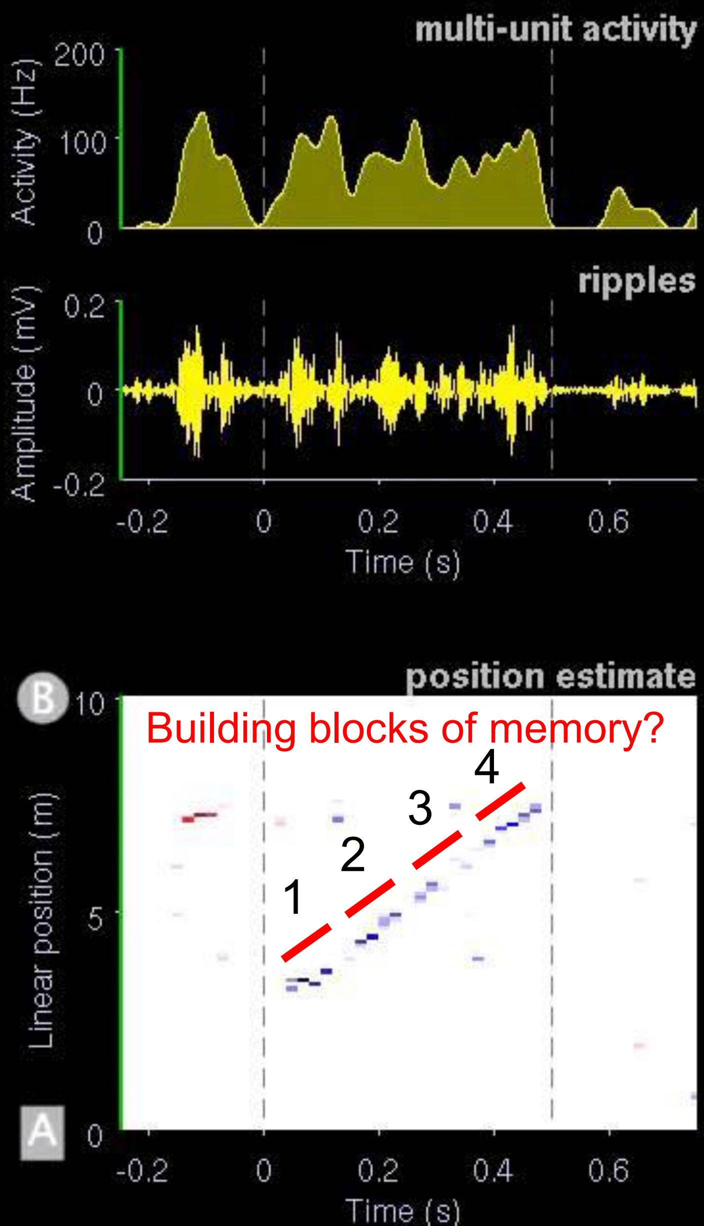
Davidson, Kloosterman and Wilson, *Neuron*, 2009

