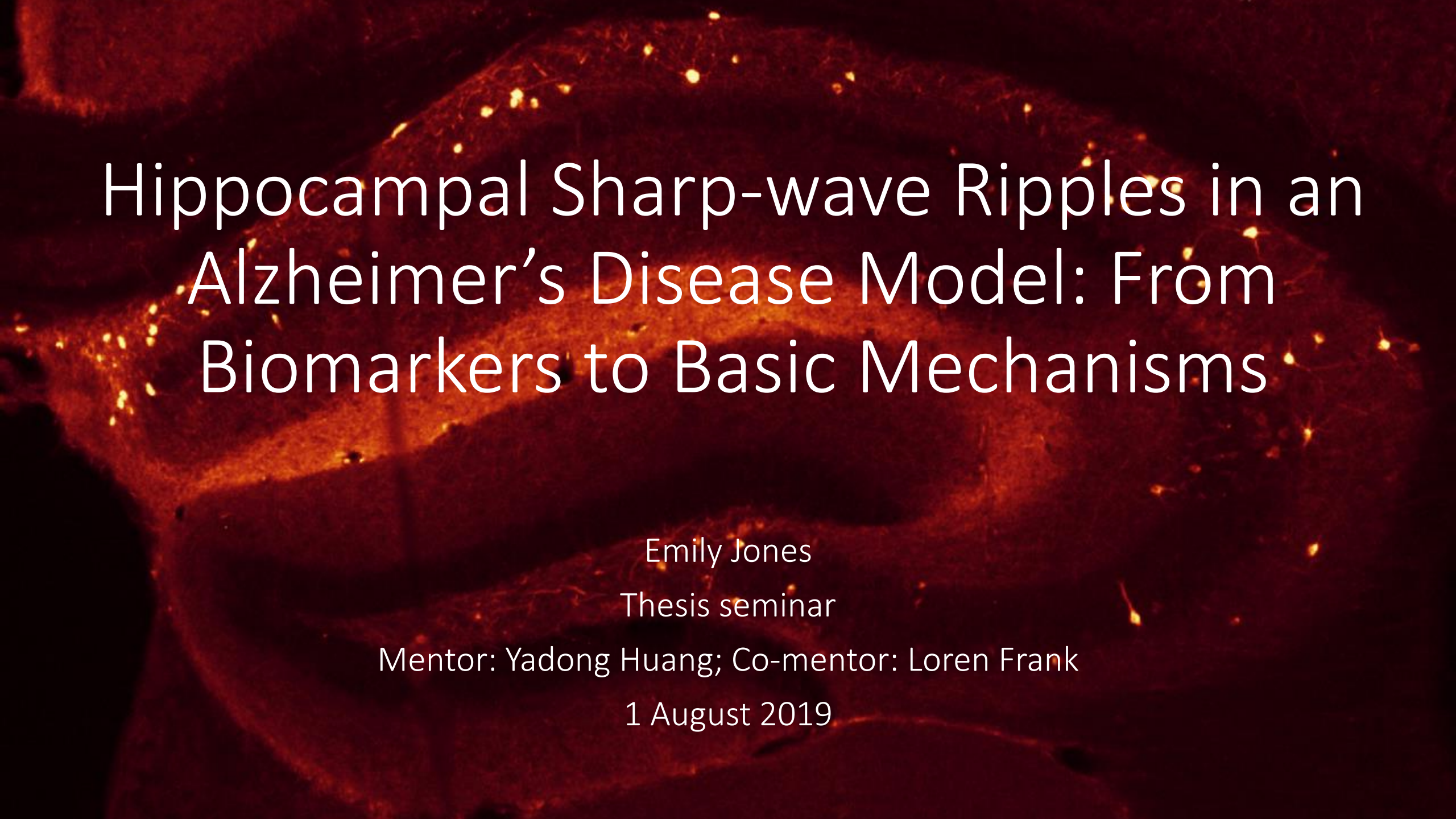


Hippocampal Sharp-wave Ripples in an Alzheimer's Disease Model: From Biomarkers to Basic Mechanisms

Emily Jones

Thesis seminar

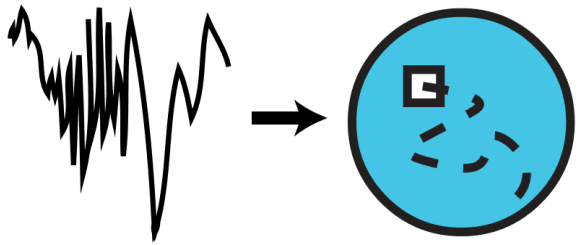
Mentor: Yadong Huang; Co-mentor: Loren Frank

1 August 2019

Motivation: Alzheimer's Disease (AD) Pathology

- 6th leading cause of death in the US
- Hundreds of clinical trials with no success since 2003
- Current biomarkers do not predict future disease

Part 1



Part 2

- GABAergic (inhibitory) interneurons reduce activity in the neurons they target, regulating firing patterns and how inputs are integrated
- GABAergic interneuron loss and dysfunction contributes to AD in ways we don't fully understand

Outline

Background

1. Alzheimer's disease and Apolipoprotein (apo) E4
2. Hippocampal sharp-wave ripples

Results

1. Early hippocampal sharp-wave ripple deficits predict later learning and memory impairments in an Alzheimer's disease mouse model
2. Hippocampal GABAergic interneurons bidirectionally modulate sharp-wave ripples

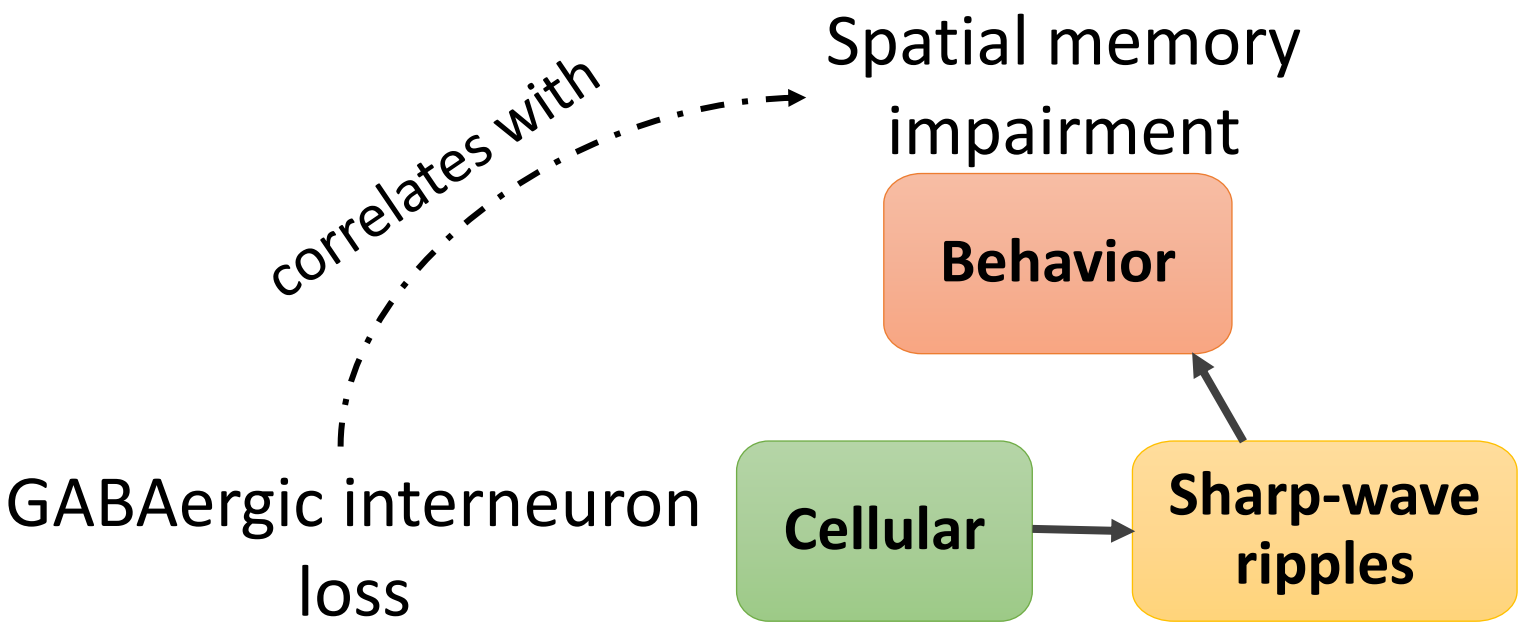
Apolipoprotein E4 (apoE4) Is the Major Genetic Risk Factor for AD

- 3 major alleles: E2 (reduces risk), E3 (neutral), and E4 (risk)
- ApoE4 is carried by 20-25% of the population and 65-80% of AD patients

Allele	Nucleotide
apoE3/E3	T
apoE4/E4	C

(Farrer et al, 1997)

Aged Female ApoE4-KI Mice Replicate Key AD Phenotypes



(Andrews-Zwilling et al, 2010)

