

Competition between internal and external drives in spatial memory processing revealed by a mouse model of neurodegeneration

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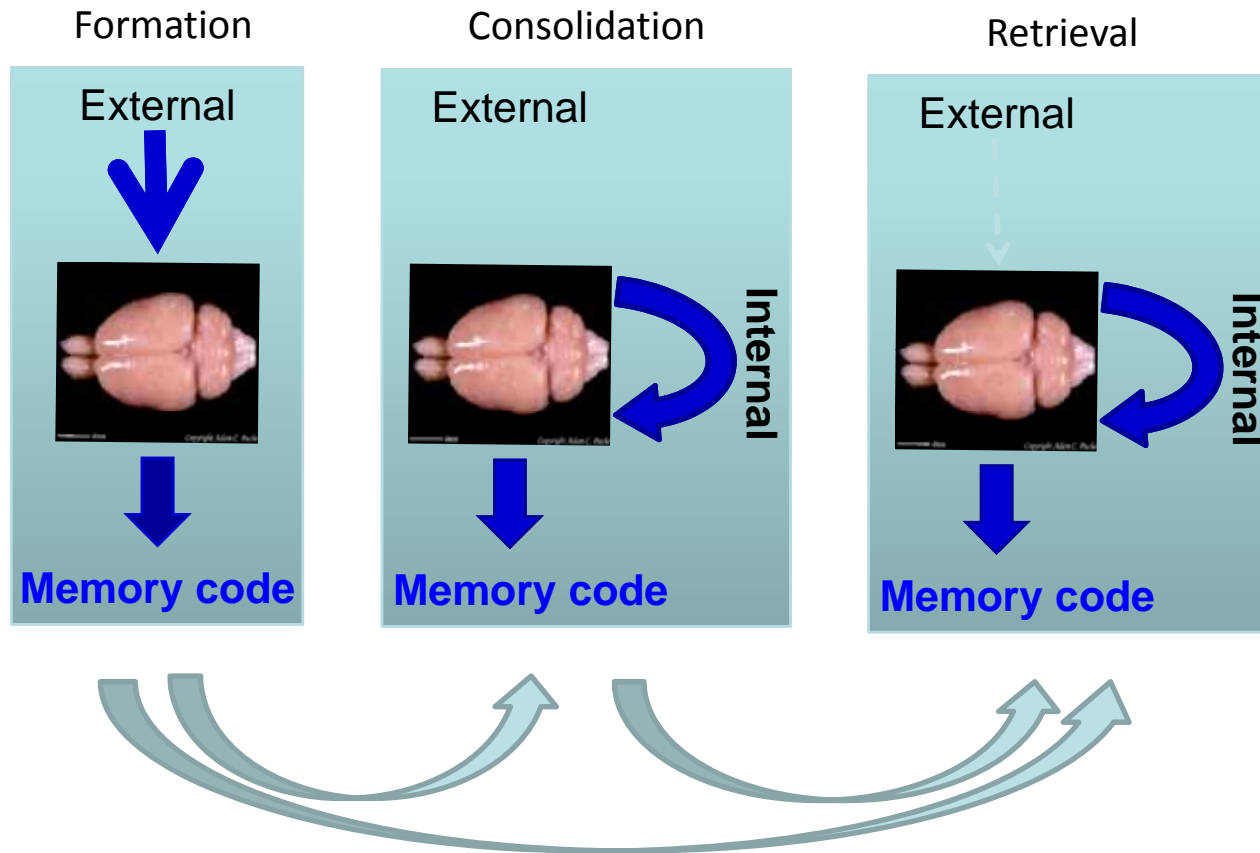
Baylor College of Medicine, Houston, Texas

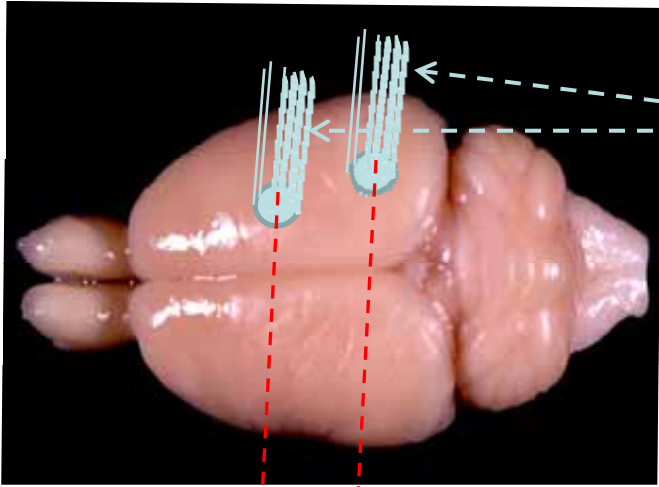


Place cells: spatial memory code

Use place cells to study memory processing

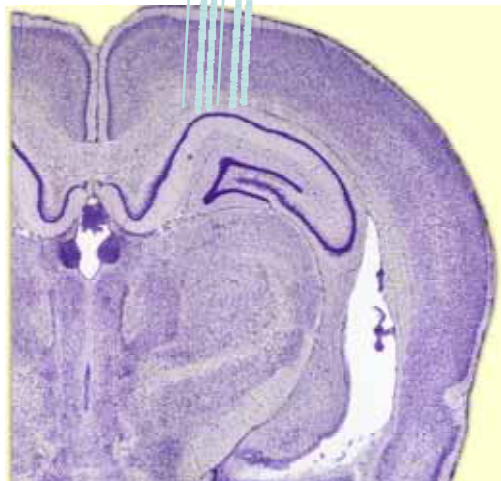
Spatial memory code



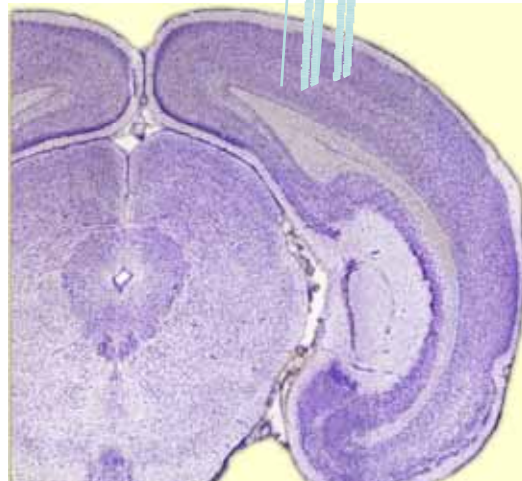


Electrodes (tetrodes)

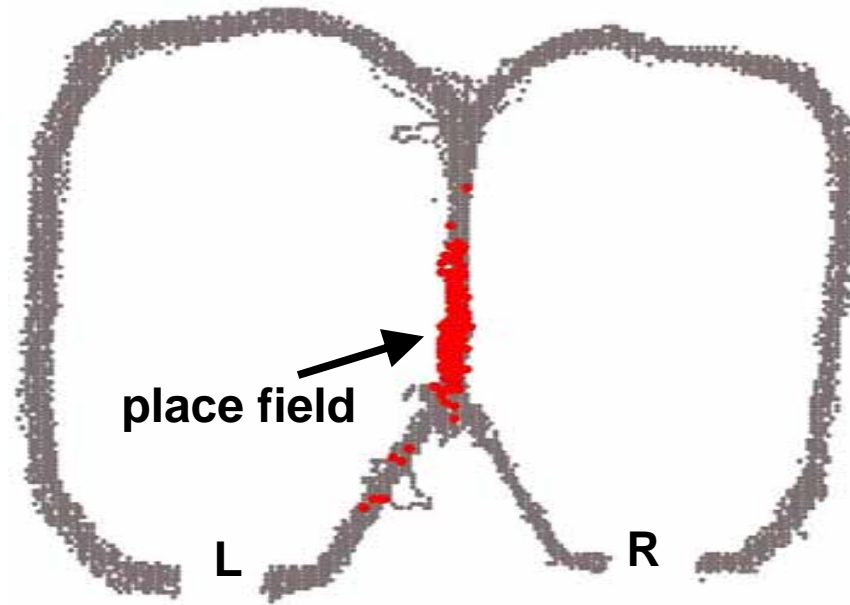
Hippocampus



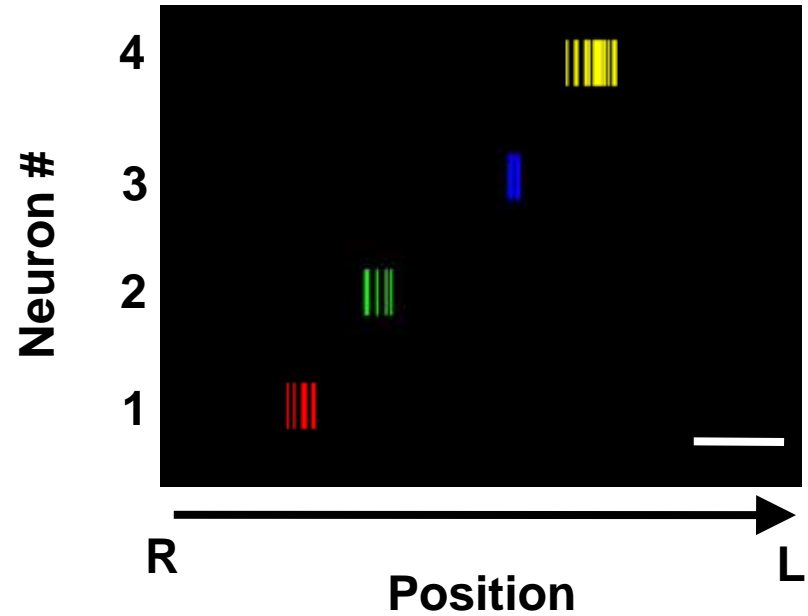
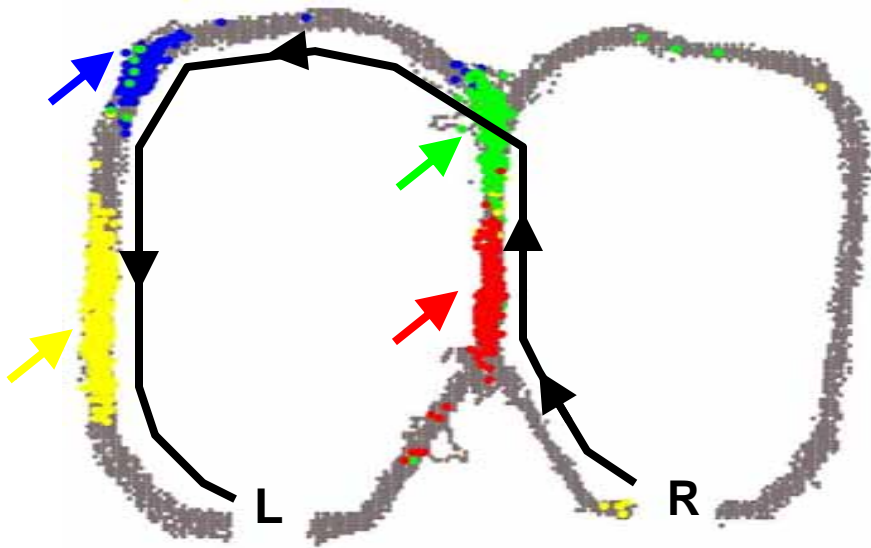
Visual cortex



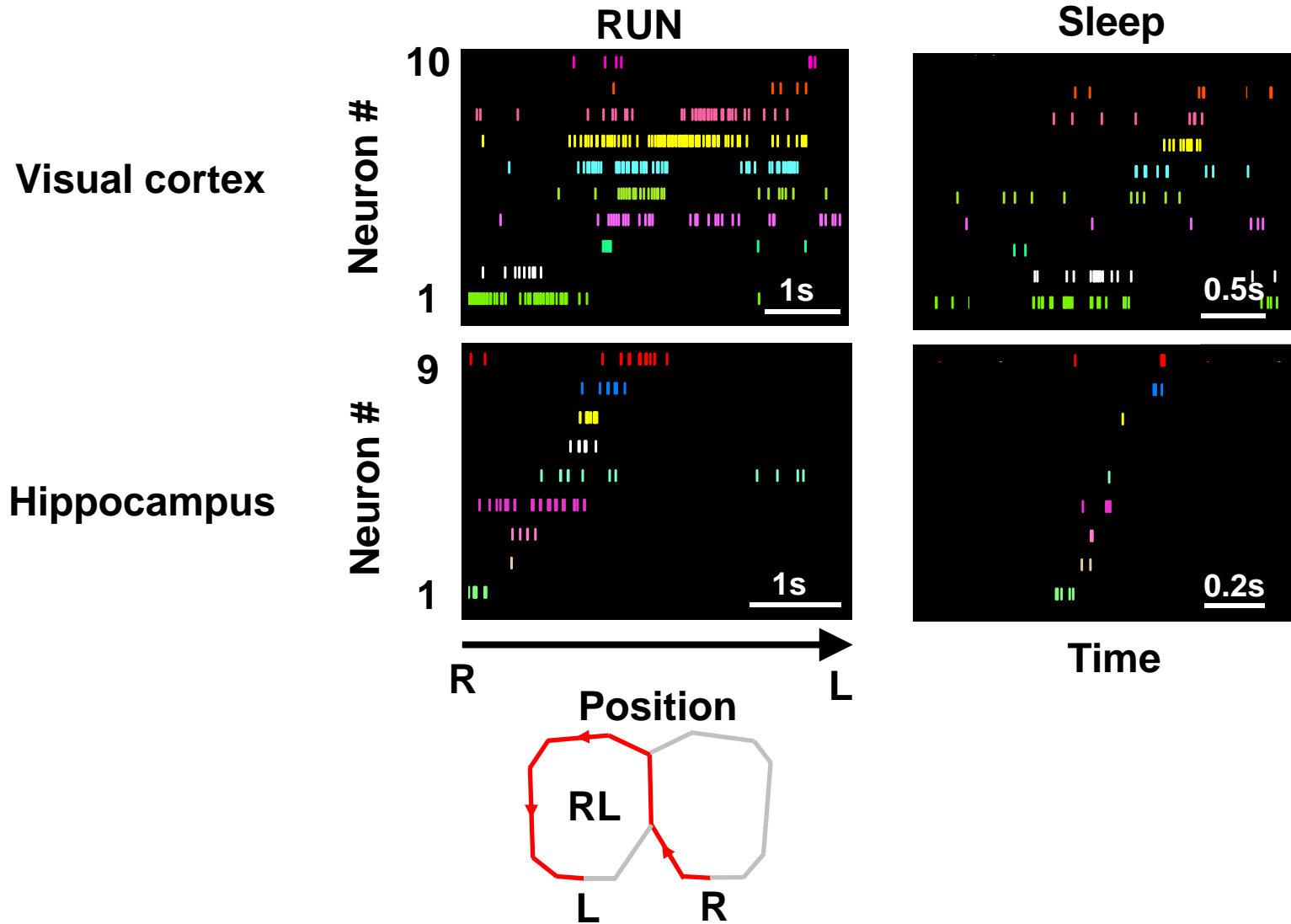
Rat hippocampal neurons (place cells)



The memory codes for spatial trajectories:
firing sequences of multiple hippocampal neurons