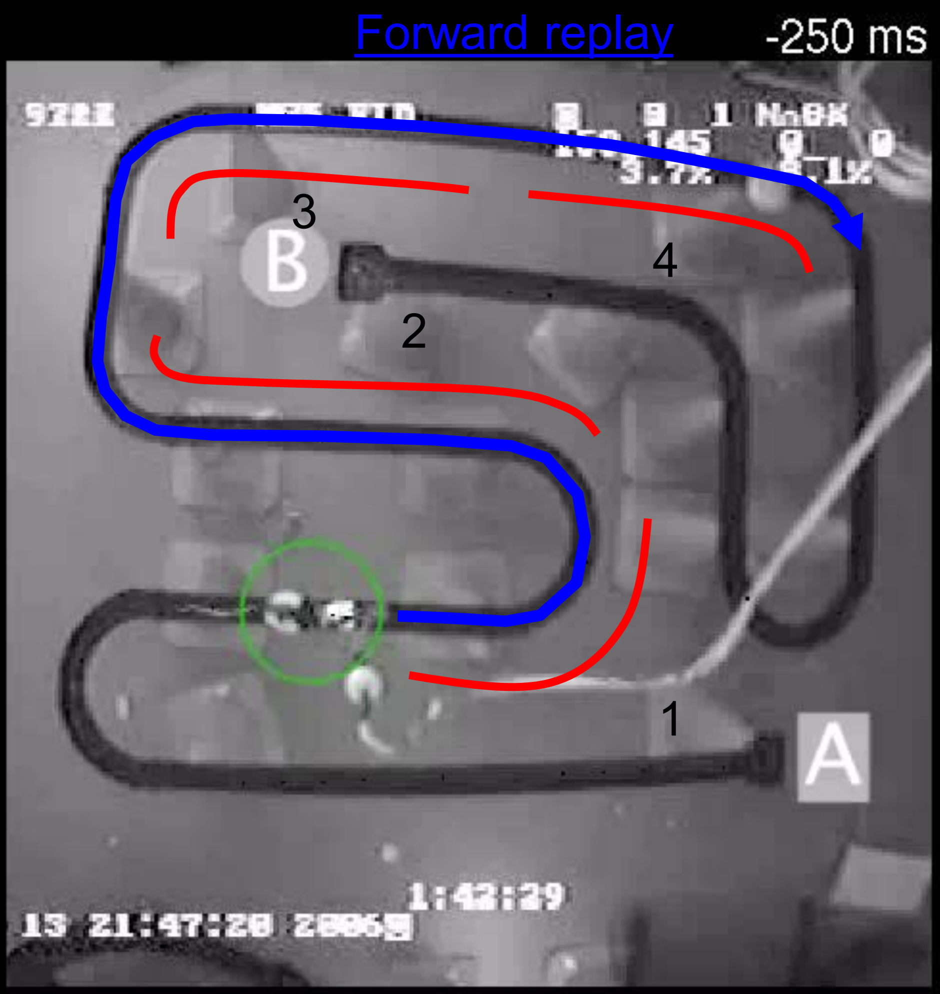
Reconstruction of extended sequence replay during quiet wakefulness



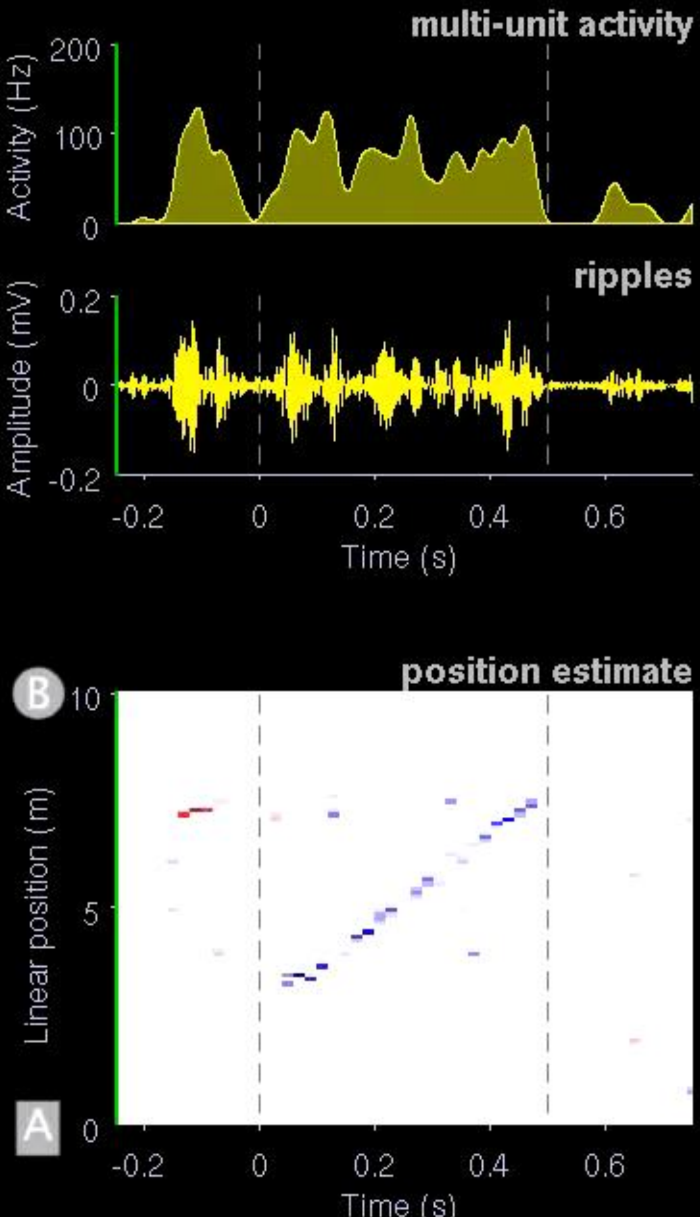
Davidson, Kloosterman and Wilson, *Neuron*, 2009