Methods: Recording from the Hippocampus of Mice at Rest

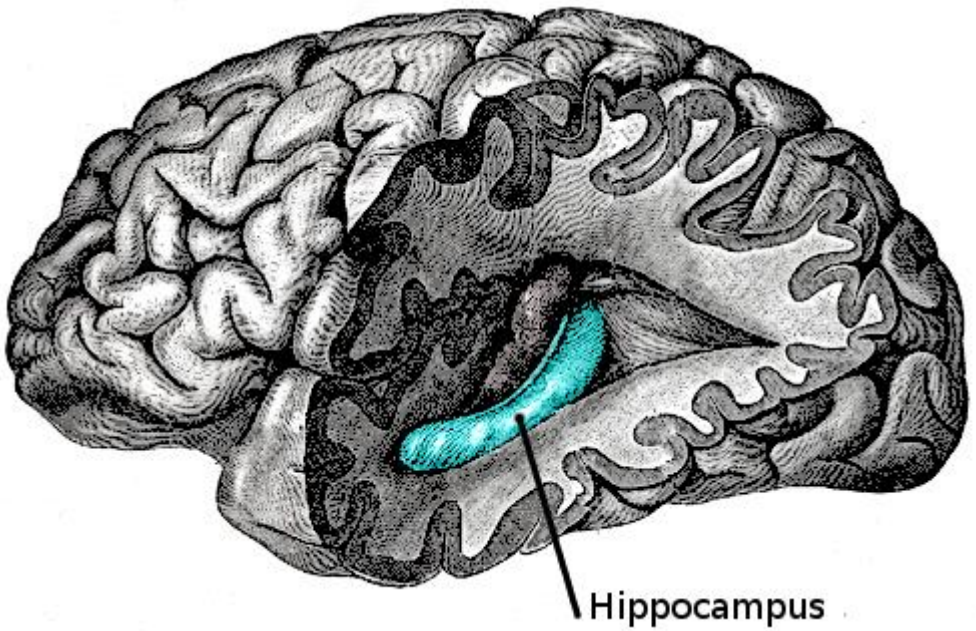
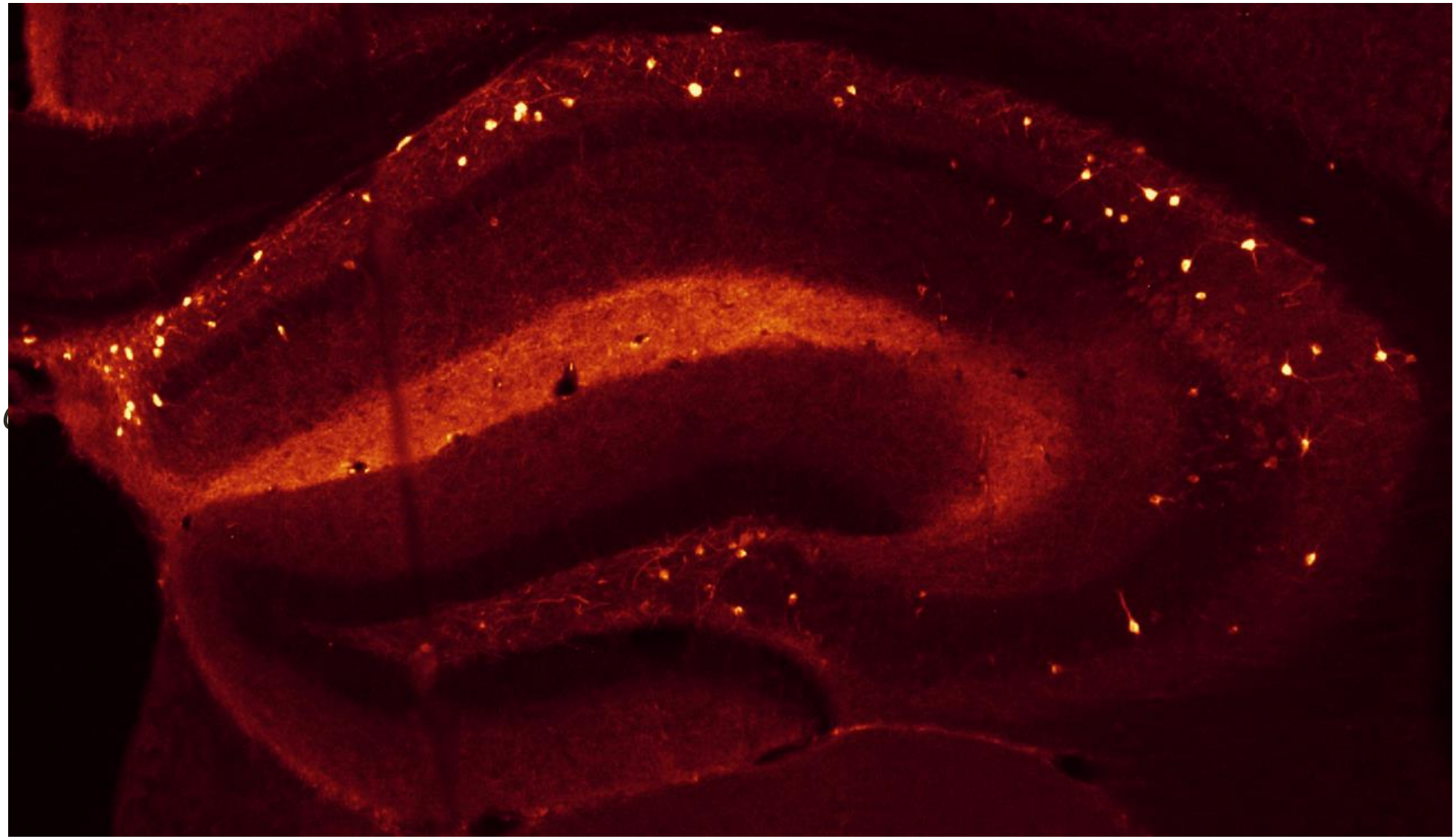