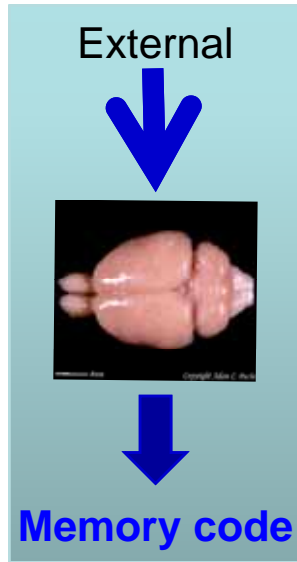


Replay of firing sequences during slow-wave sleep

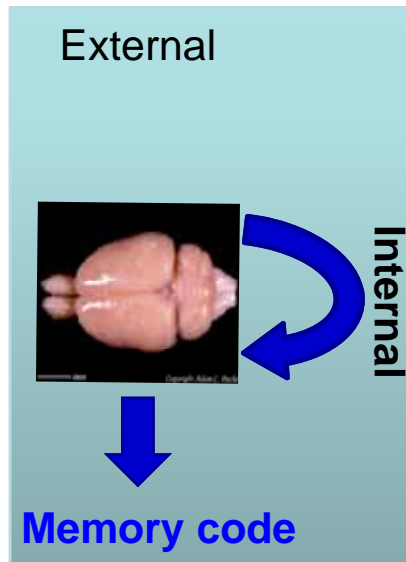


Spatial memory code

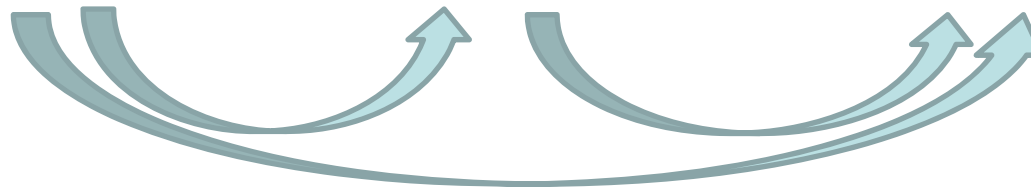
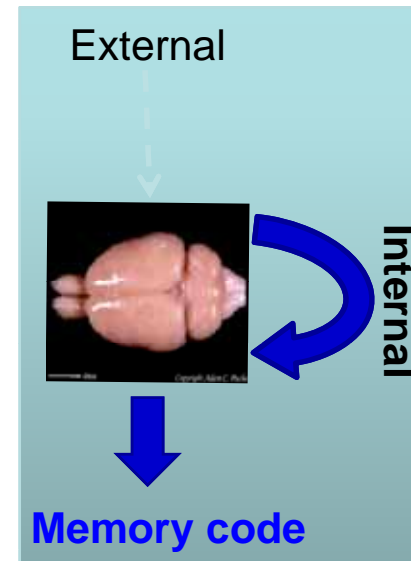
Memory formation



Memory consolidation

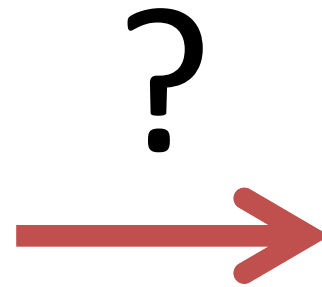
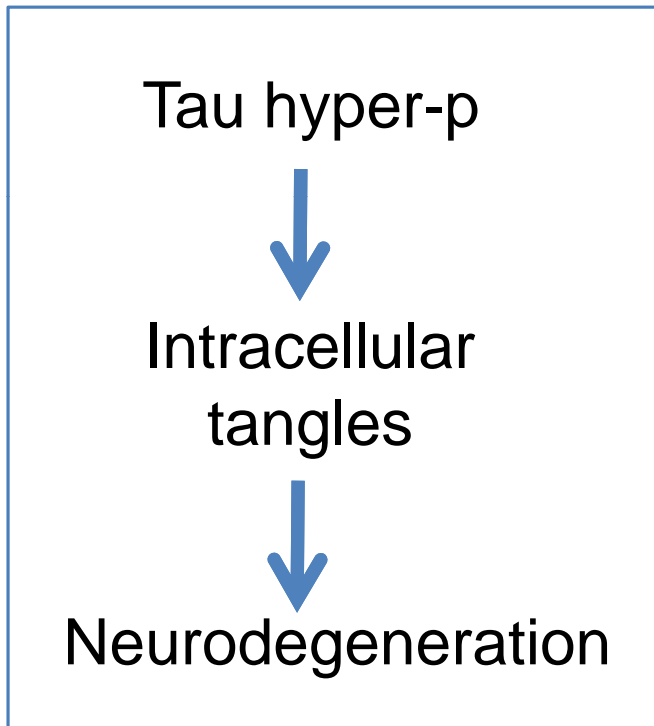


Memory retrieval



Question

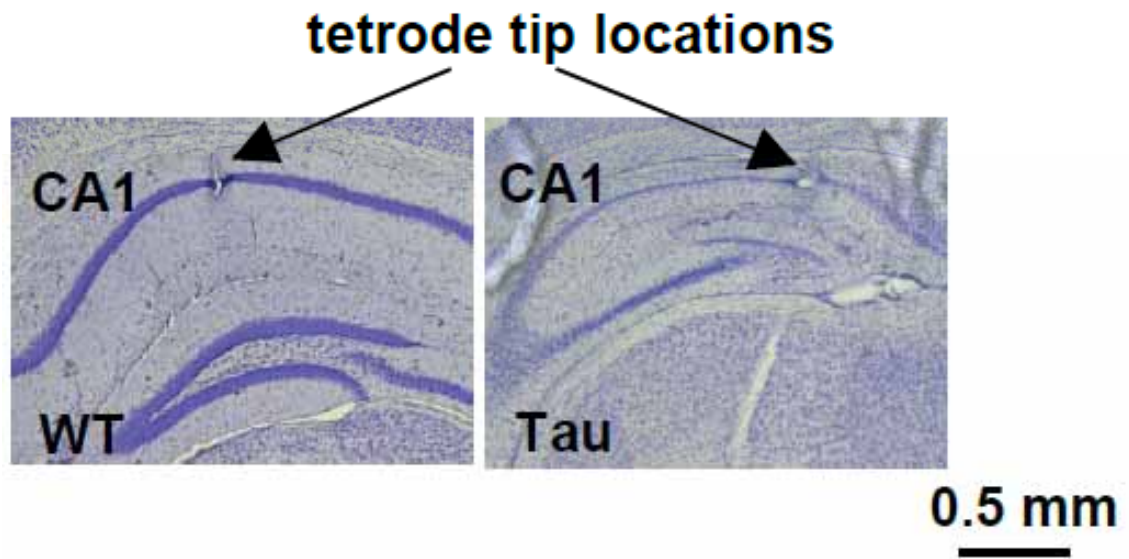
Tauopathies (including
Alzheimer's disease)



Memory
deficits

The rTg4510 (Tau) mice

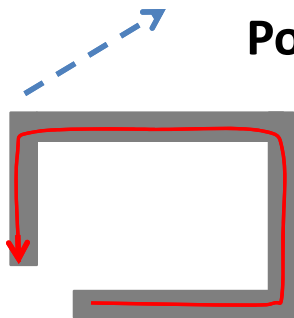
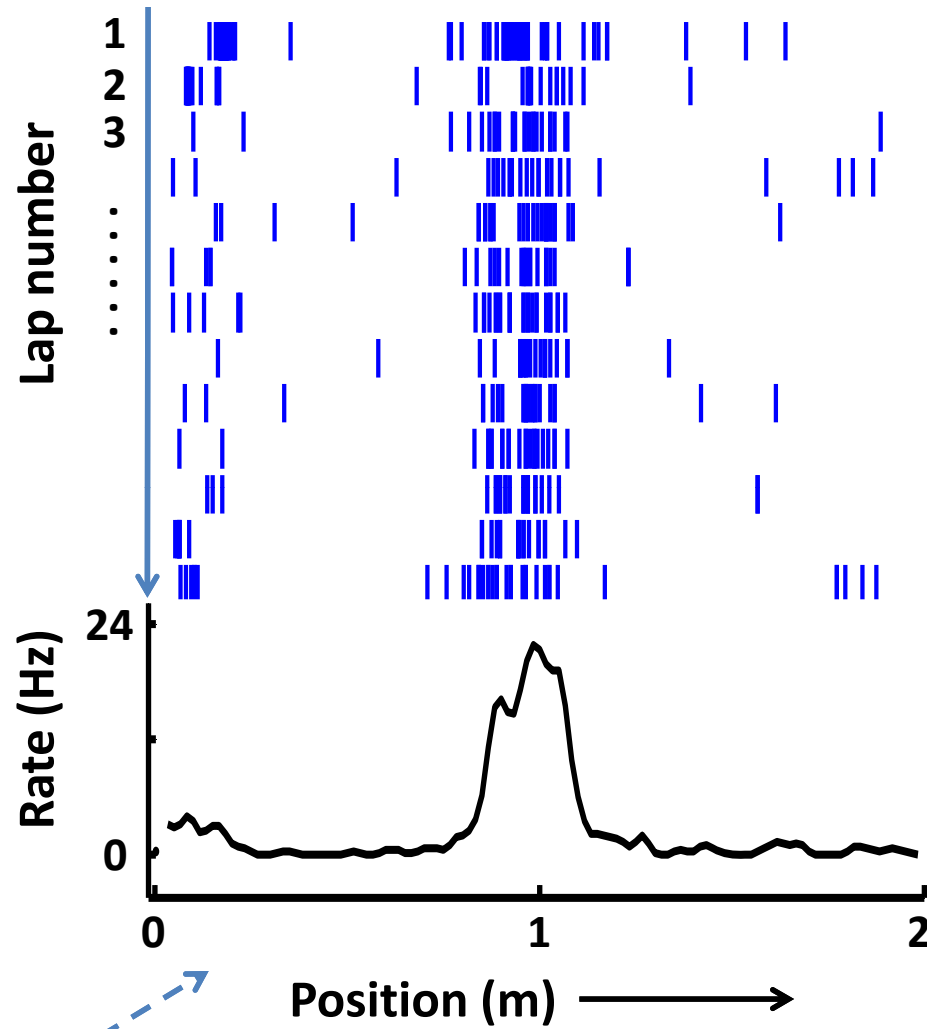
- Tau pathology: overexpression of a mutated human tau gene (P301L) in the forebrain leads to tau tangles and neurodegeneration.
- Memory deficits: clear spatial memory problems at 7-9 month old.



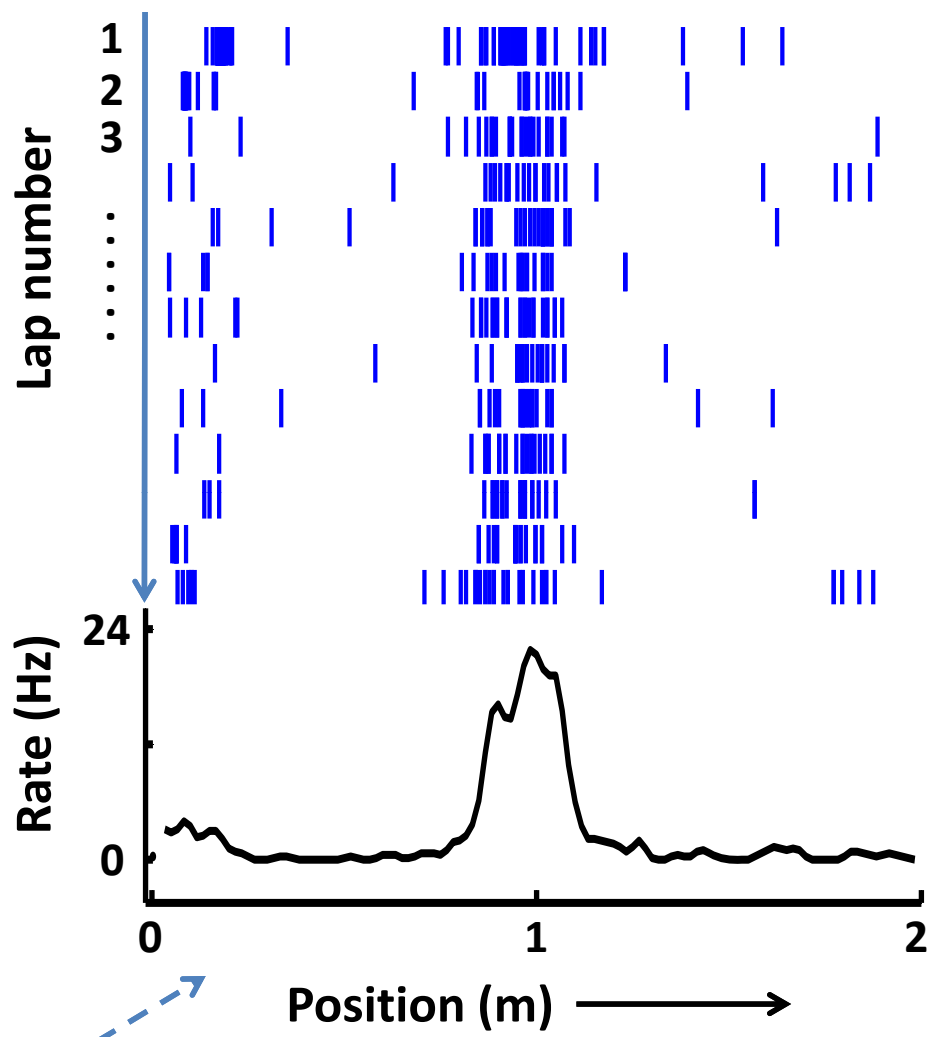
The familiar maze



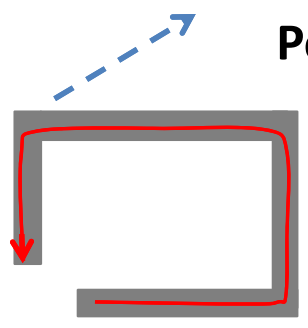
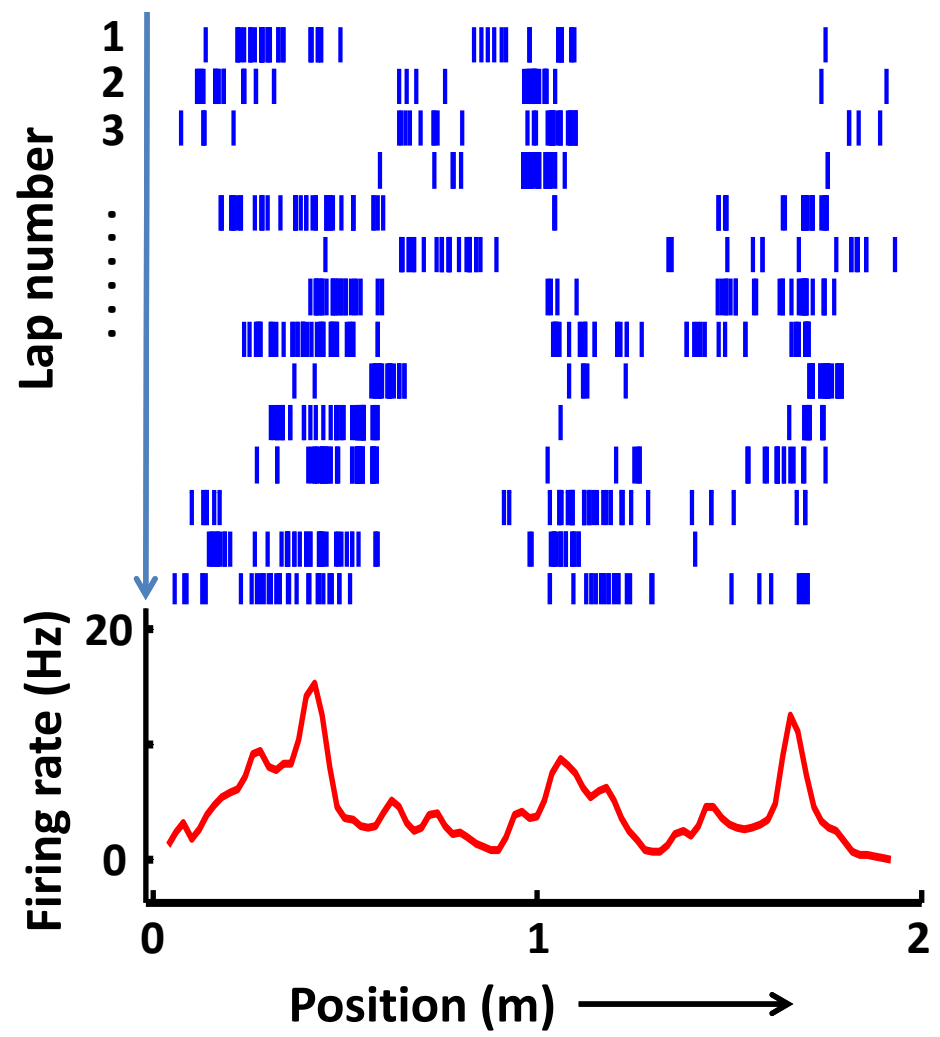
Hippocampal place cells during track running