Forward Replay from A to B

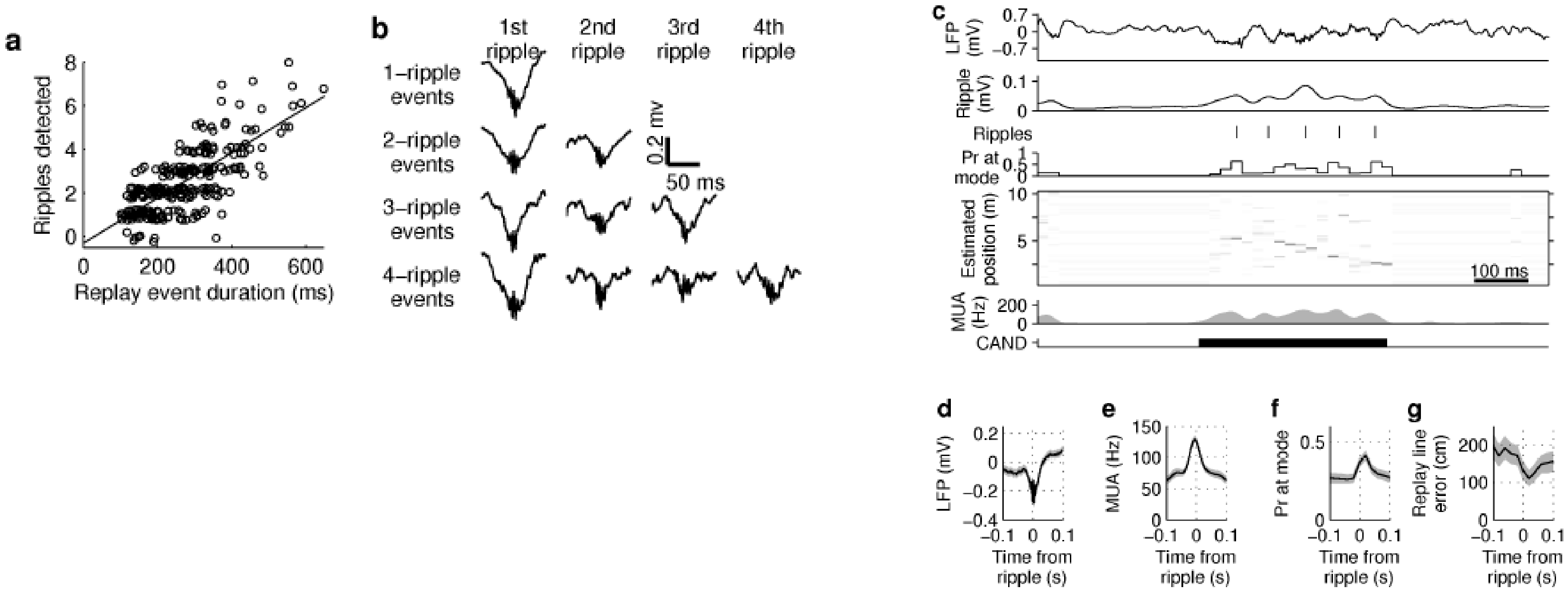




Forward Replay from A to B



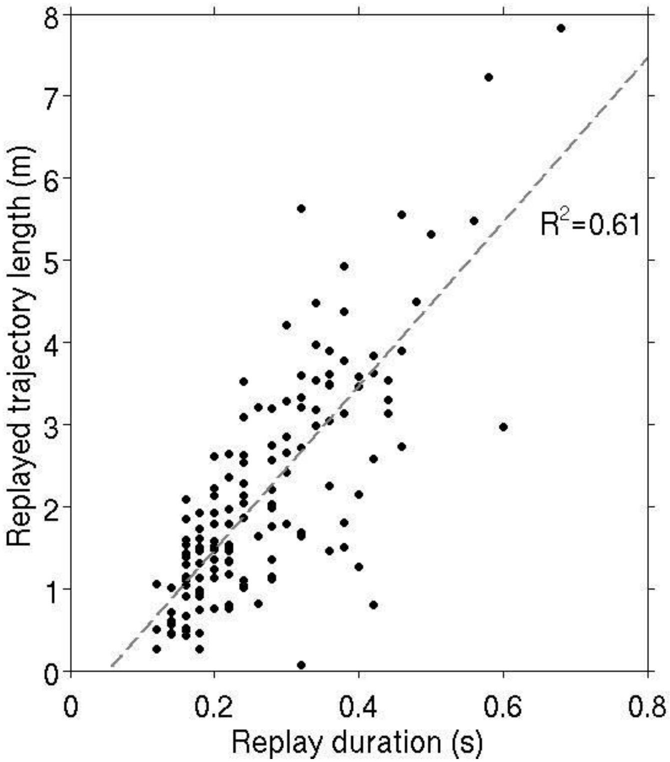
Extended replay spans multiple ripple events

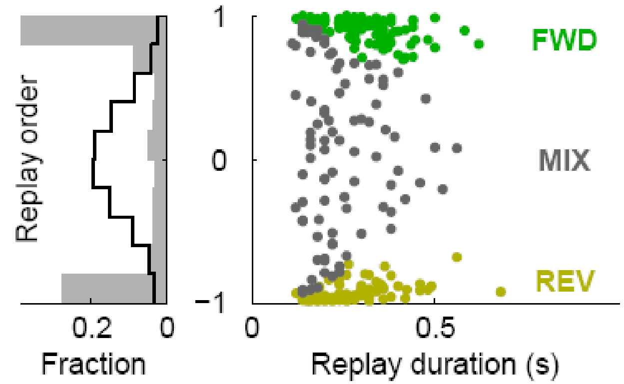


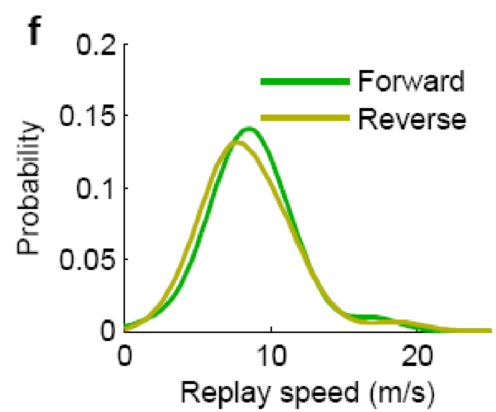
Source: Davidson, Thomas J., Fabian Kloosterman, and Matthew A. Wilson. "Hippocampal replay of extended experience." Neuron 63, no. 4 (2009): 497-507. https://doi.org/10.1016/j.neuron.2009.07.027.