Image credit: Wikipedia

The Hippocampal Circuit

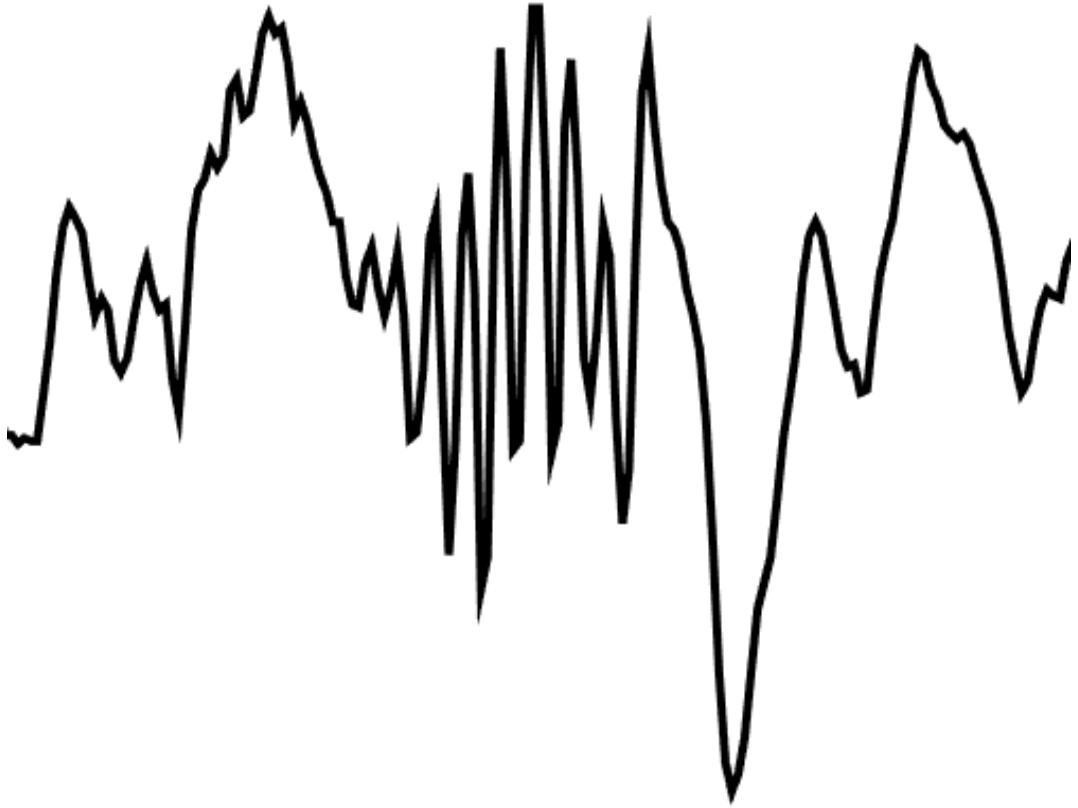
Entorhinal



Adapted from Gillespie et al, 2016

Local Field Potentials

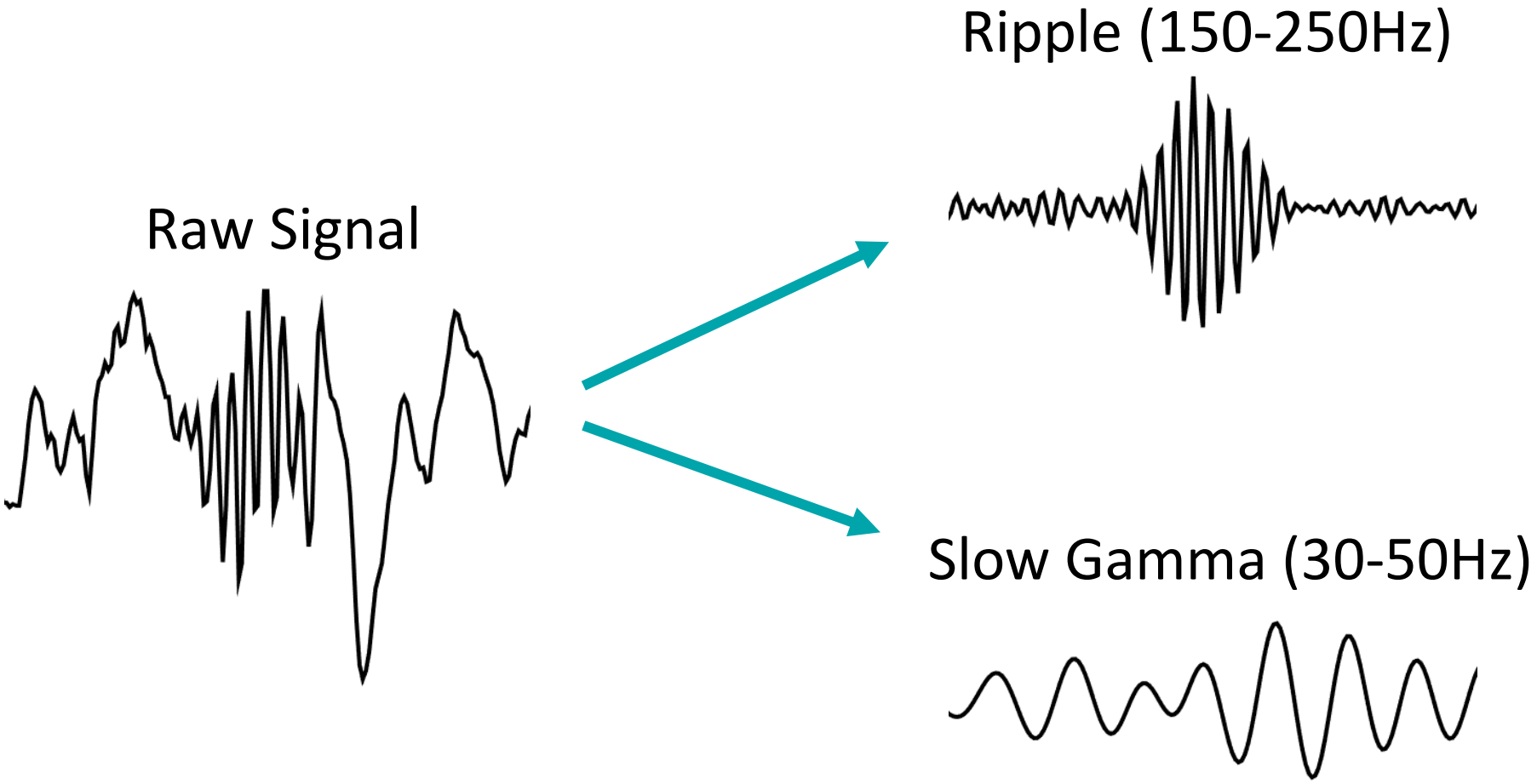
- Voltage measured by electrodes inside the brain
- Reflect local activity of neurons near the electrode



Measurements:

- Event rate
- Power
- Frequency
- Length (cycles)

Local Field Potentials Can Be Filtered into Frequency Components



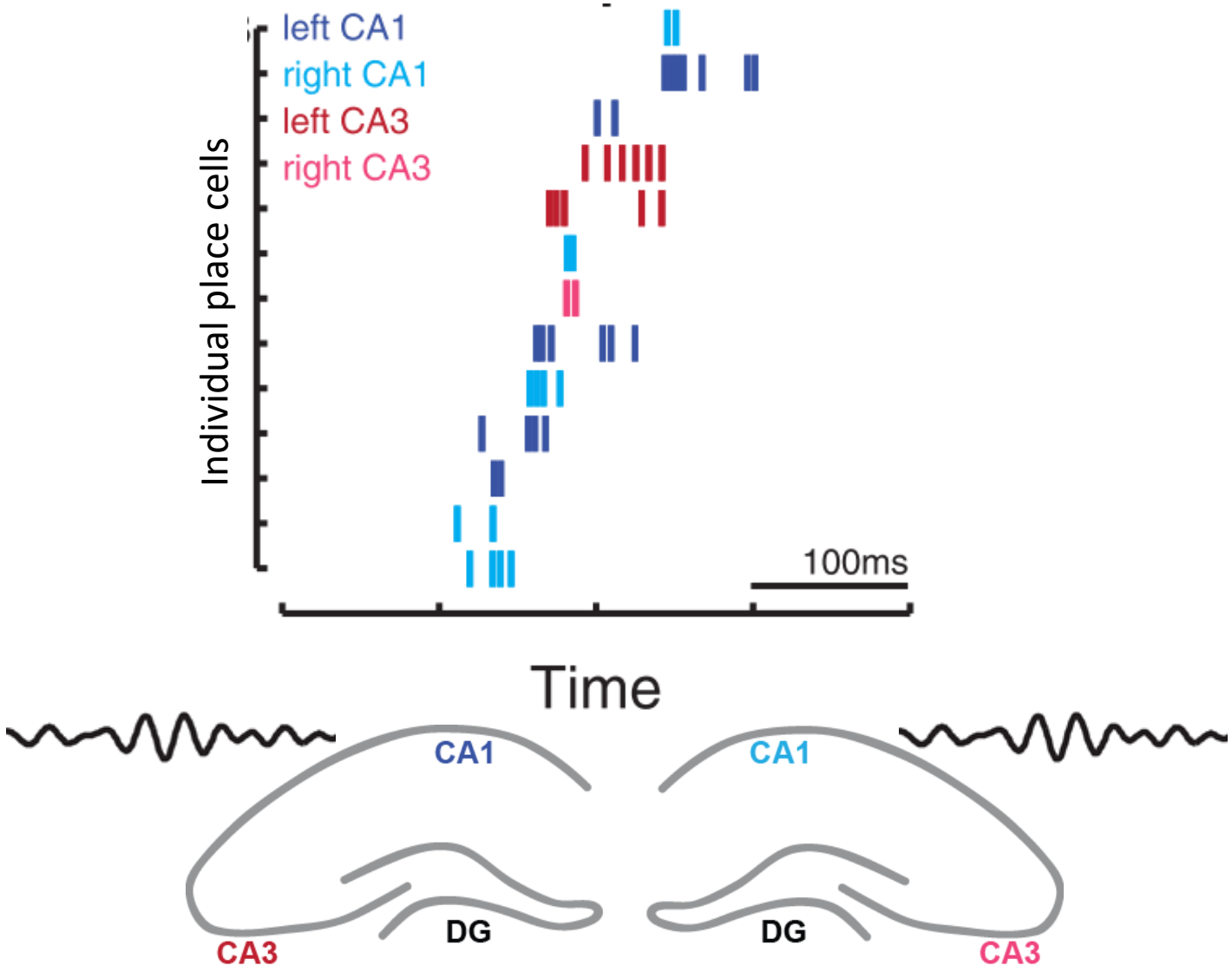
Sharp-Wave Ripples (SWRs, 150-250Hz) Are a Hippocampal Signature of Memory Replay

Place cell

1
2
3
4
5
6
7
8
9
10

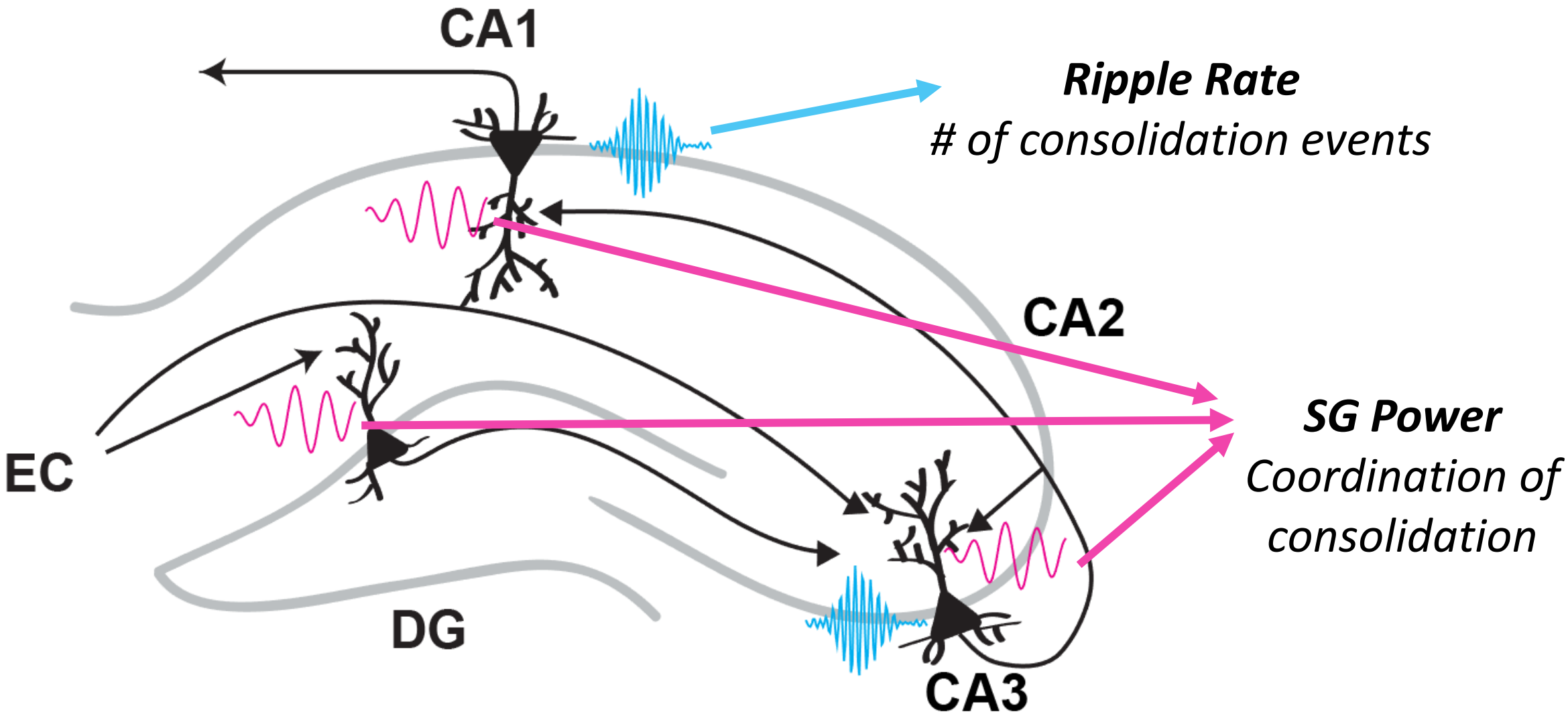
Video credit:
Shantanu Jadhav

Slow Gamma (SG, 30-50Hz) Is a Hippocampal Signature of Memory Replay Coordination