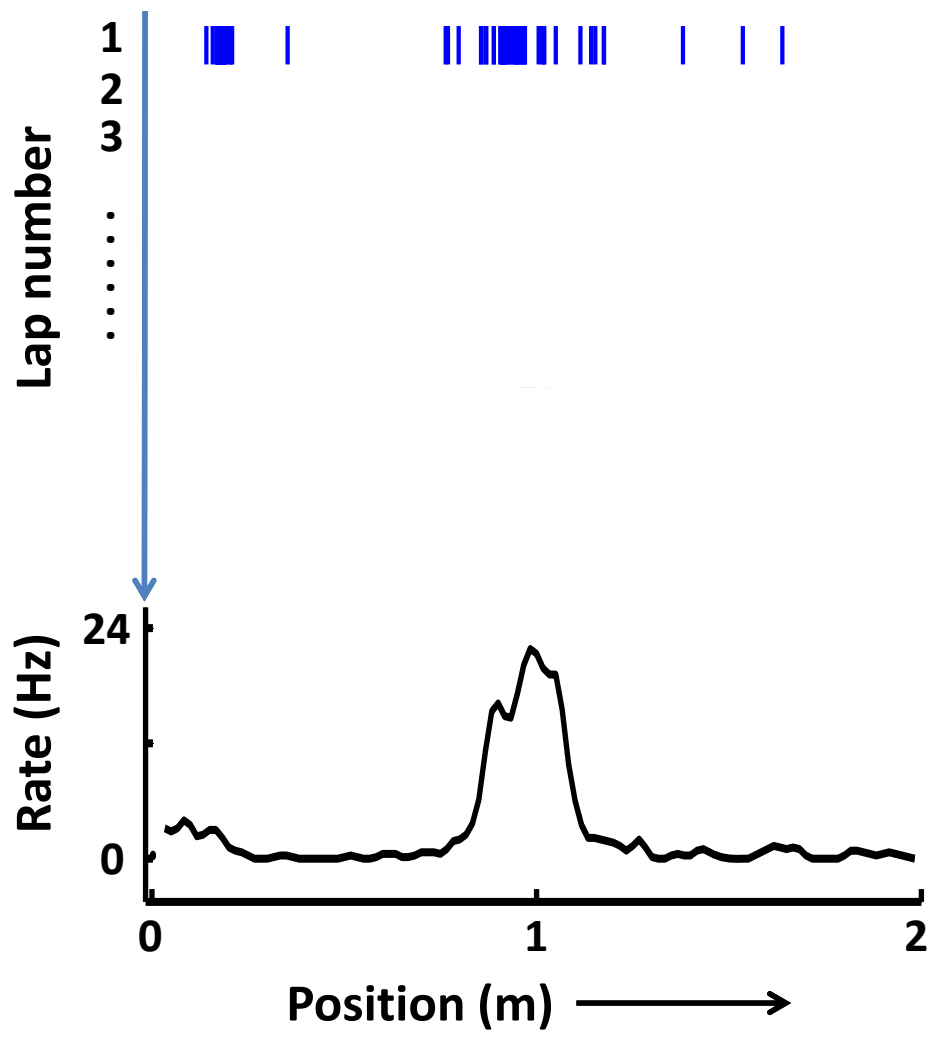
WT



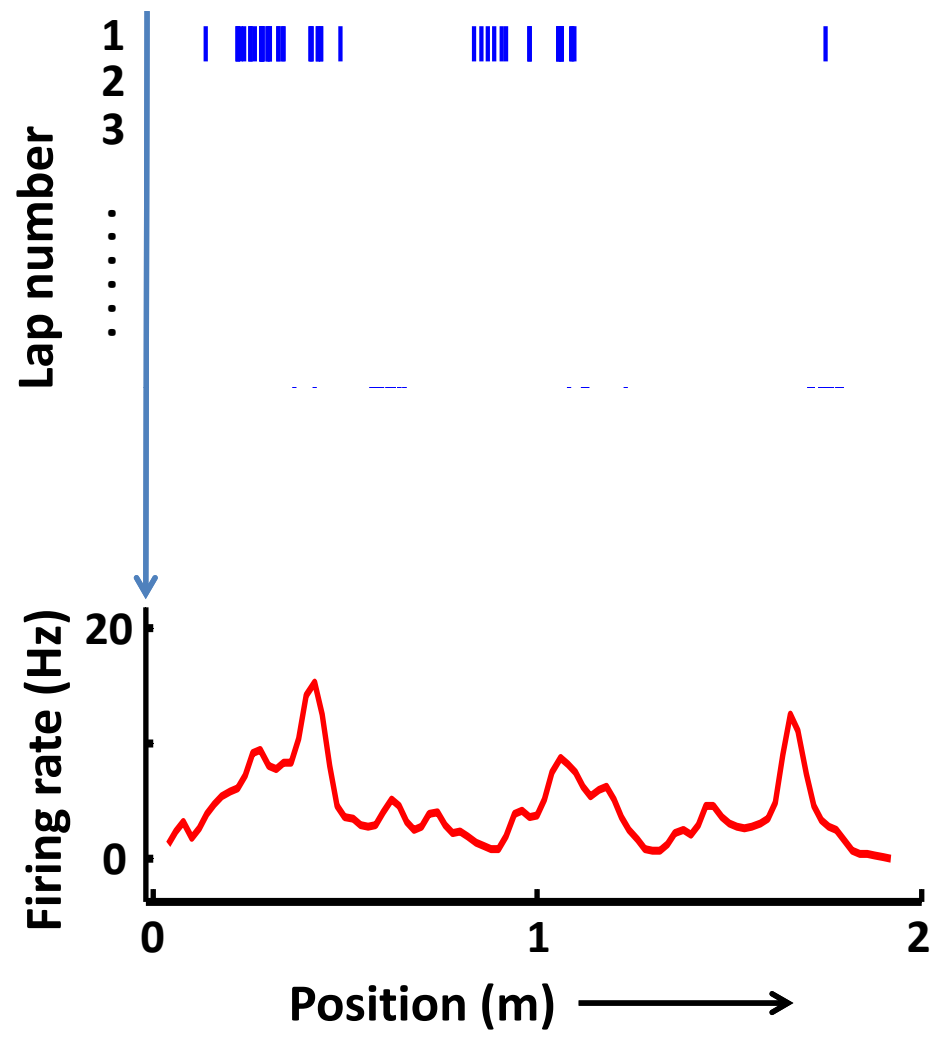
Tau



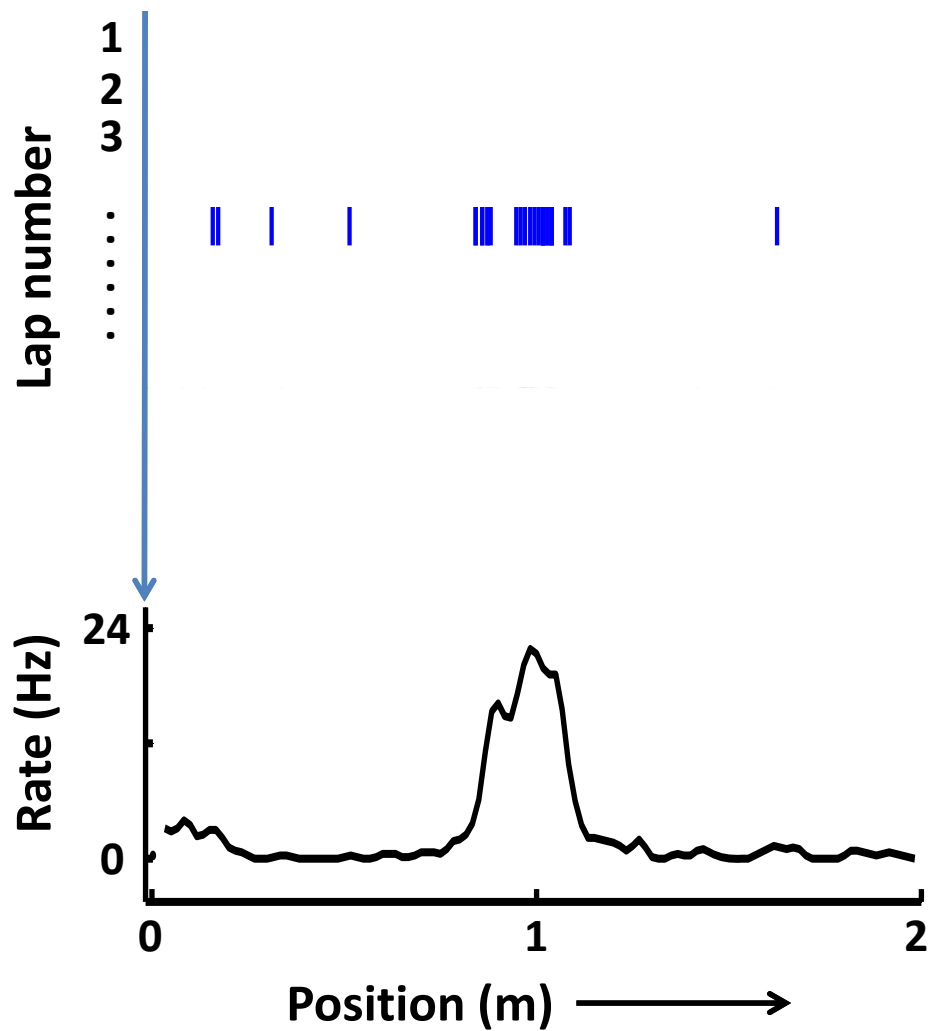
WT



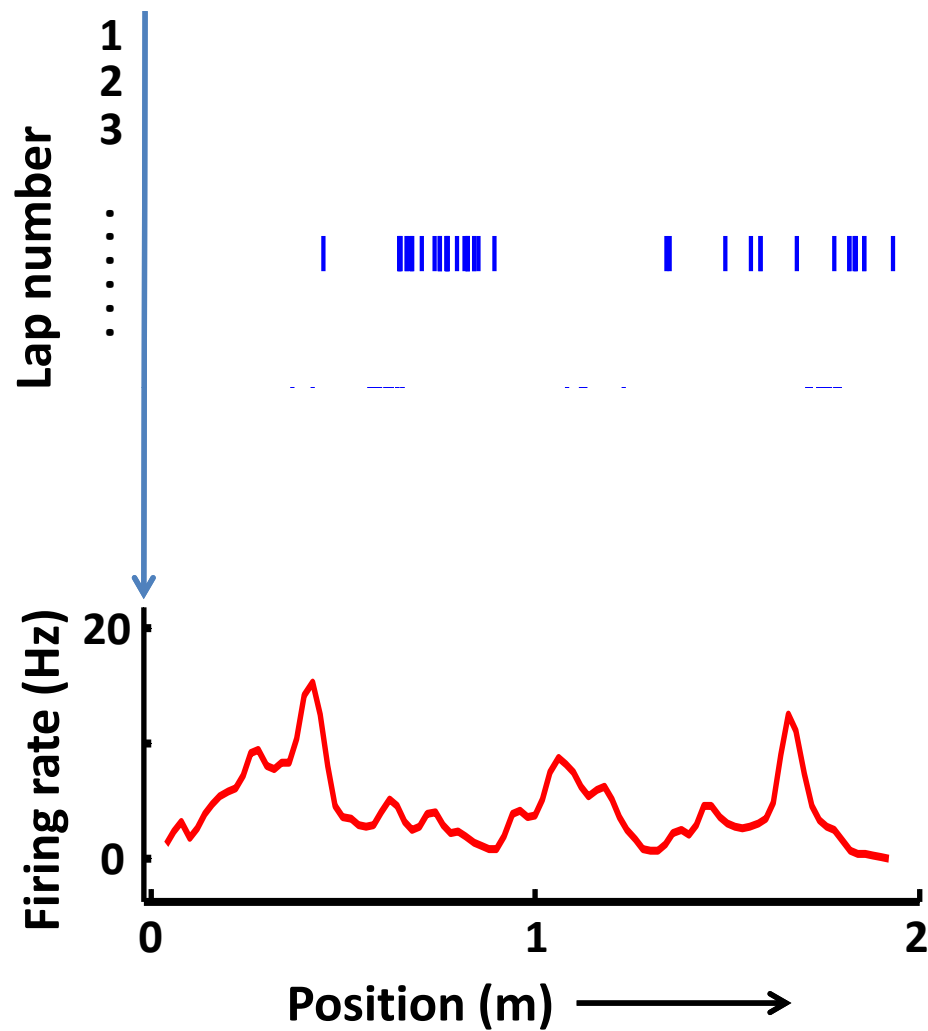
Tau