Davidson, Kloosterman and Wilson, *Neuron*, 2009

Extended replay has a characteristic speed



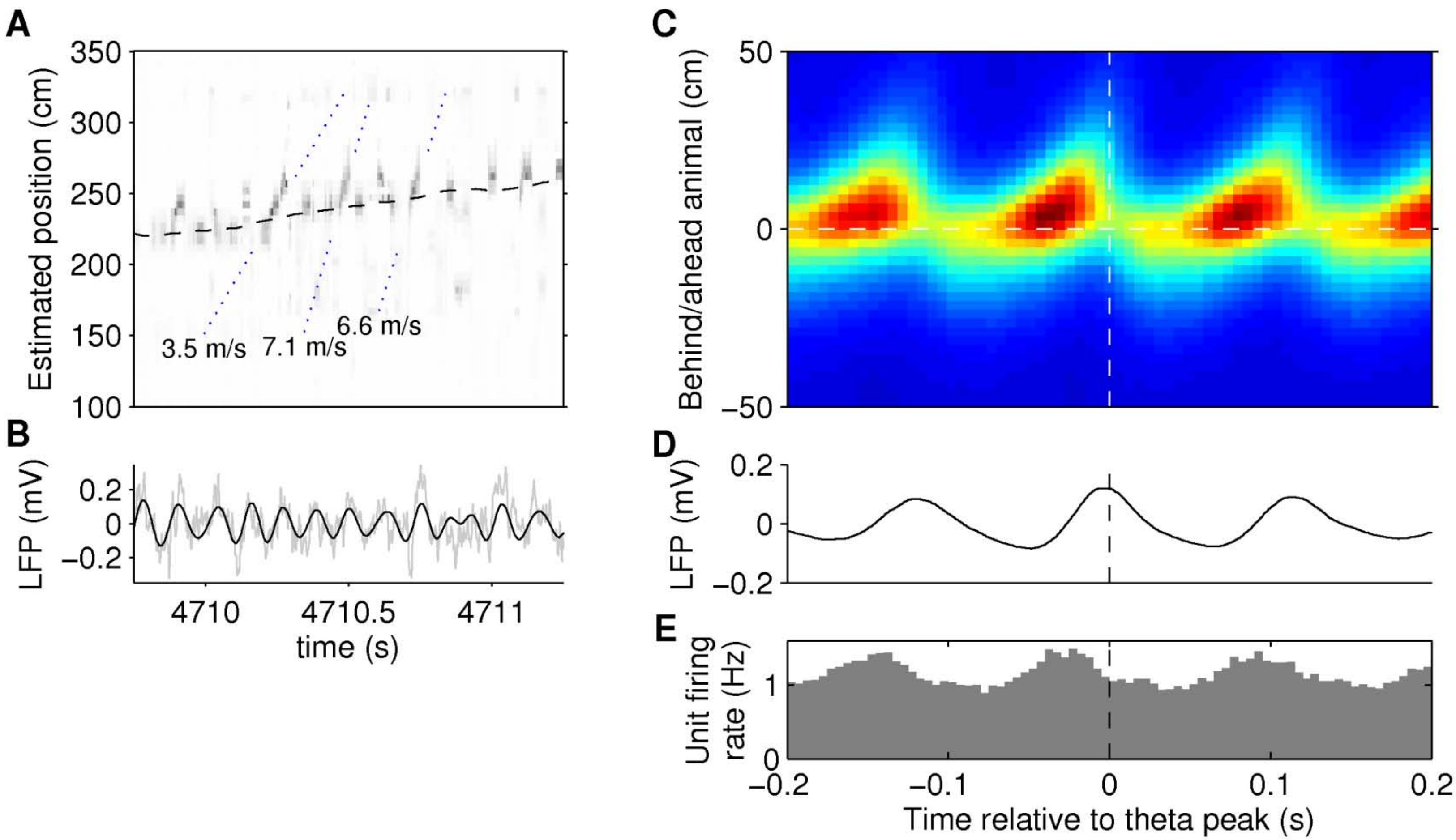




Source: Davidson, Thomas J., Fabian Kloosterman, and Matthew A. Wilson. "Hippocampal replay of extended experience." Neuron 63, no. 4 (2009): 497-507.

Davidson, Kloosterman and Wilson, *Neuron*, 2009

Single ripple sequences are at same scale as theta sequences



Source: Davidson, Thomas J., Fabian Kloosterman, and Matthew A. Wilson. "Hippocampal replay of extended experience." Neuron 63, no. 4 (2009): 497-507.

Davidson, Kloosterman, and Wilson, *Neuron*, 2009

Overall summary

- Sequence memory can be encoded in the hippocampus during active behavior.
- Sequence memory is subsequently replayed during sleep in both the hippocampus and neocortex.
- The content of reactivated memory during sleep can be biased by external manipulation.
- Sequence memory replayed during quiet wakefulness is associated reward information and may serve a different role in learning than replay during sleep.