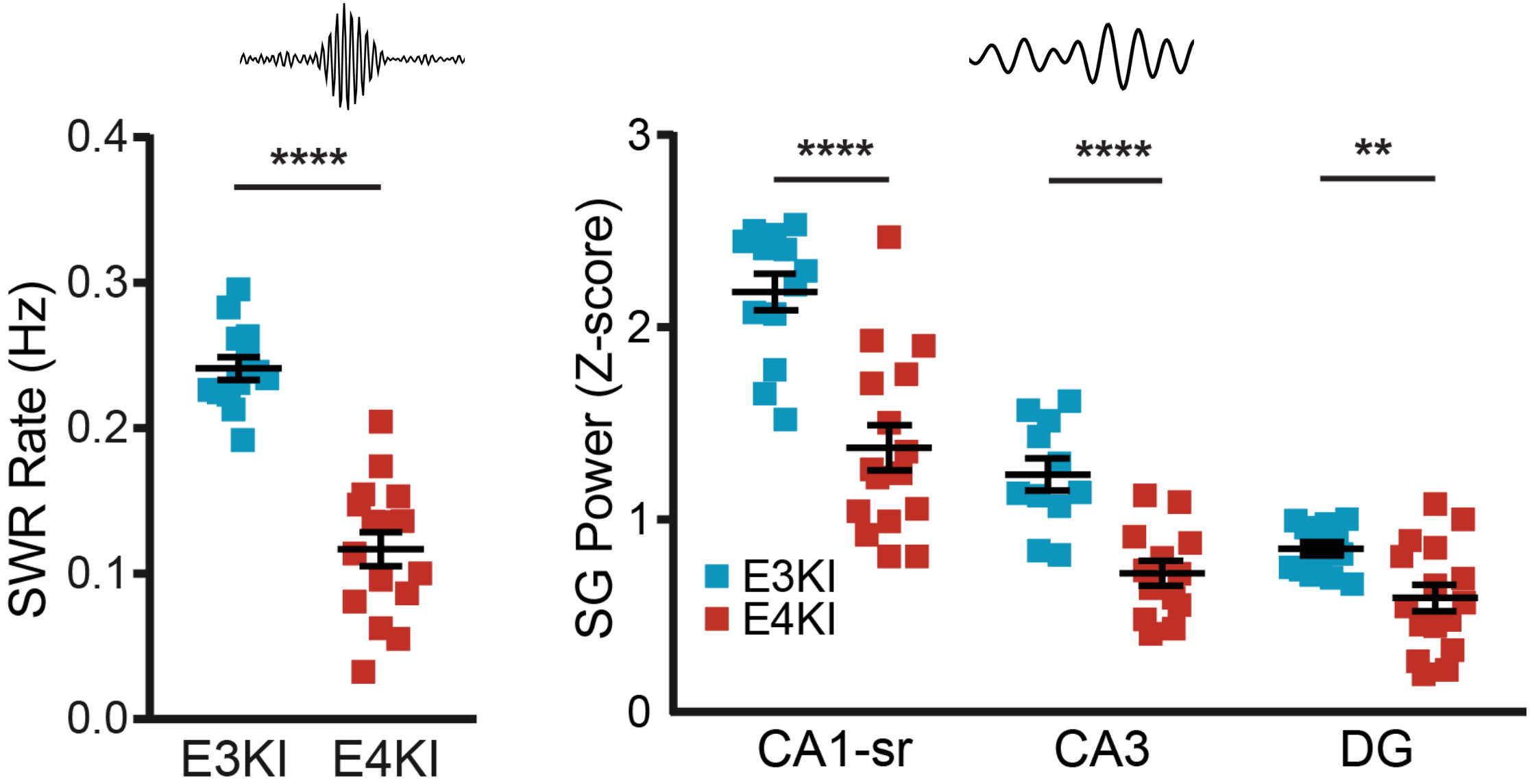
(Carr et al, 2012)

SWRs and Associated SG in the Hippocampal Circuit



Adapted from Gillespie et al, 2016

ApoE4 Impairs SWR Rate and Associated SG Power



Replication of Gillespie et al, 2016

Outline

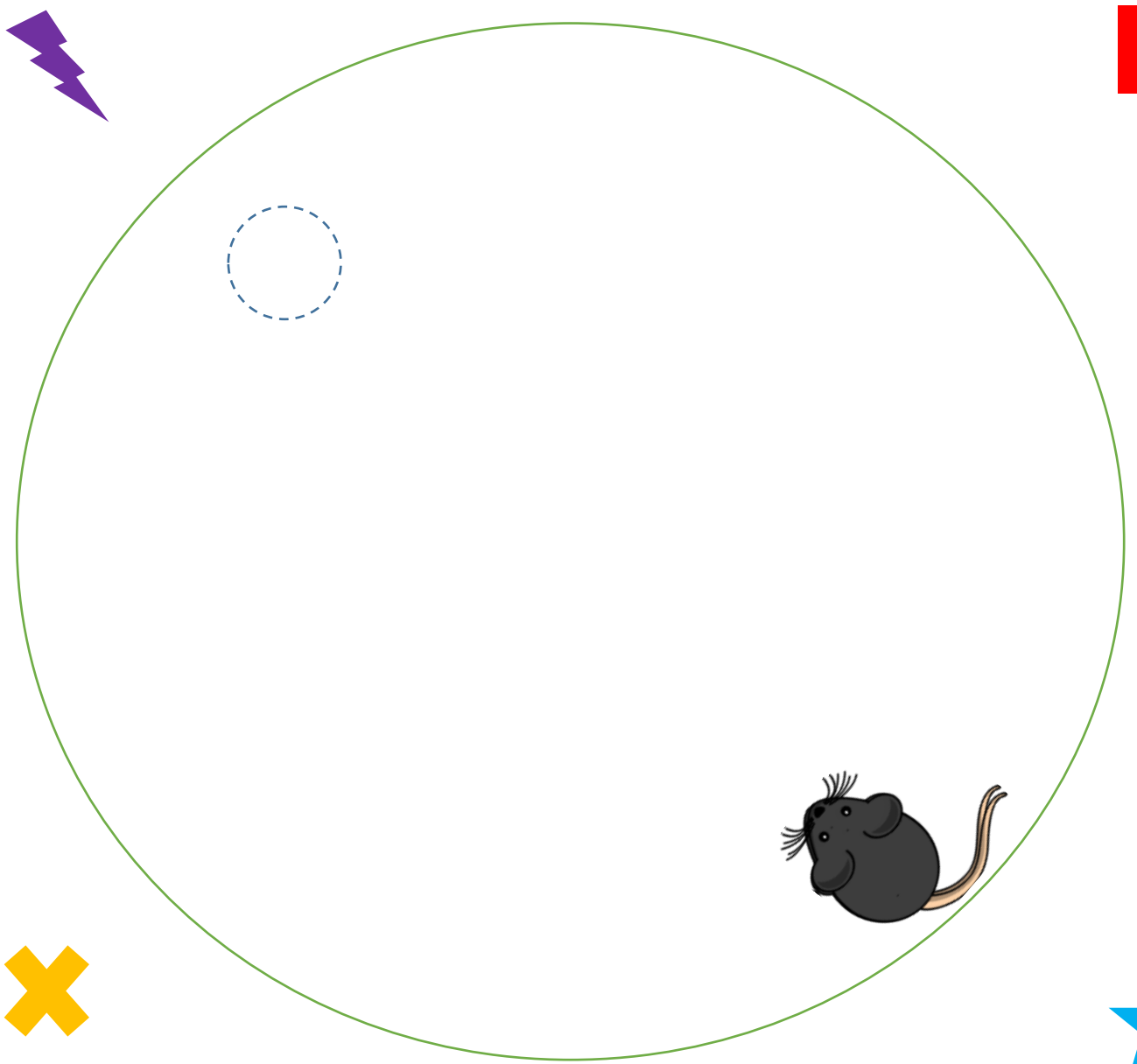
Background

1. Alzheimer's disease and Apolipoprotein (apo) E4
2. Hippocampal sharp-wave ripples

Results

1. Early hippocampal sharp-wave ripple deficits predict later learning and memory impairments in an Alzheimer's disease mouse model
2. Hippocampal GABAergic interneurons bidirectionally modulate sharp-wave ripples