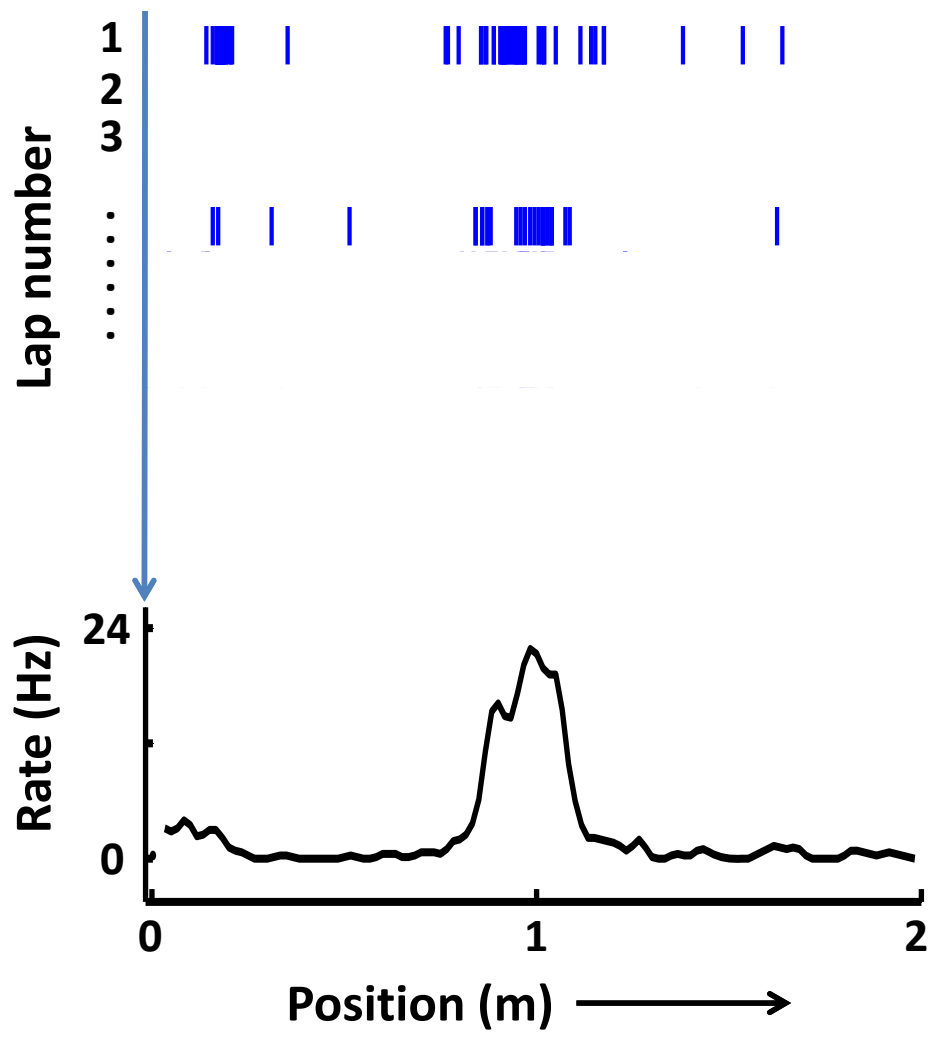
WT



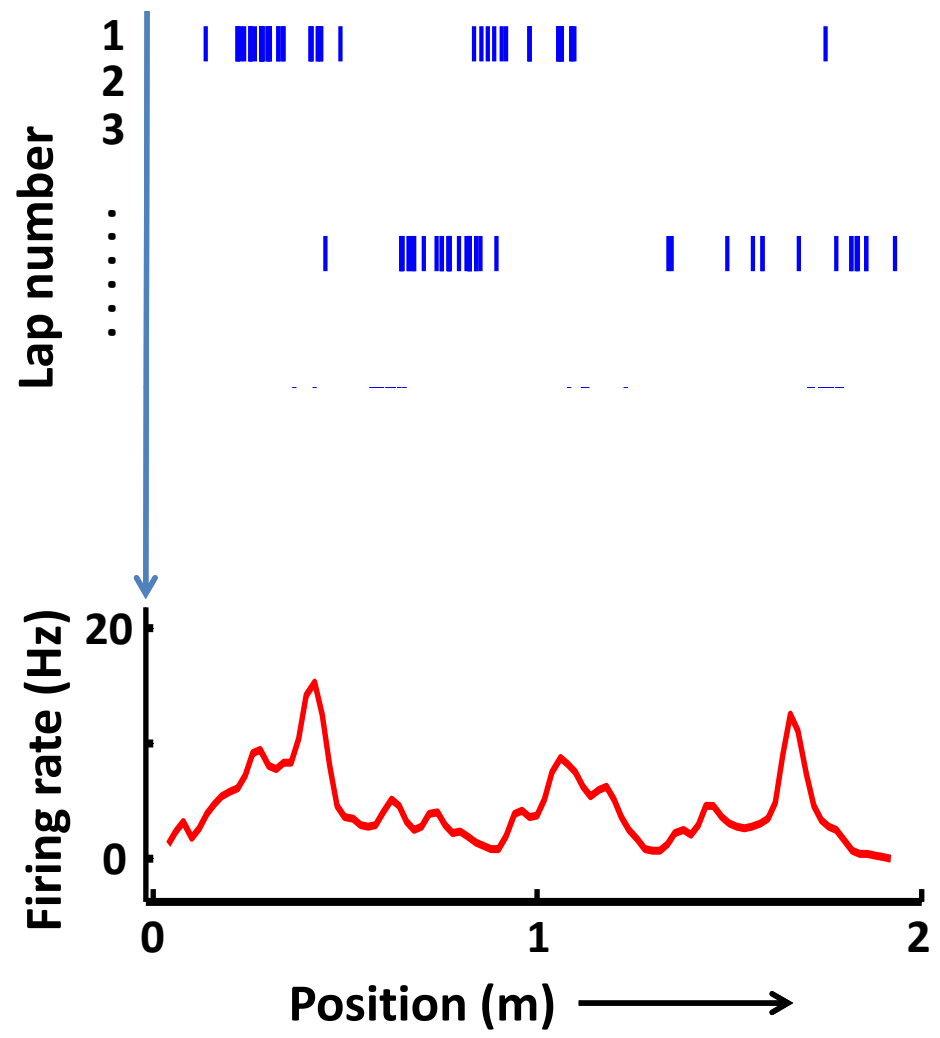
Tau



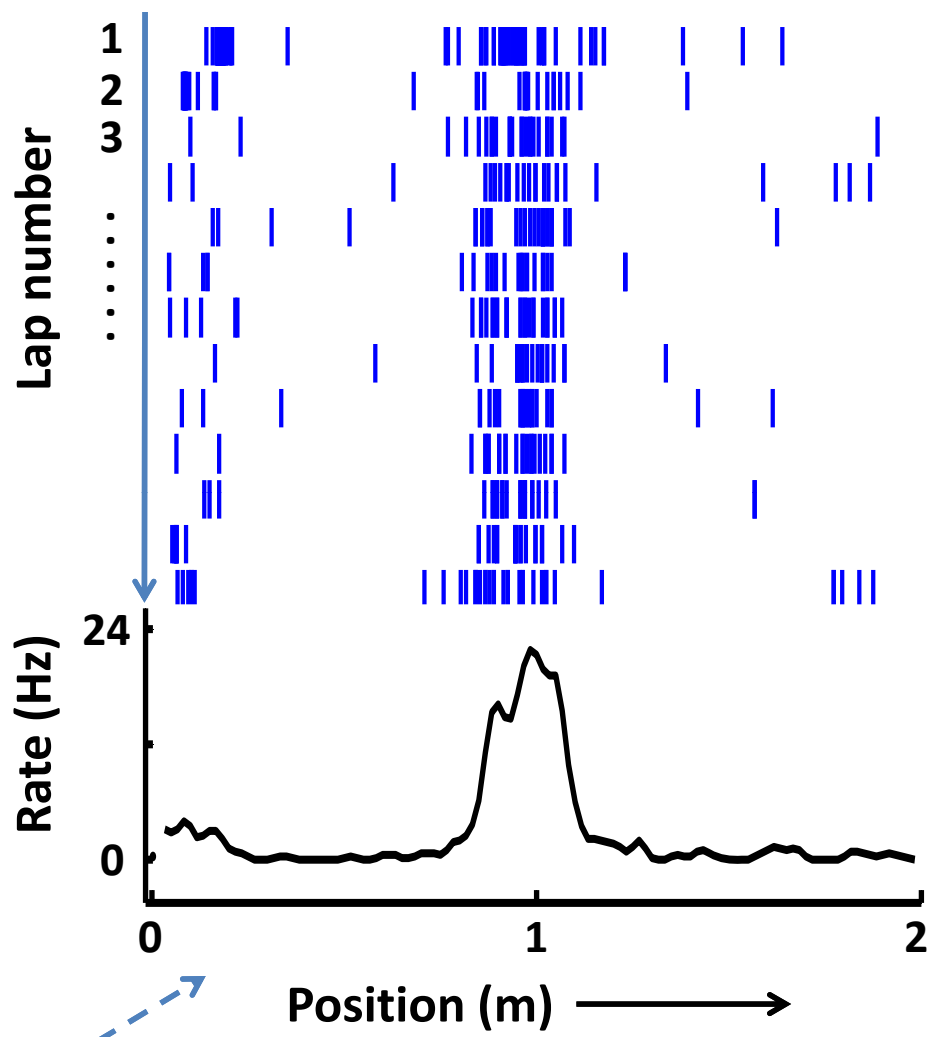
WT



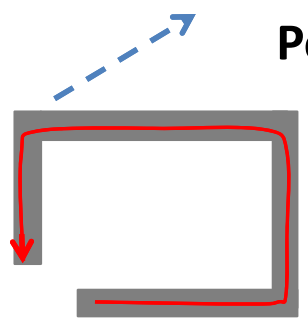
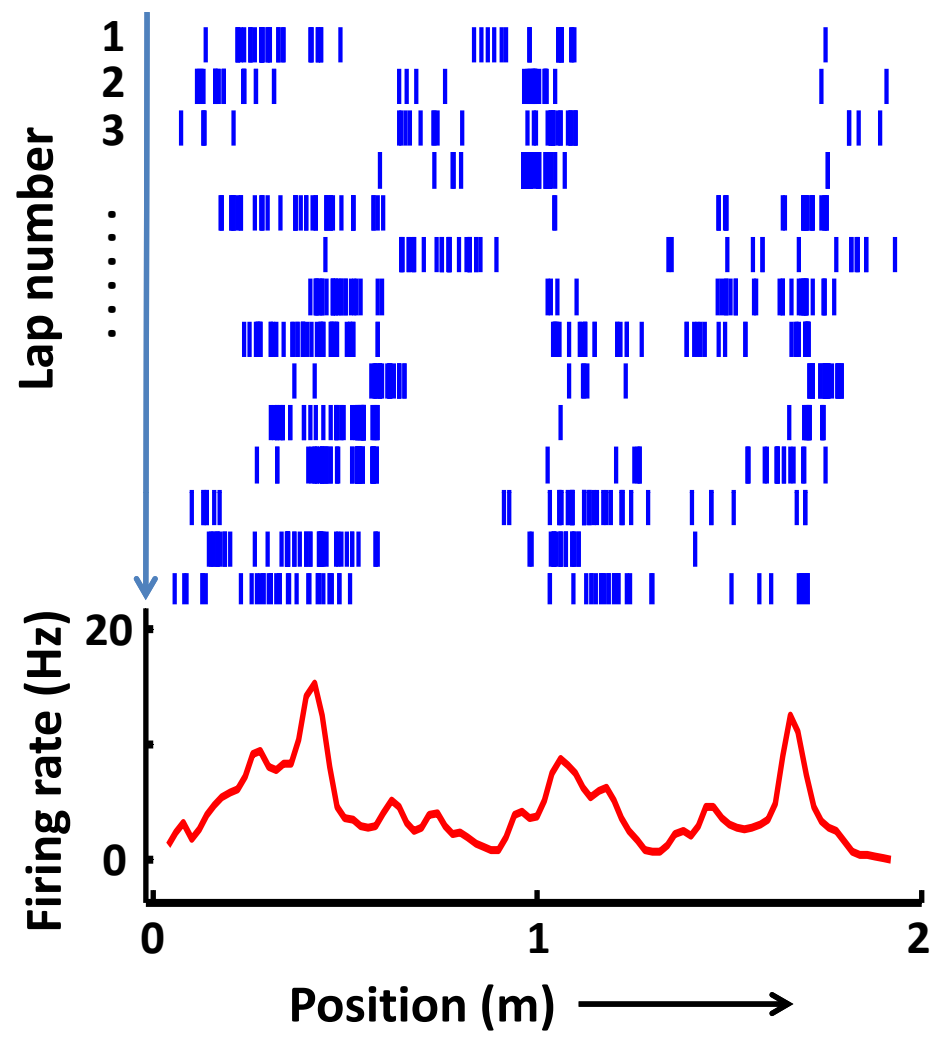
Tau