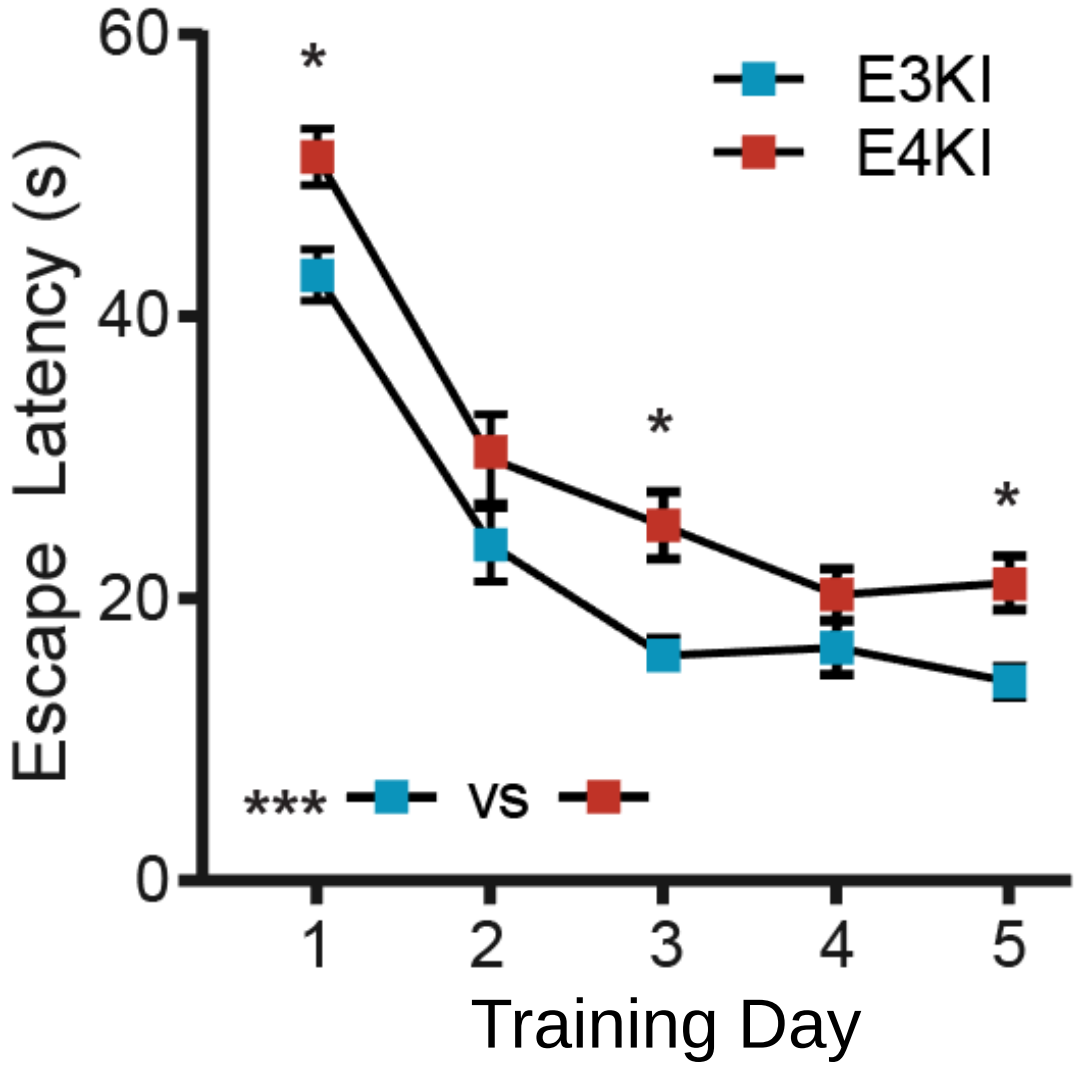
Water Maze

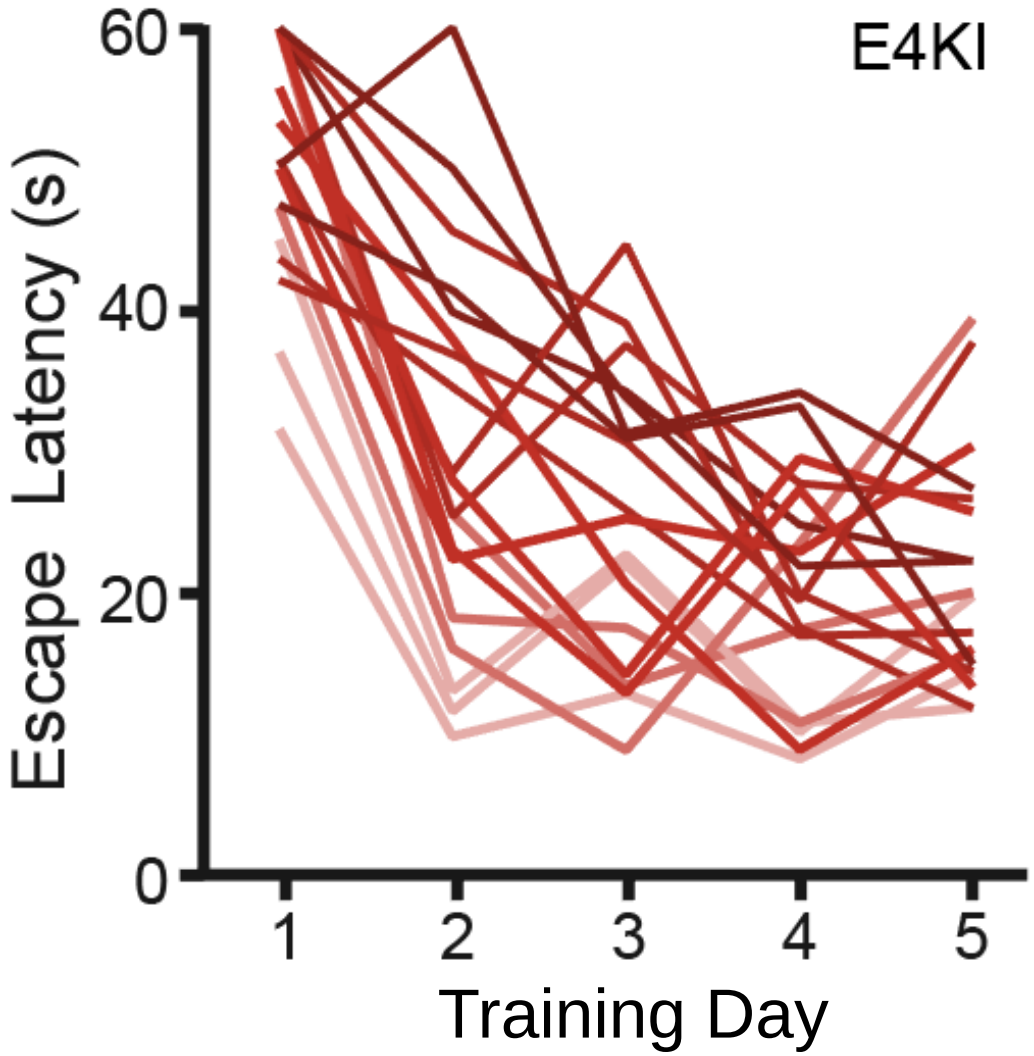


Probe trial

4 trials, 1/3/5 days for 5 days

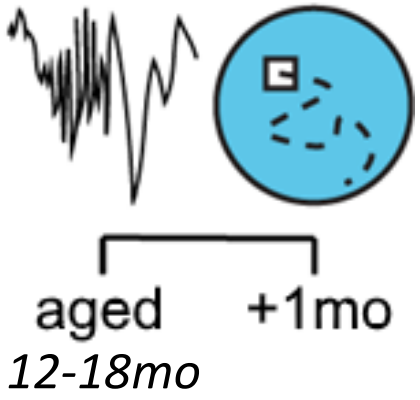
Aged ApoE4-KI Mice Show Water Maze Impairments and Variability



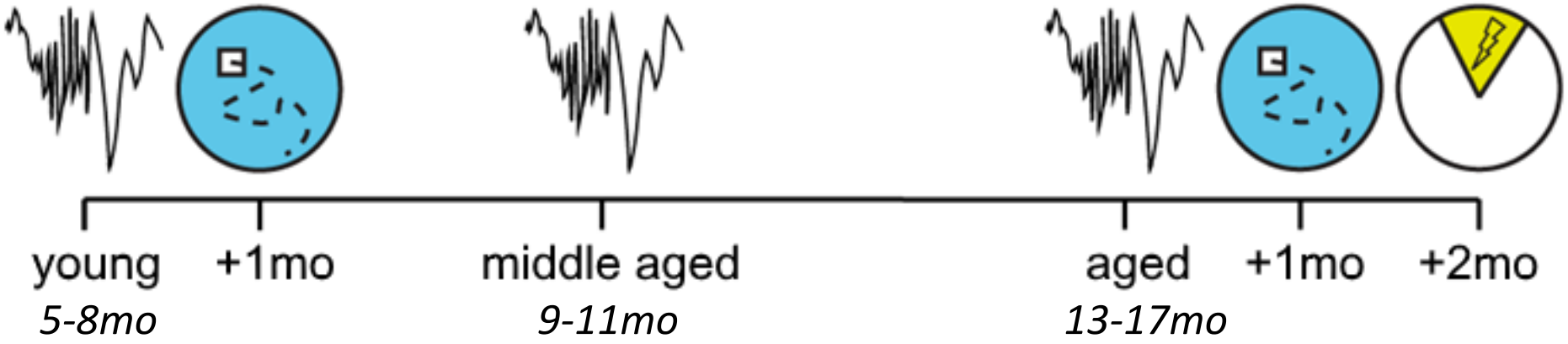


Experimental Design: Testing if SWR Properties Can Predict Memory Impairments

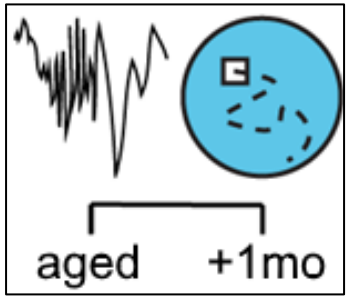
Screen Cohort



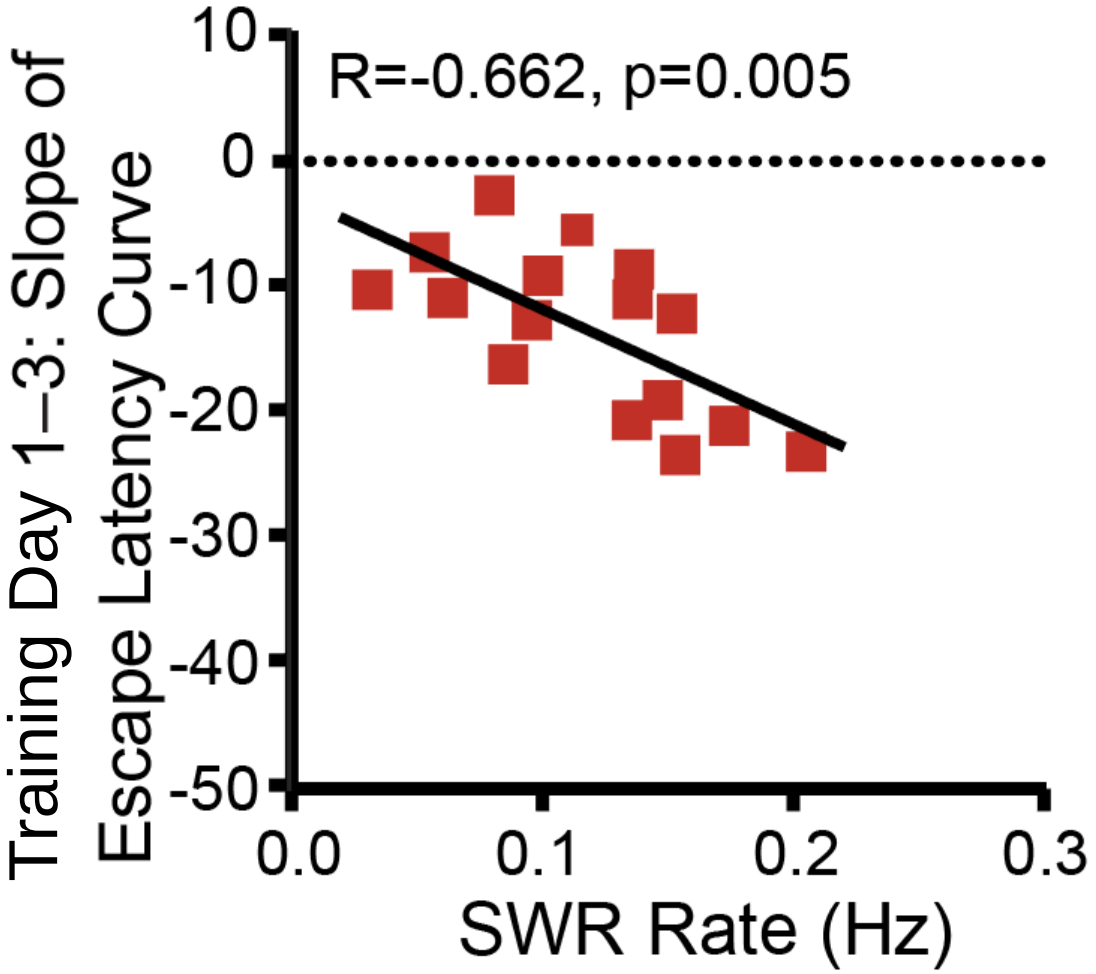
Replication, Validation, & Prediction Cohort



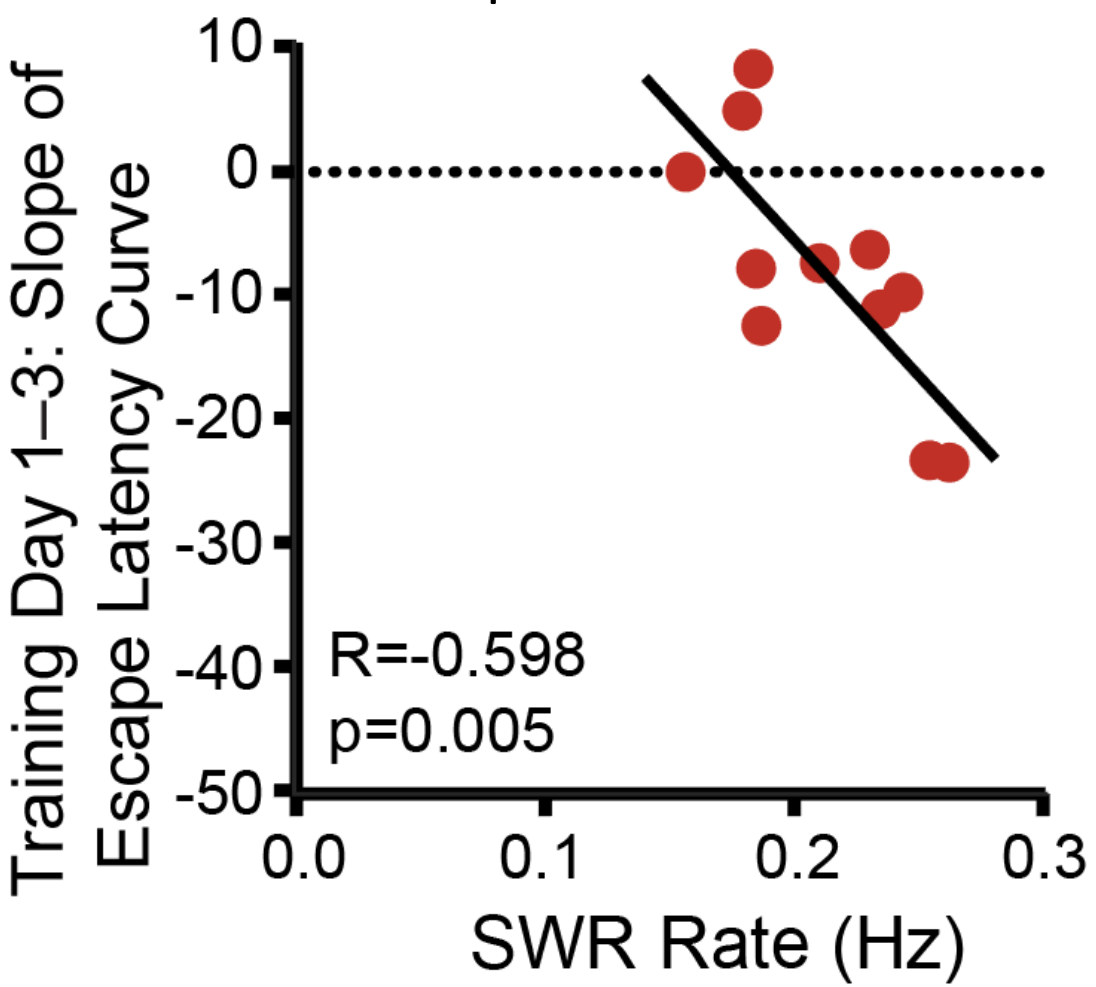
SWR Rate Deficits Predict Water Maze Learning Speed Impairment