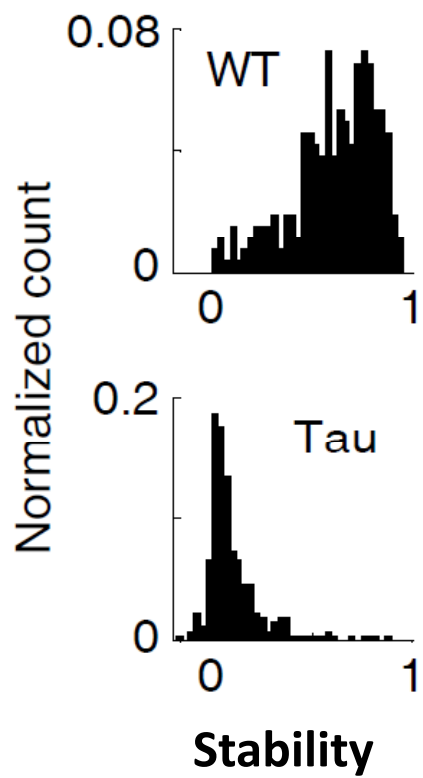
WT



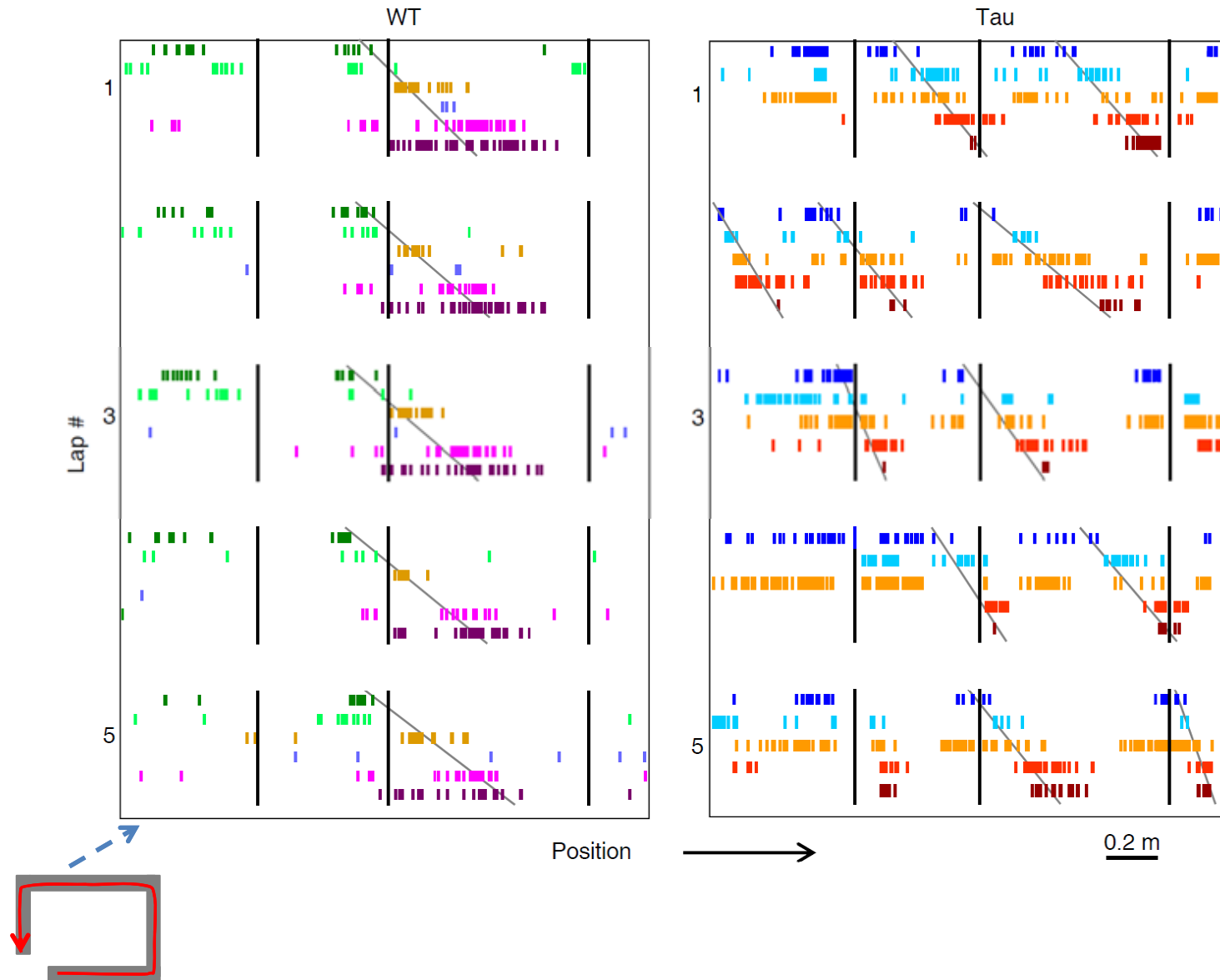
Tau

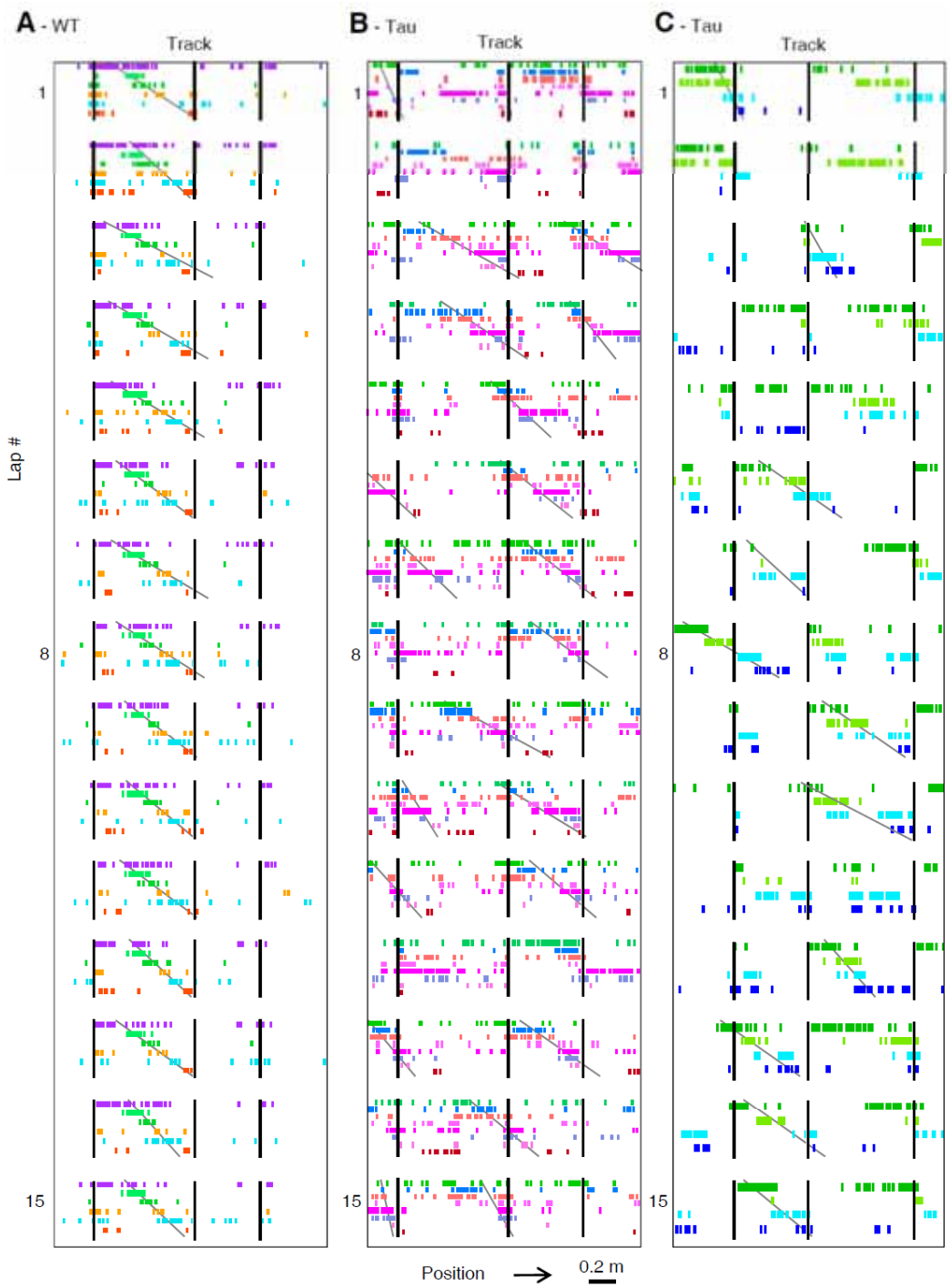


Unstable firing locations of hippocampal cells in Tau mice

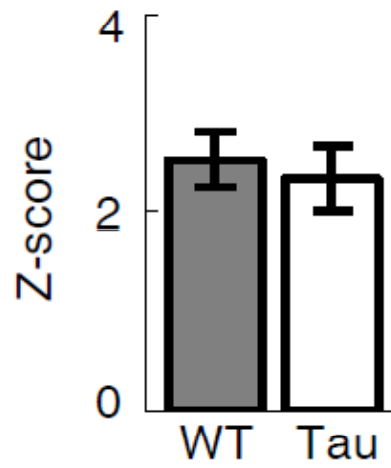


Consistent firing sequences despite unstable firing locations in Tau mice

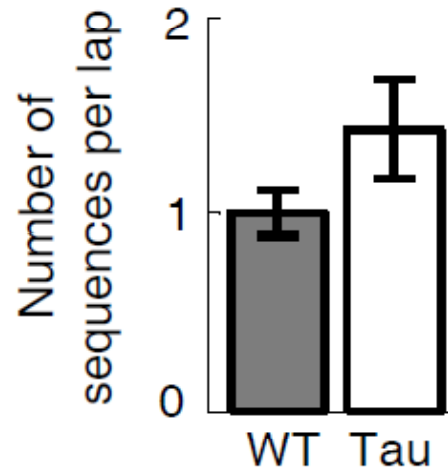




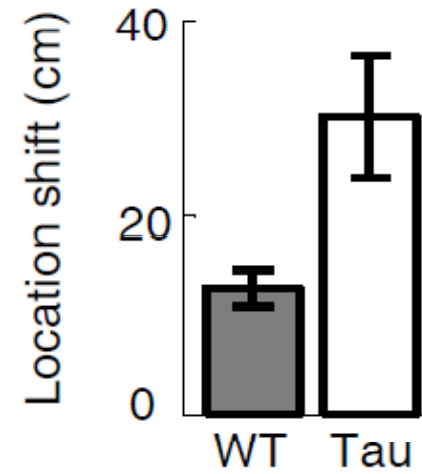
Number of sequences per session



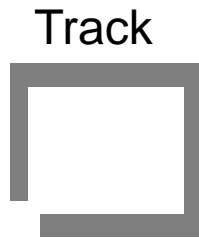
Number of sequences per lap



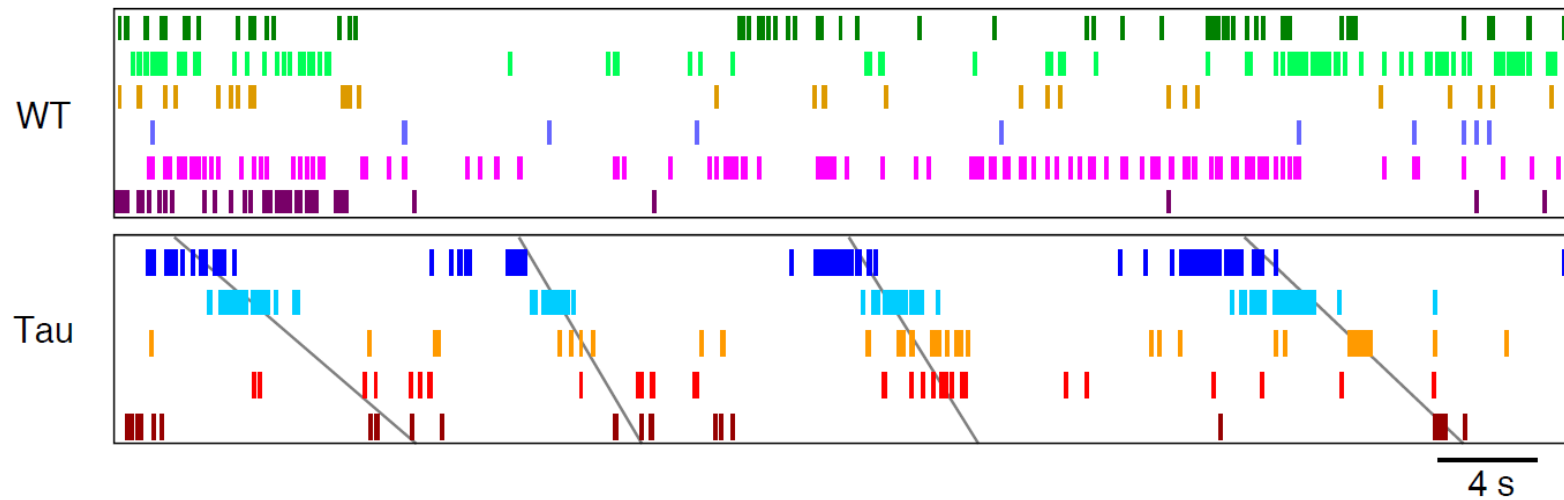
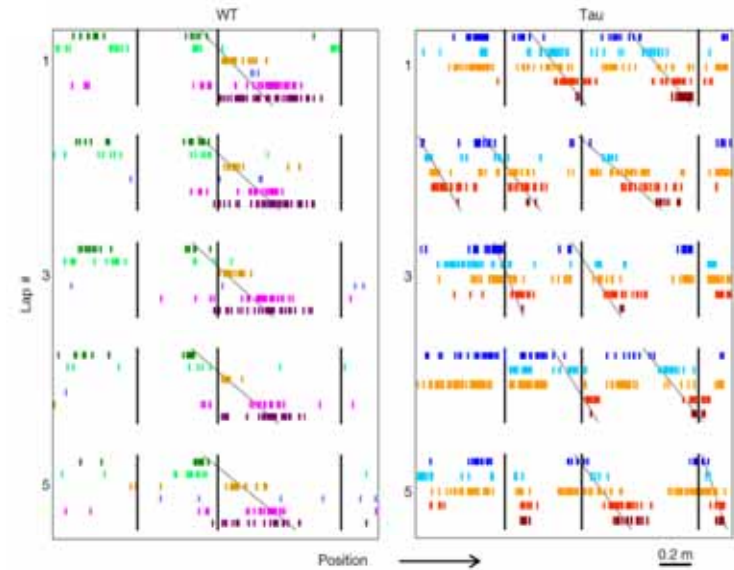
Lap-to-lap location shift



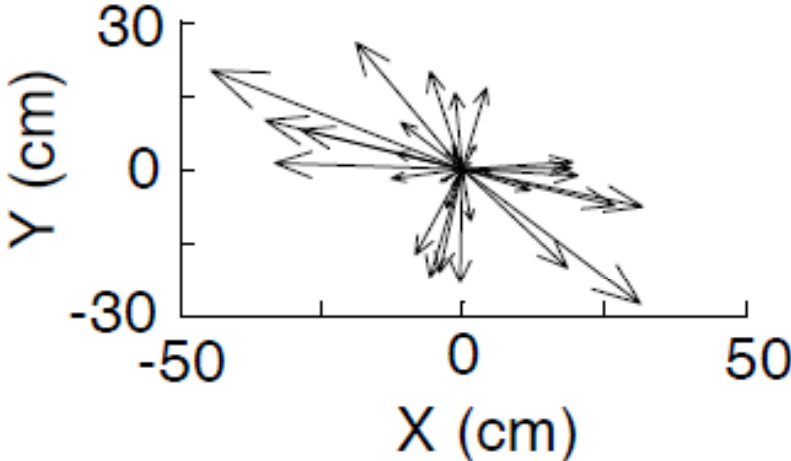
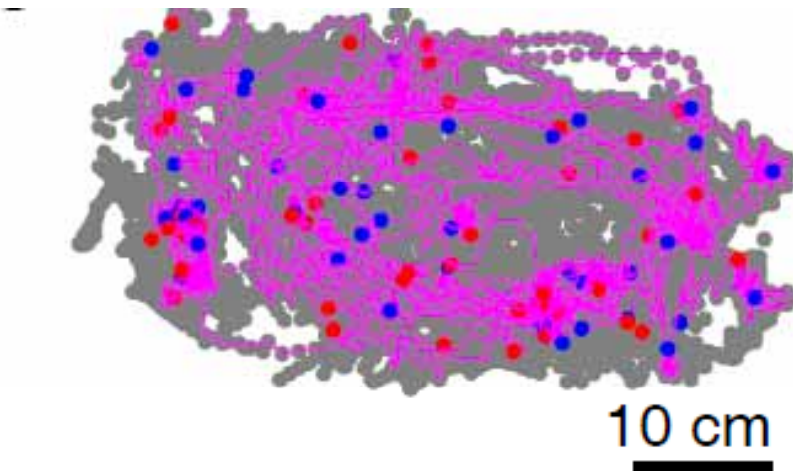
Common firing sequences on the track and in an open box.

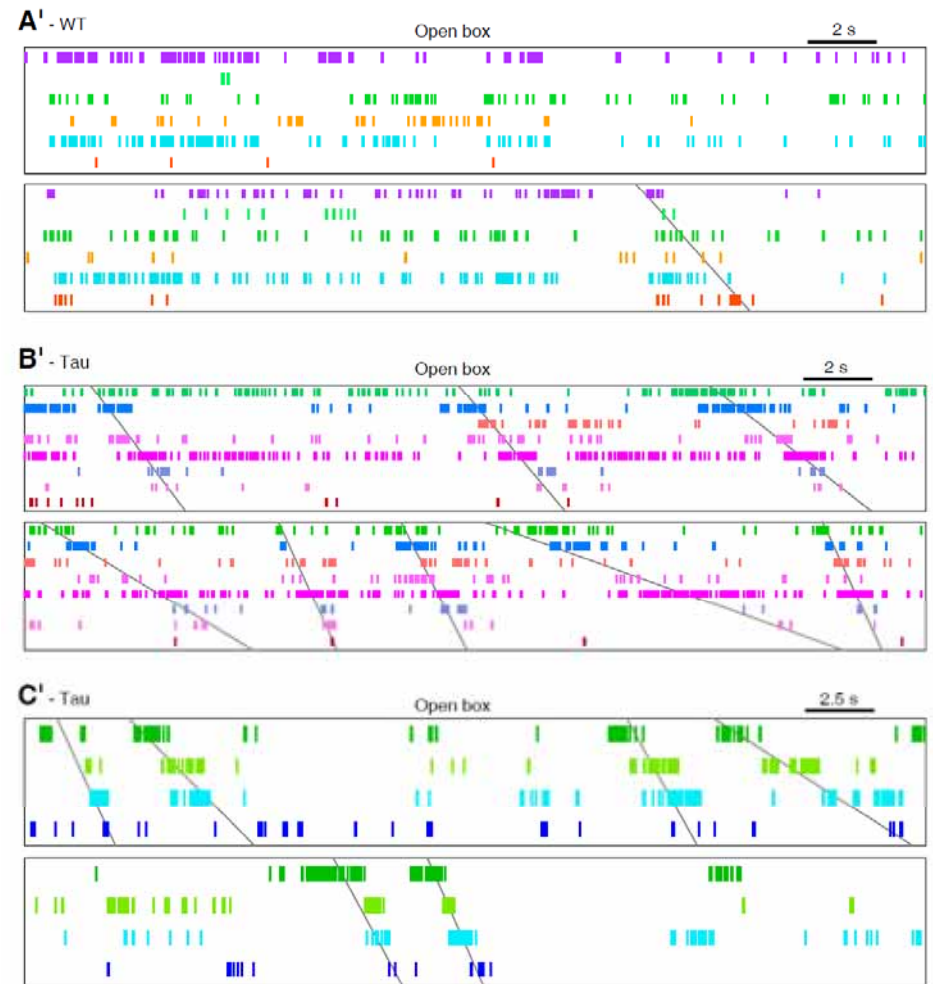
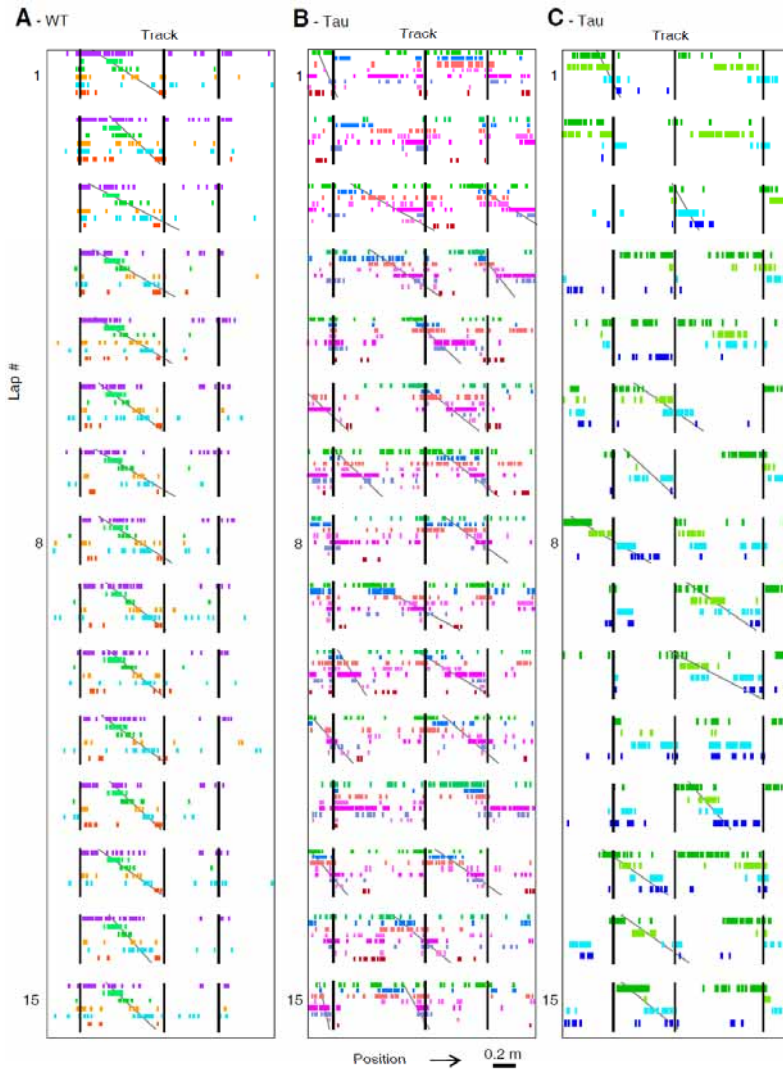
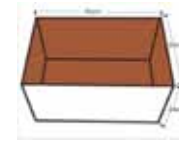


Open box:

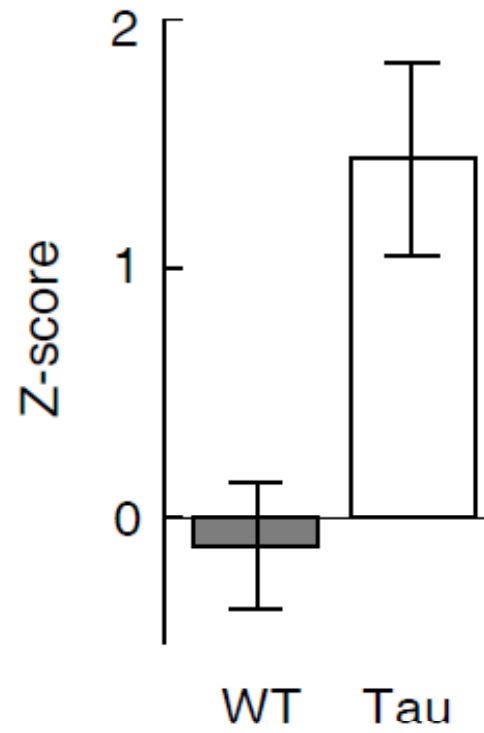


Random behavior during the expression of sequences in the open box

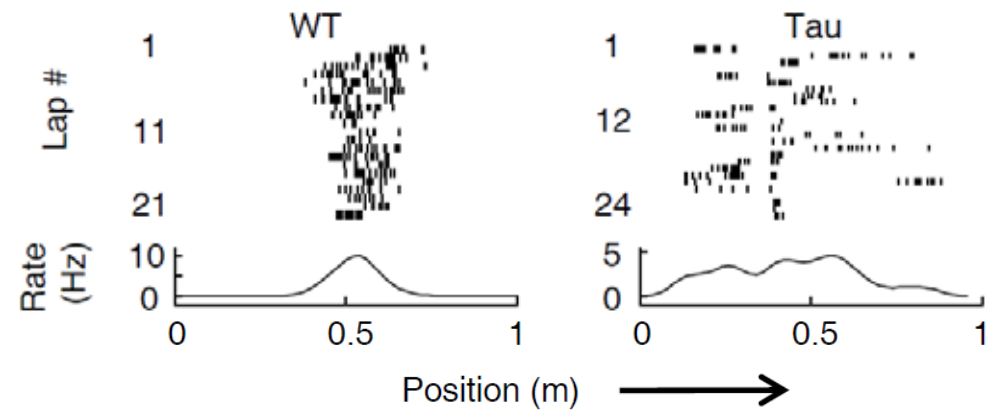
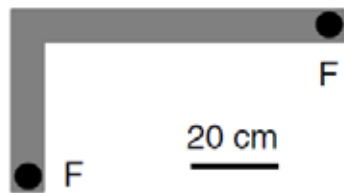




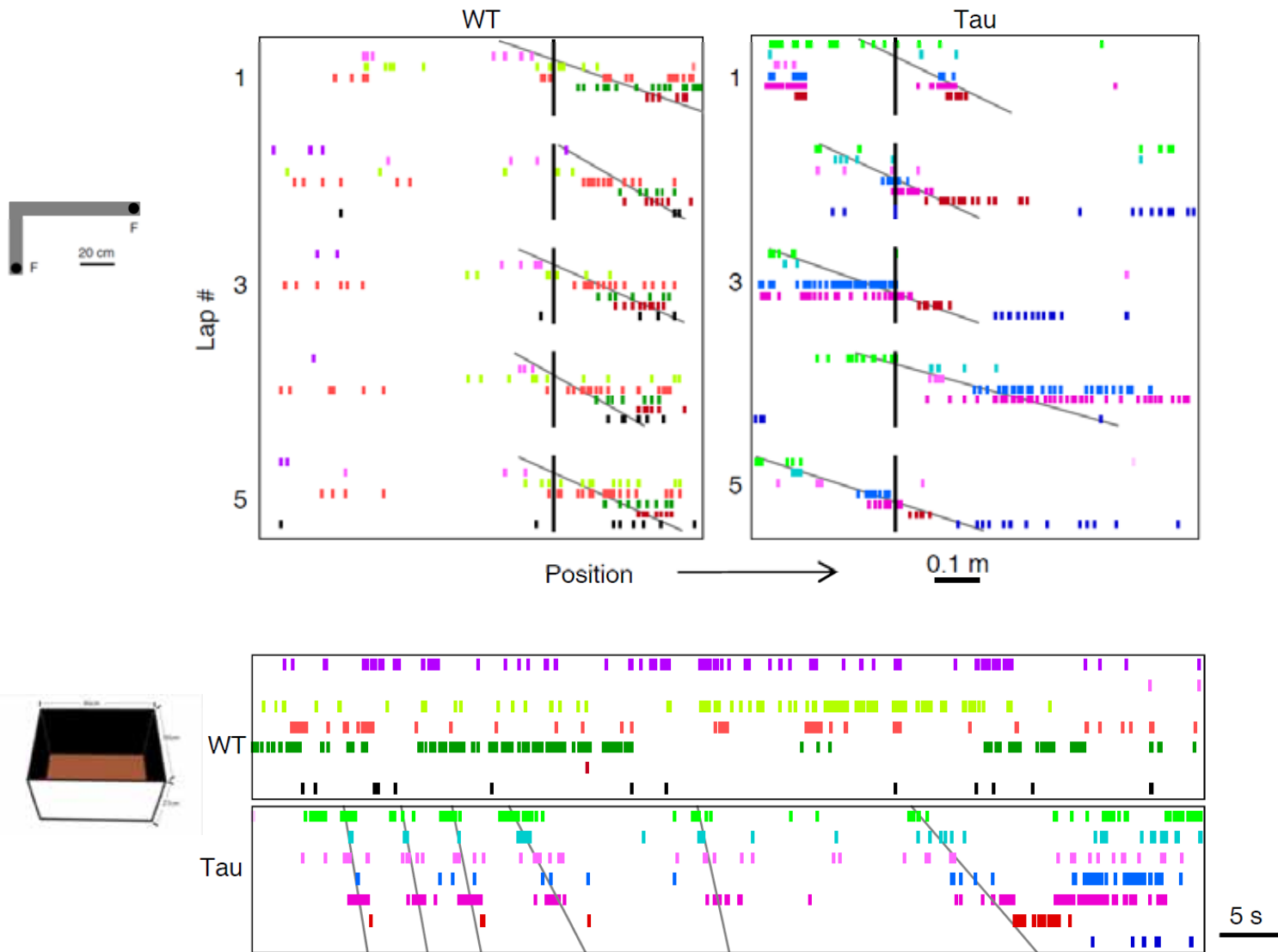
Number of sequences per (open box) session



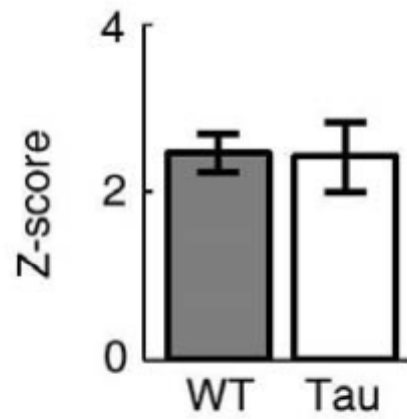
Unstable firing locations on a novel maze



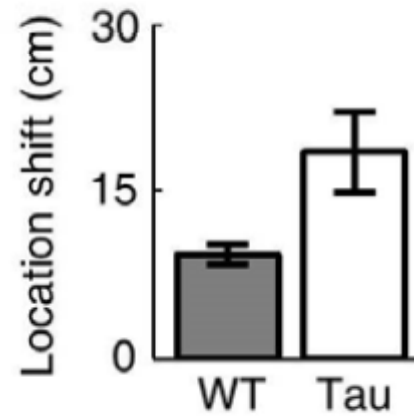
Common firing sequences on the novel maze and in a novel open box



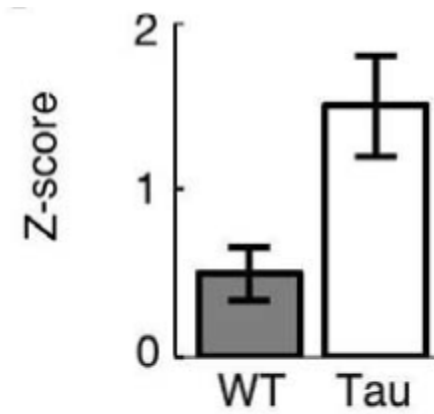
Number of sequences per track session



Lap-to-lap location shift



Number of sequences per open box session



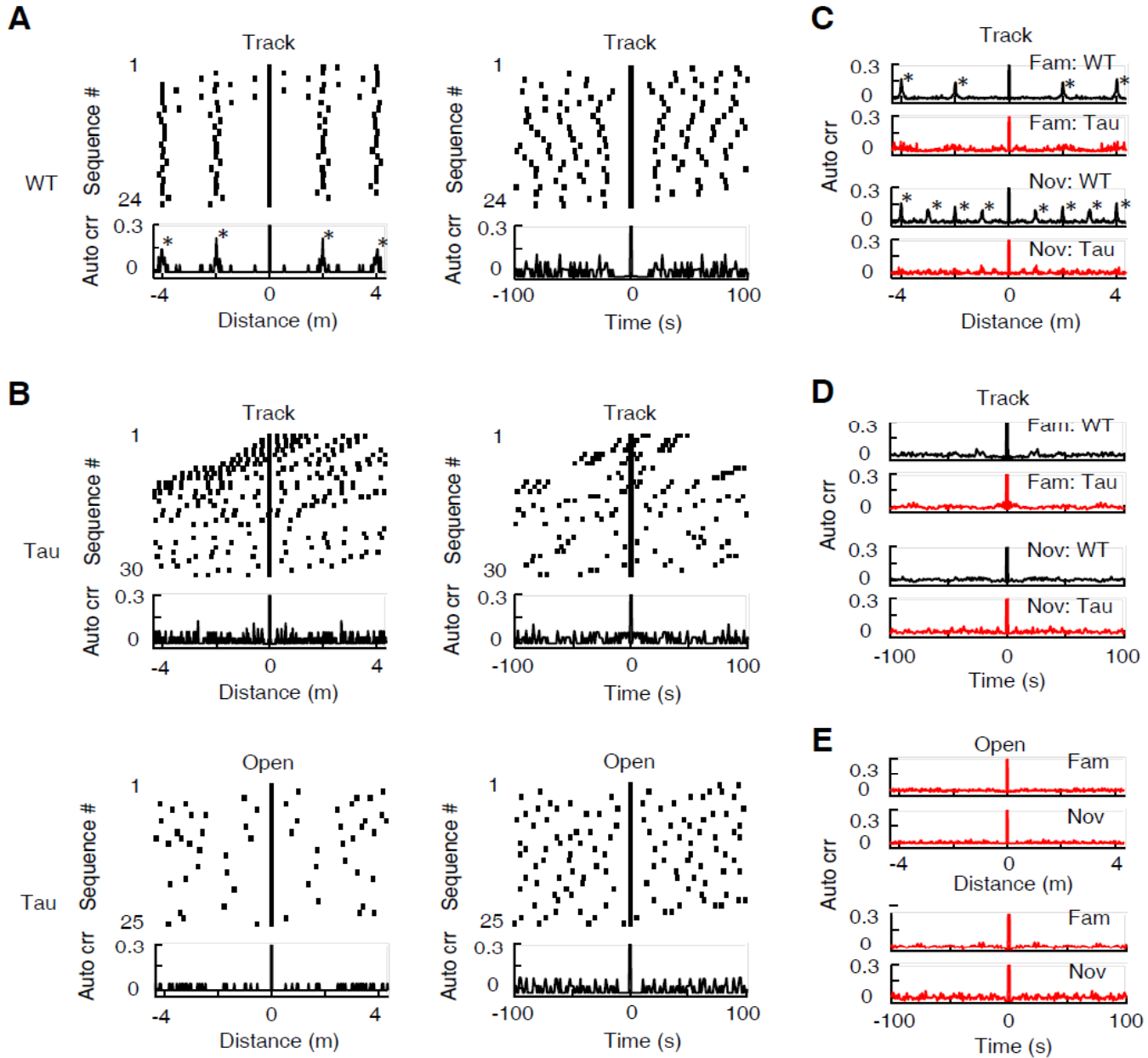
Summary: Tau mouse model

The data:

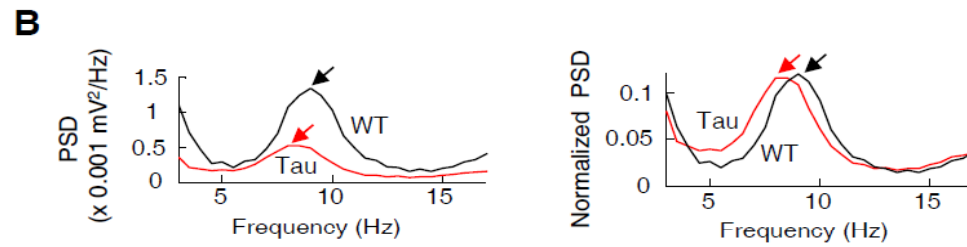
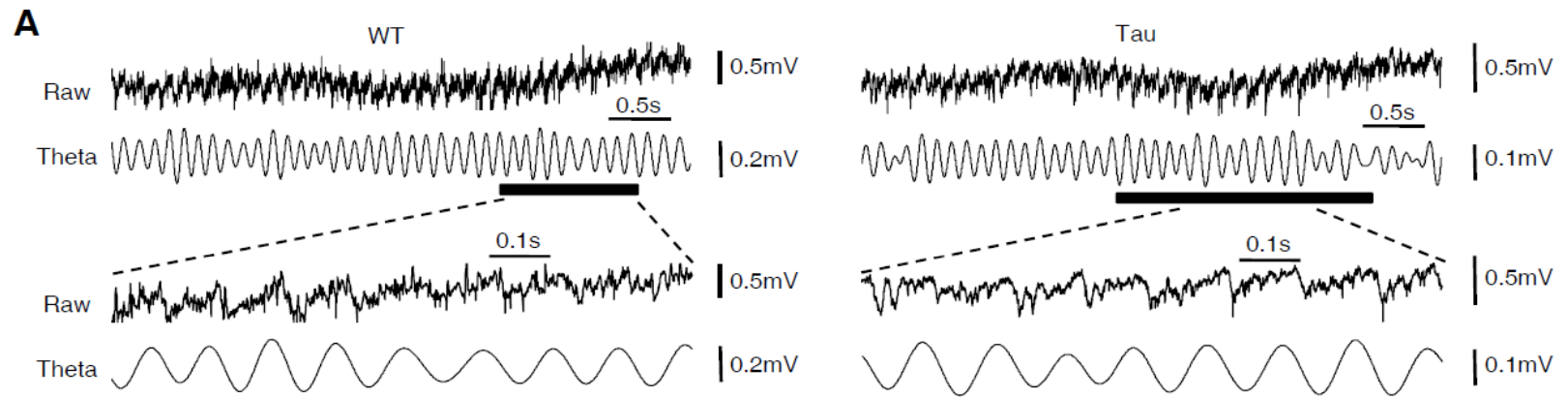
Stable firing sequences on familiar/novel linear tracks

- **Not anchored to specific places**
- **Fail to “remap” in open boxes**
- **Occur in the open box even prior to the novel track**