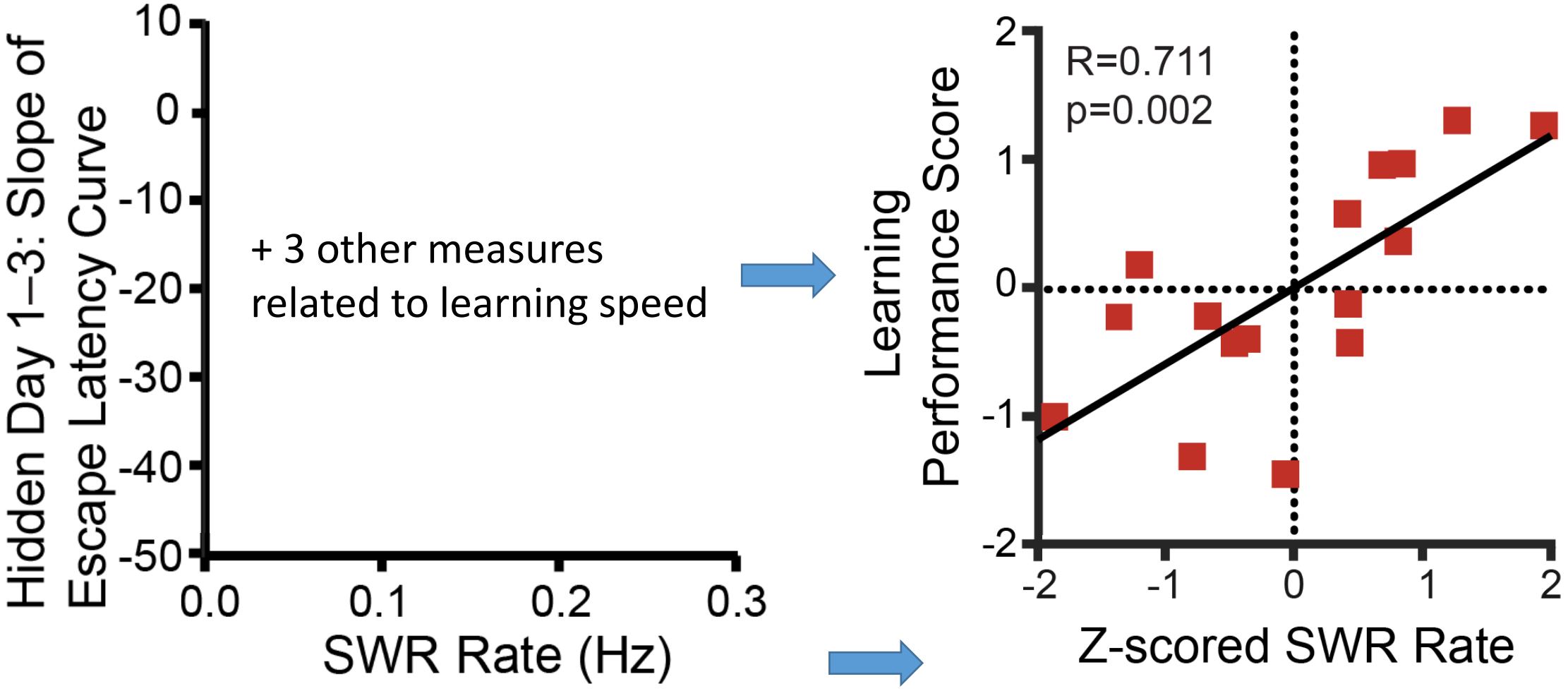
Screen cohort



Replication cohort

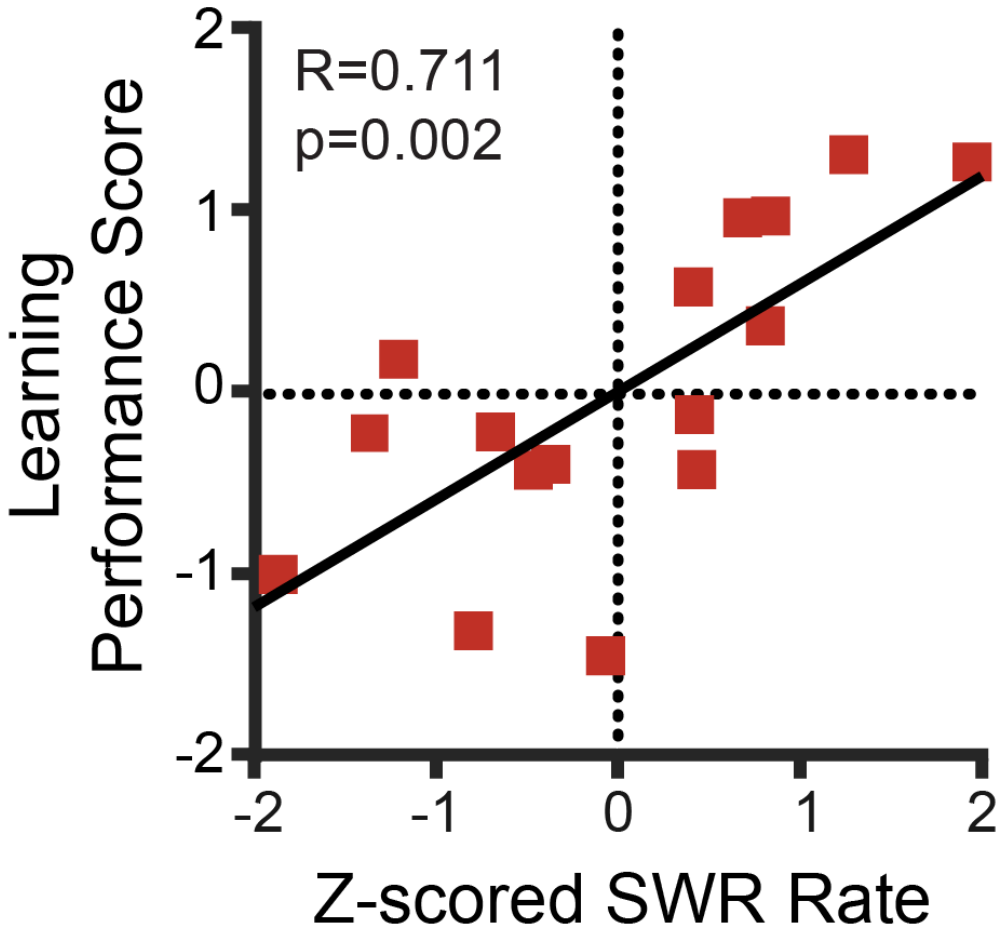


Combining Behavior Measurements into Performance Scores

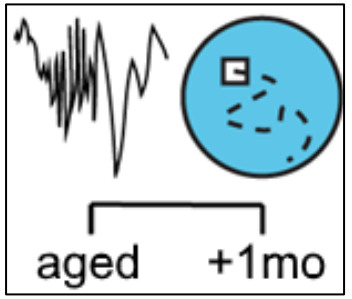


SWR Rate Predicts Learning Speed Score

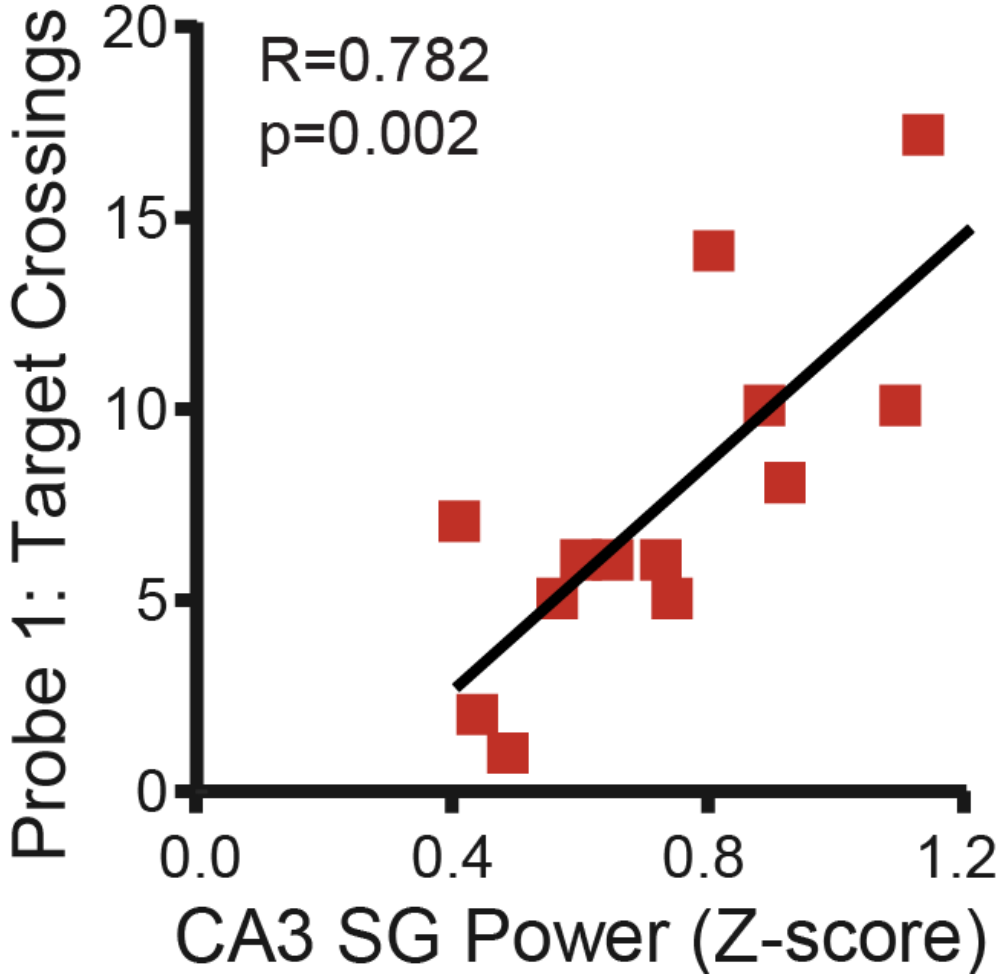
→ apply relationship to replication cohort



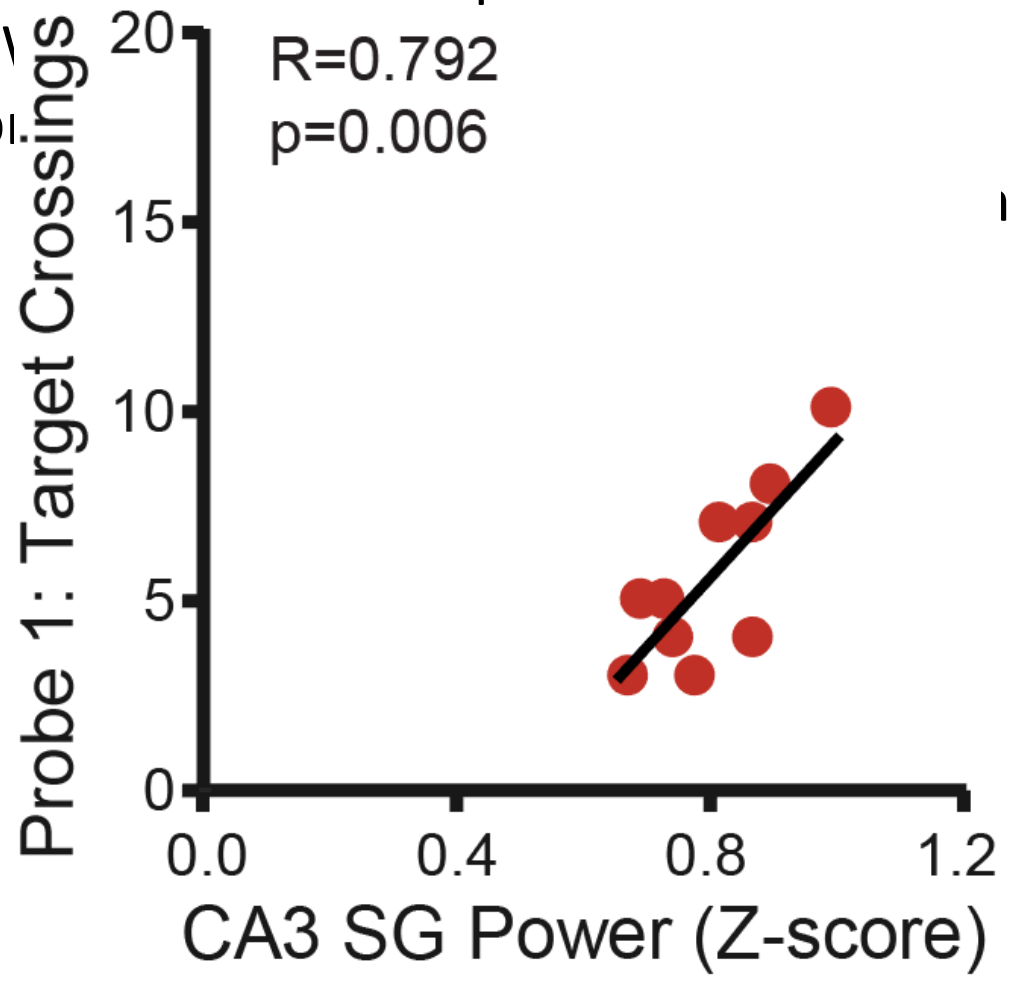
SWR-Associated CA3 SG Power Deficits Predict Water Maze Memory Precision Impairment