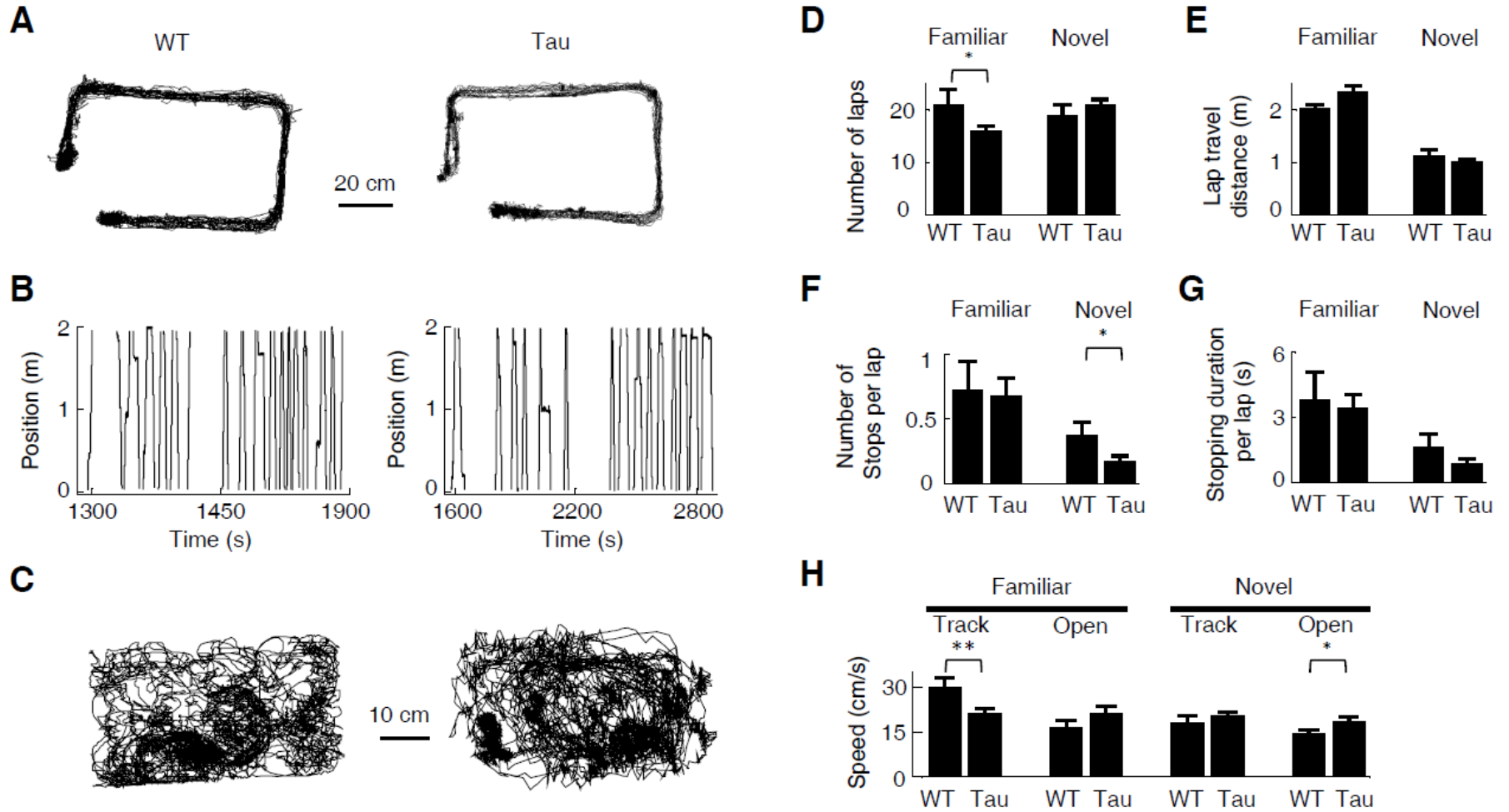
Sequences in Tau mice lack spatial or temporal periodicity



Normal theta oscillations in Tau mice



Behavioral parameters of WT and Tau mice



Summary: Tau mouse model

The data:

Stable firing sequences on familiar/novel linear tracks

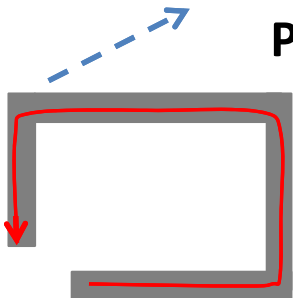
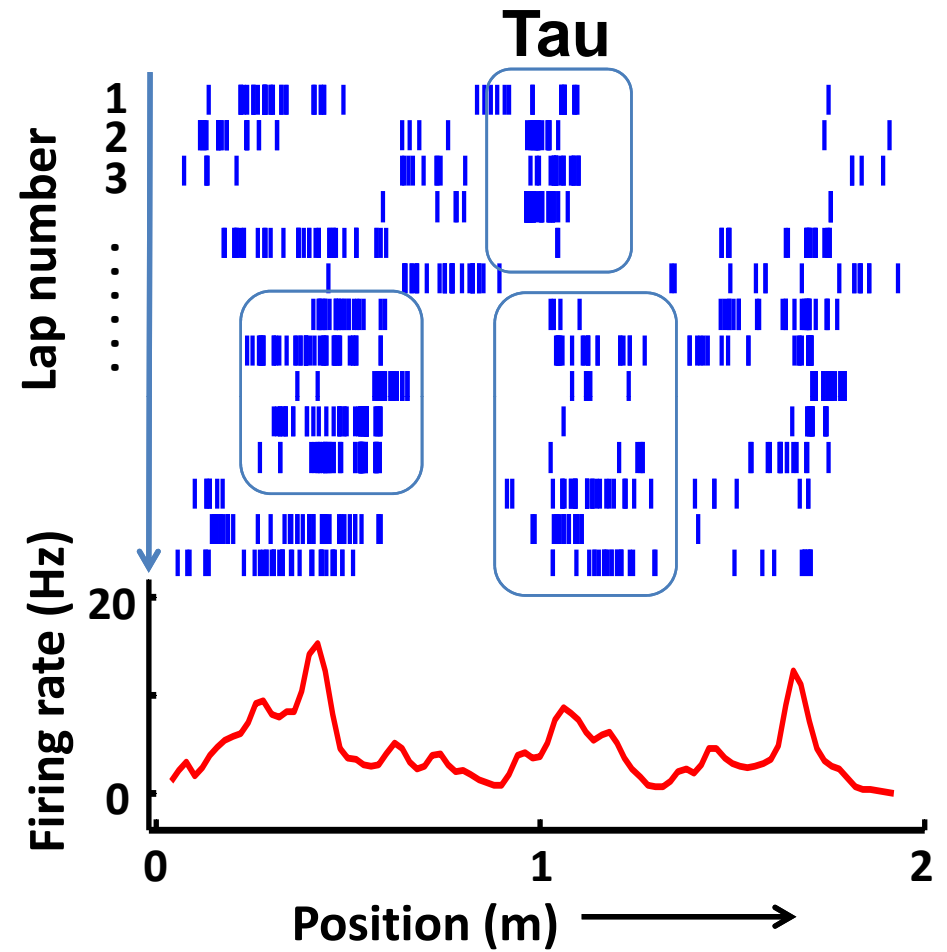
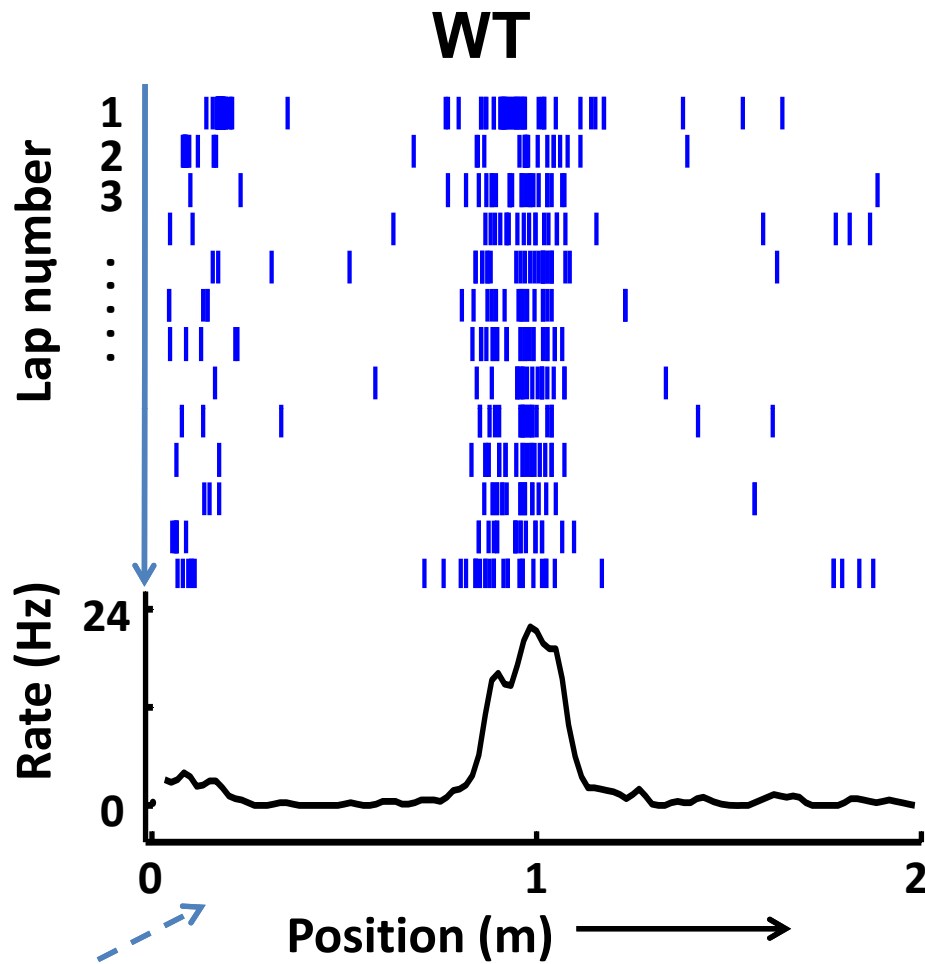
- Not anchored to specific places
- Fail to “remap” in open boxes
- Occur in the open box even prior to the novel track

- No periodicity
- With normal theta oscillations
- Not explained by simple behavioral parameters

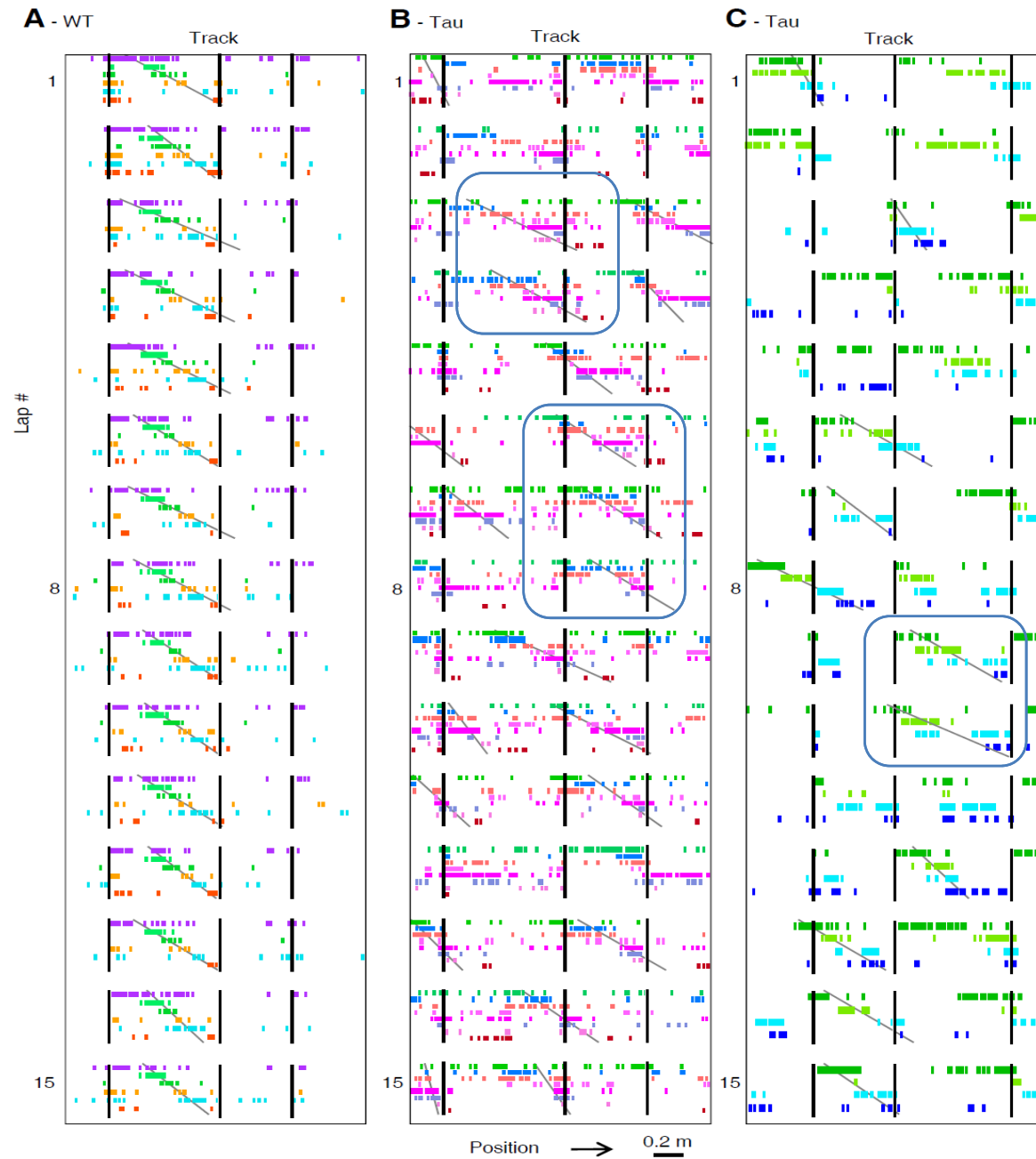
The interpretation: CA1 neurons

Mainly driven by internal input (as compared to external sensory input)

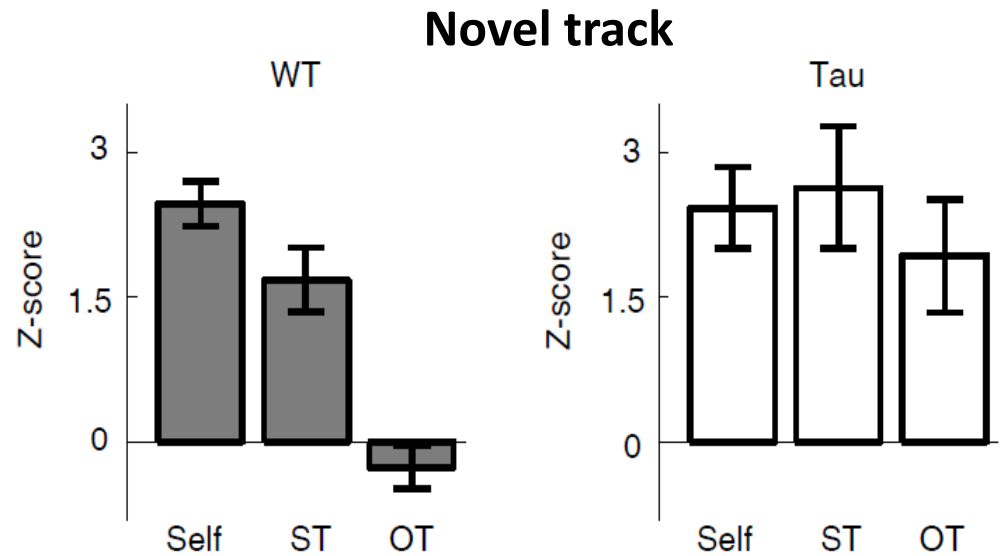
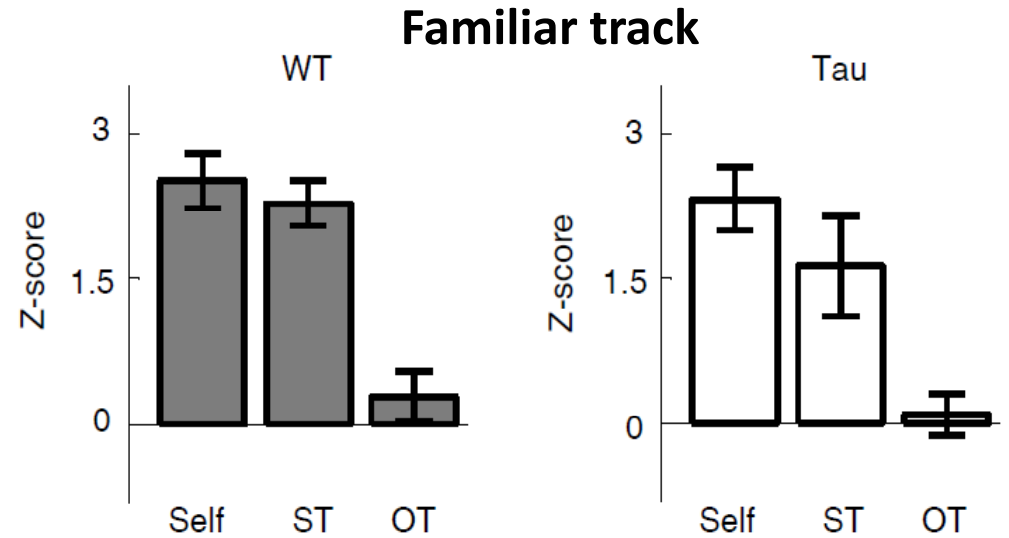
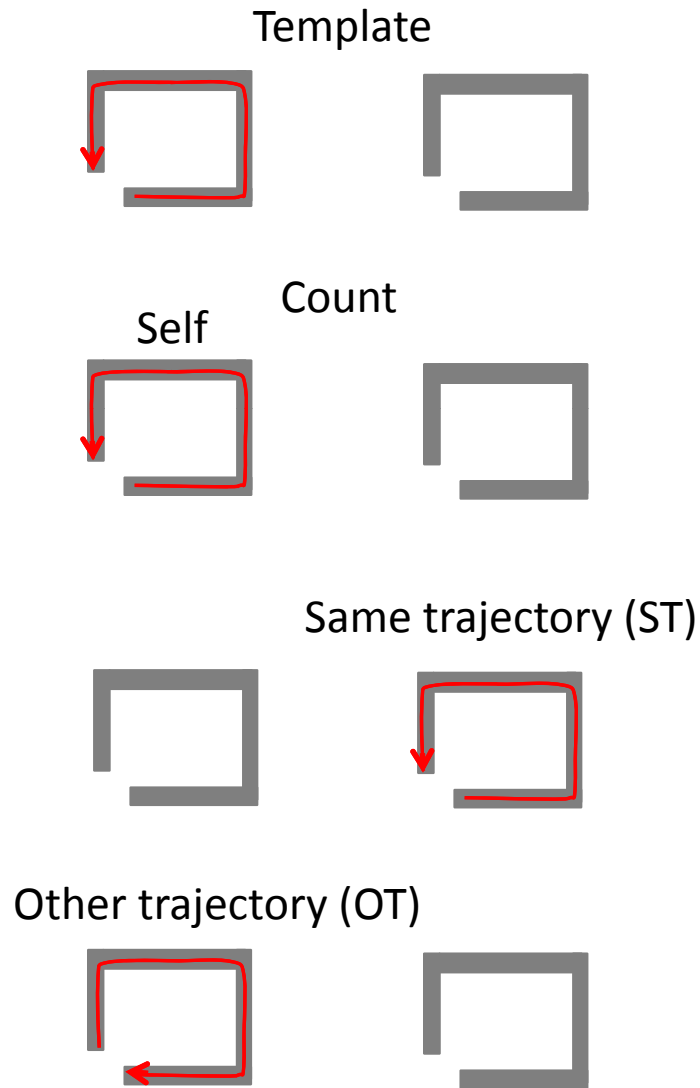
Not just internal: firing locations are not random



Not just internal: sequence locations are not random



Not just internal: firing sequences distinguish trajectories in an experience-dependent fashion



Summary: Tau mouse model

The interpretation: CA1 neurons

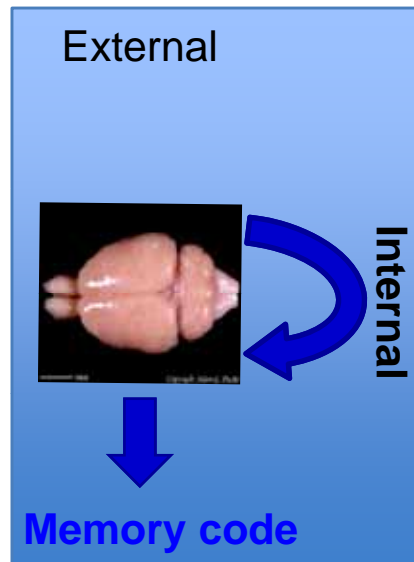
Mainly driven by internal input.

There is also an external component.

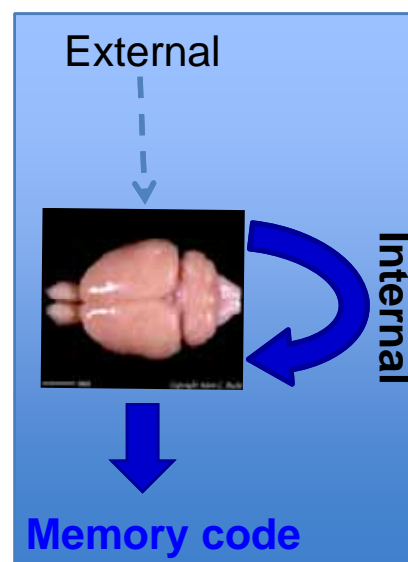
Memory formation



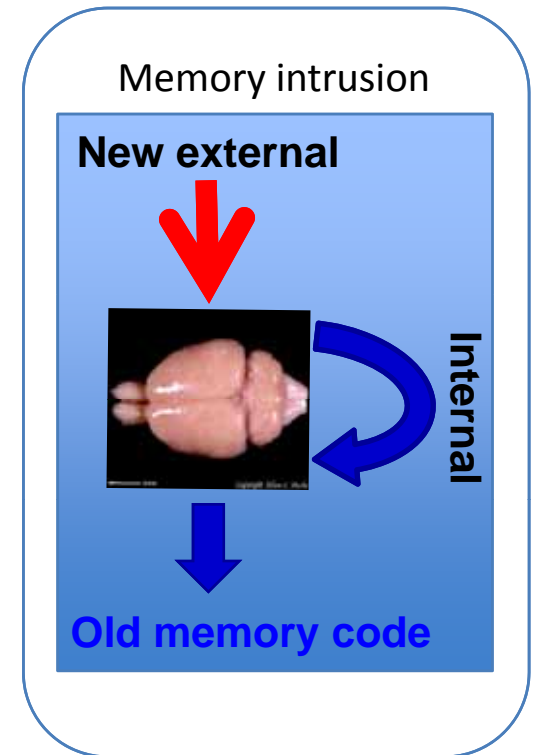
Memory consolidation



Memory retrieval



Memory intrusion



Summary: Tau mouse model

Instead of responding to external space and encoding new memories, CA1 neurons are dominated by old memories. This could contribute to

- **Inability to form new episodic memories, and**
- **Intrusion of old memories in AD patients.**

Current lab members



Daniel Haggerty



Karienn Montgomery



Devdeep Aikath



Xiang Mou



Jingheng Cheng



Chun-Ting Wu



Sarah Bourdon



Sara Kee

Collaborators



Joanna Jankowsky



Hui-Chen Lu



Hui Zheng

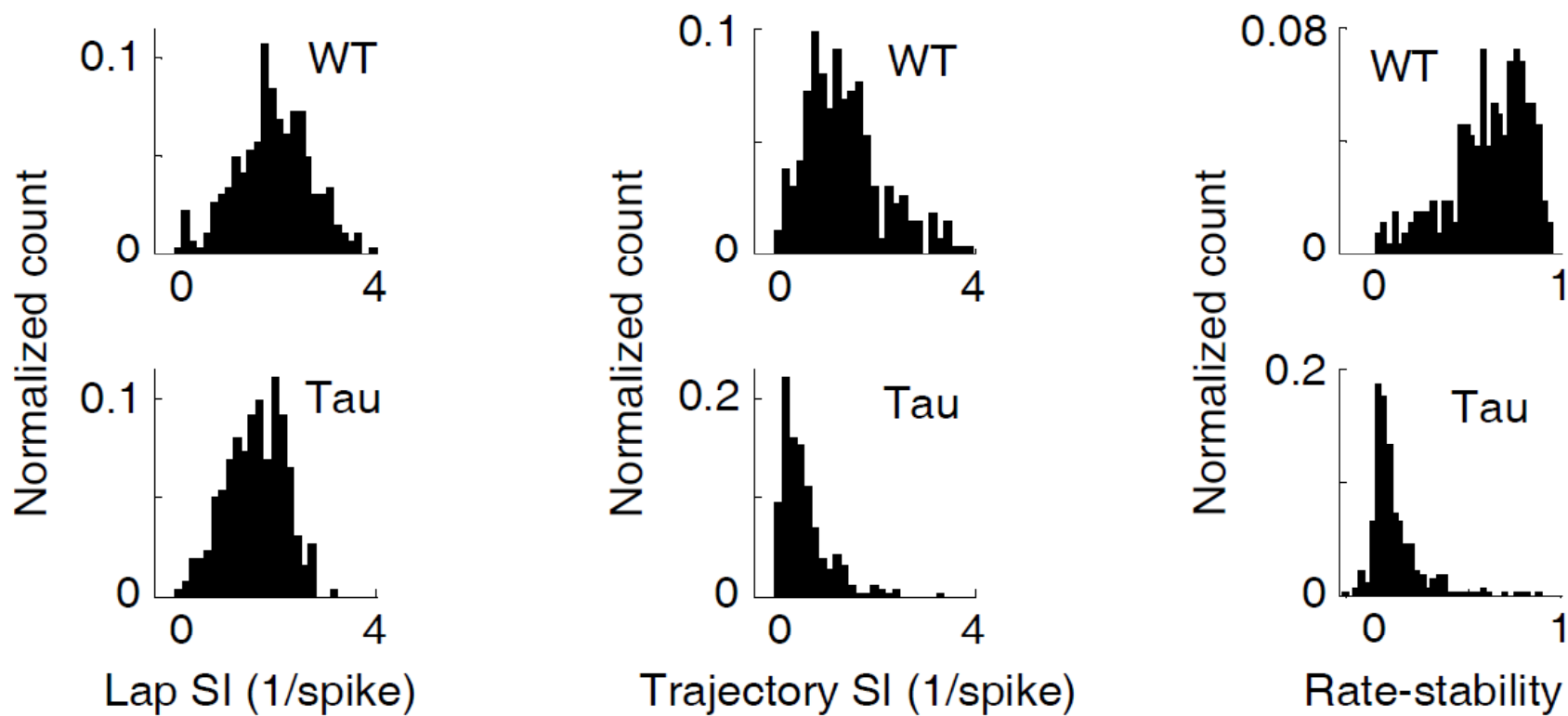


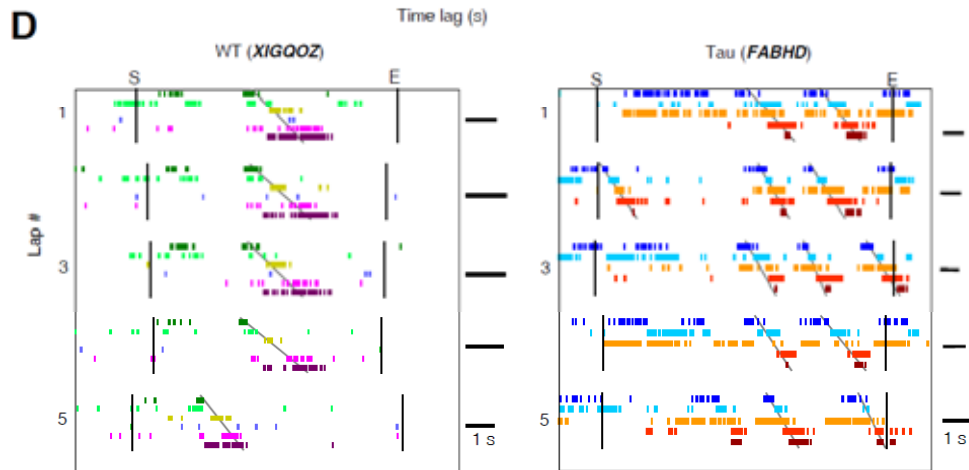
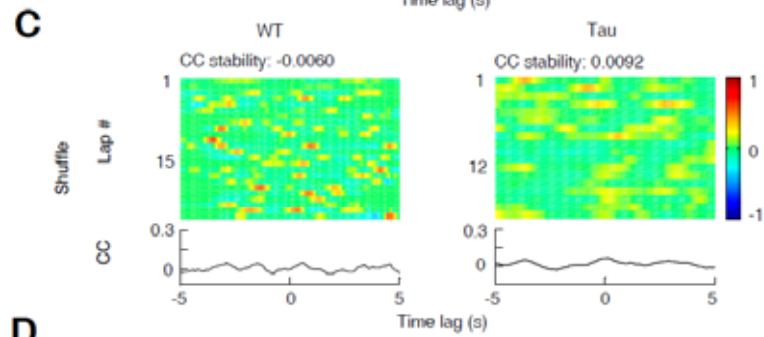
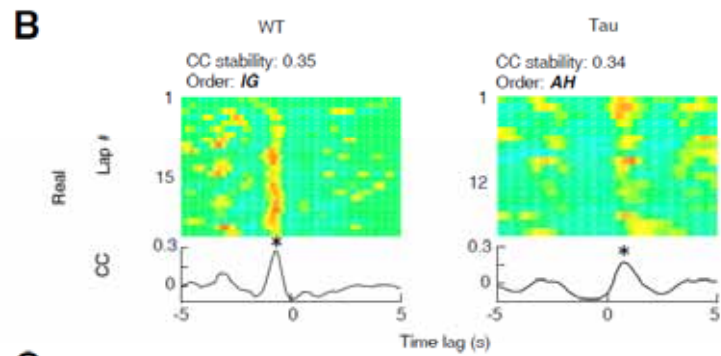
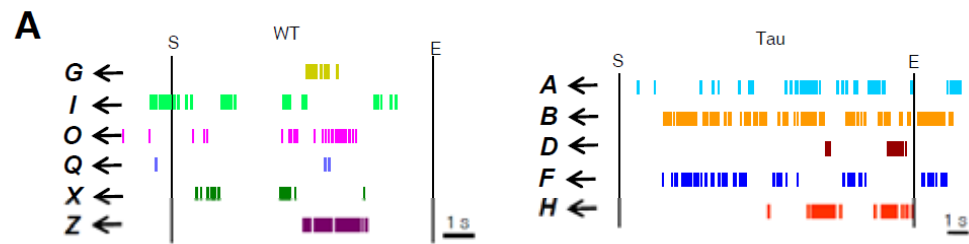
Huda Zoghbi

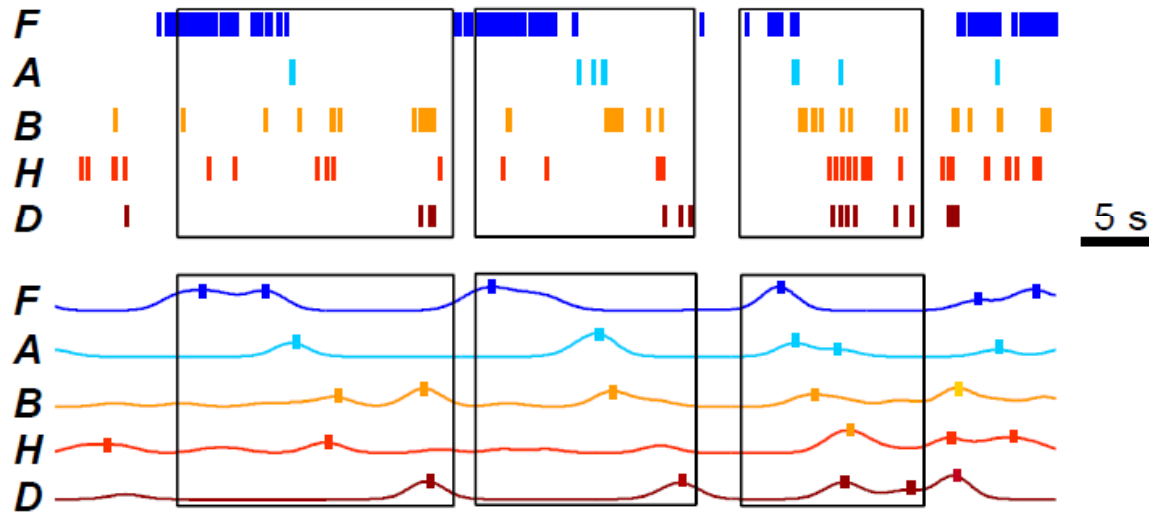
Funding sources:

**National Eye Institute
National Institute of Neurological Disorders and Stroke
Simons Foundation
Whitehall Foundation
W. M. Keck Foundation**

Unstable firing locations of hippocampal cells in Tau mice





ATemplate: *F A B H D***B****C**

Raw sequence:

H *F F A H B B D* *F A B D* *F A B A D H D* *H D B F A H F*

D

F F A H B B D

Template rank:

1.5 1.5 3 6 4.5 4.5 7

Time rank:

1 2 3 4 5 6 7

$R = 0.873$, $P = 0.0103$ (shuffle $P = 0.0095$)