Screen cohort



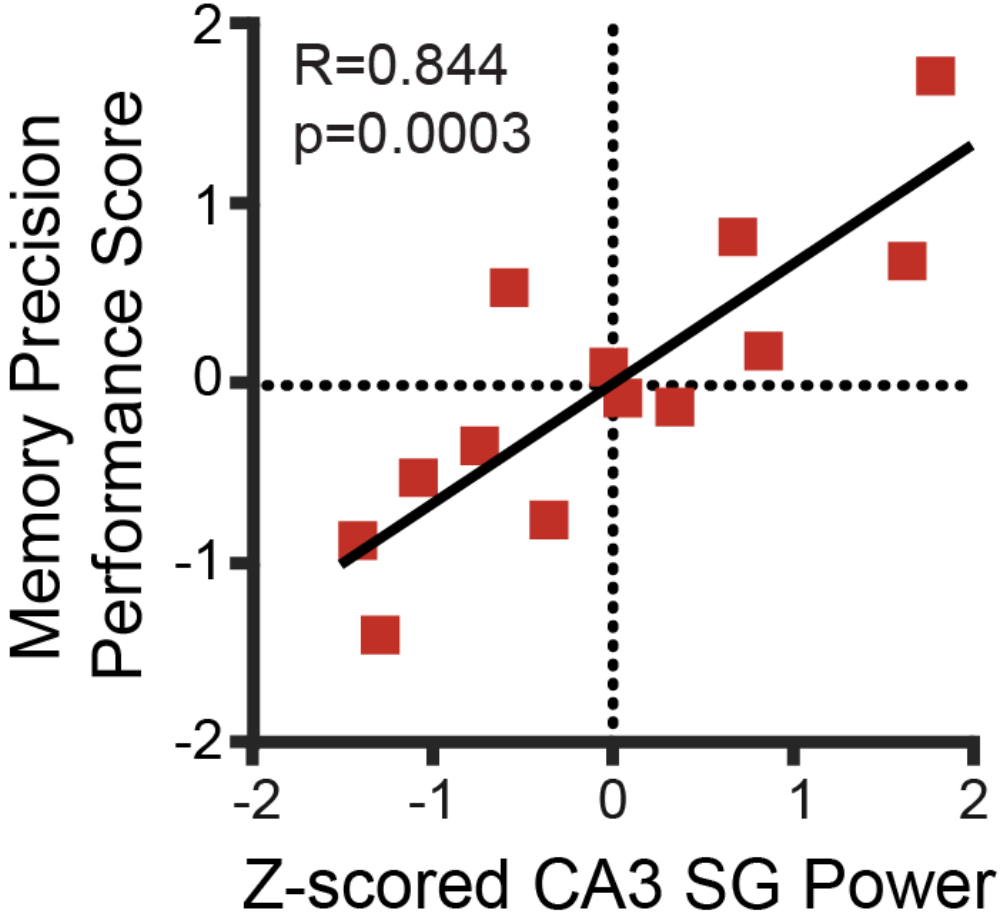
Replication cohort

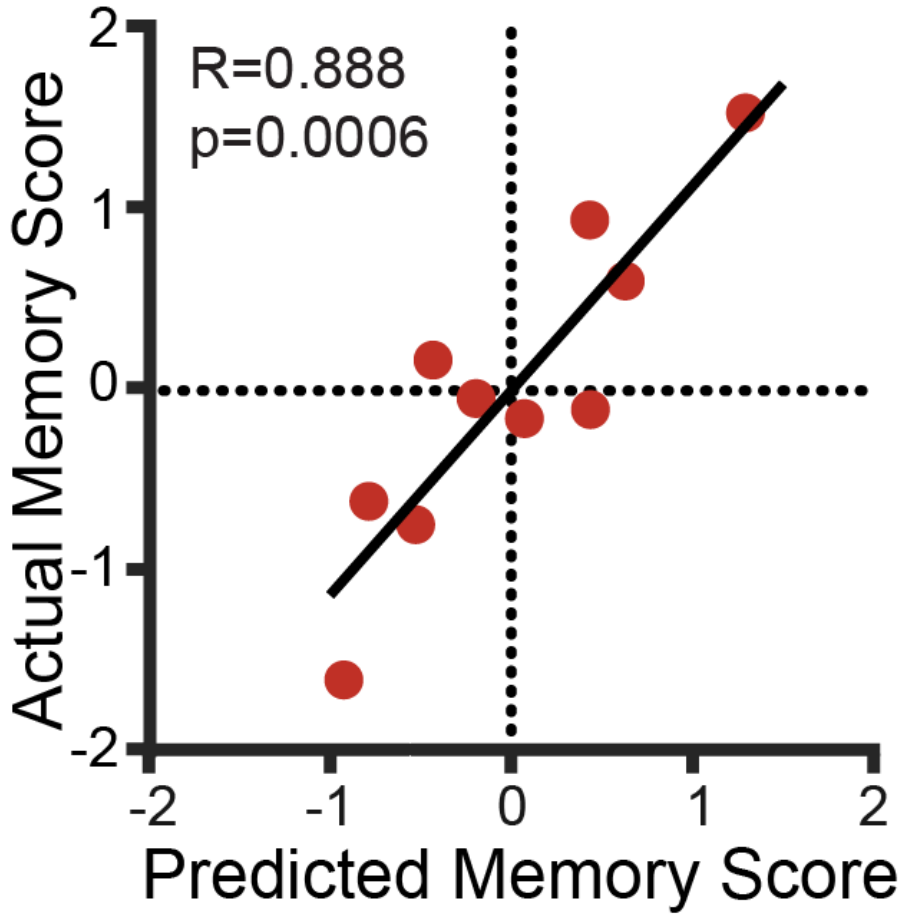


SWR-associated CA3 SG Power Predicts Memory Precision Score

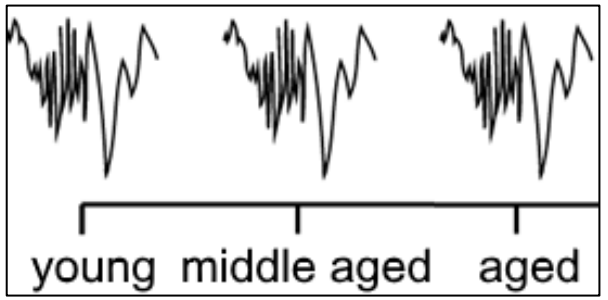
5 metrics related to memory precision

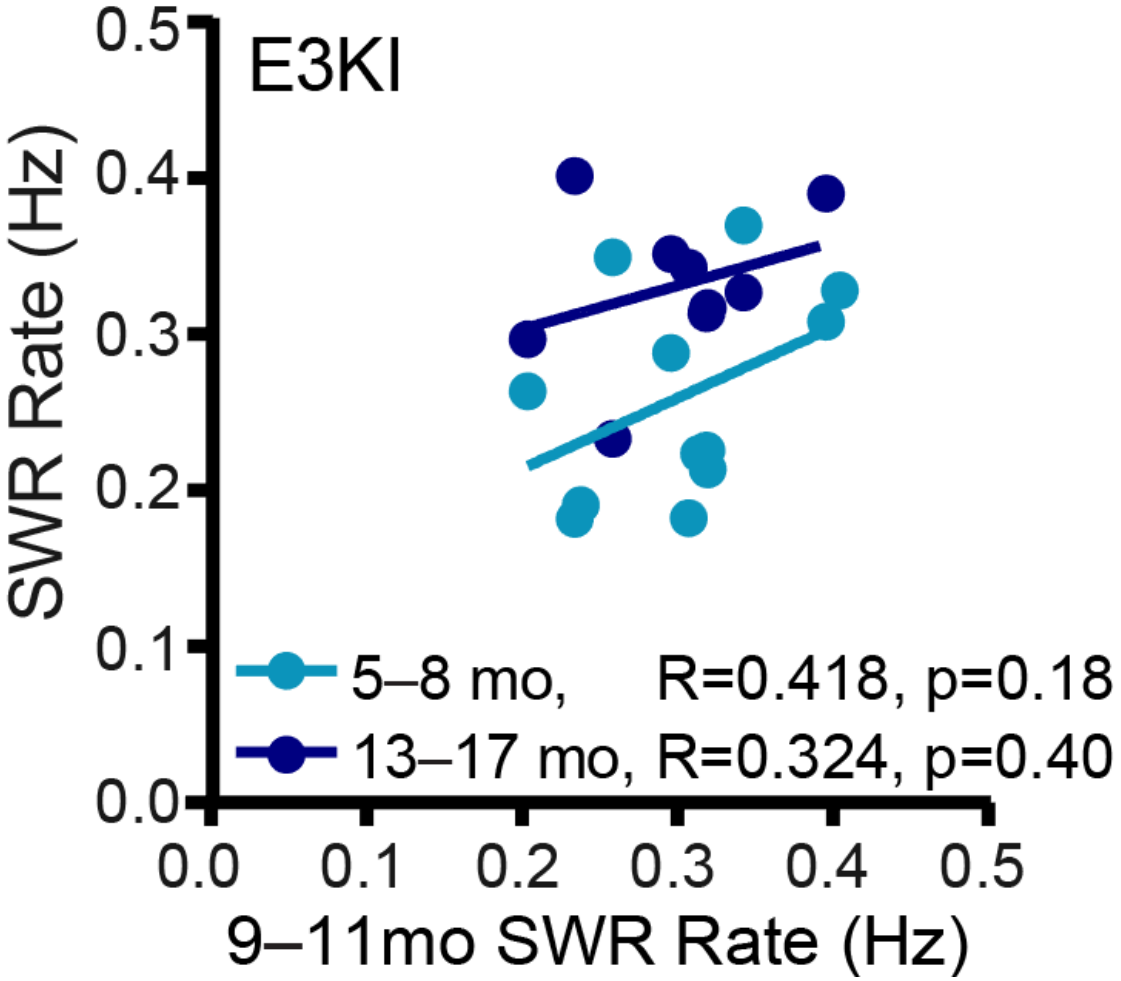
→ apply relationship to replication cohort

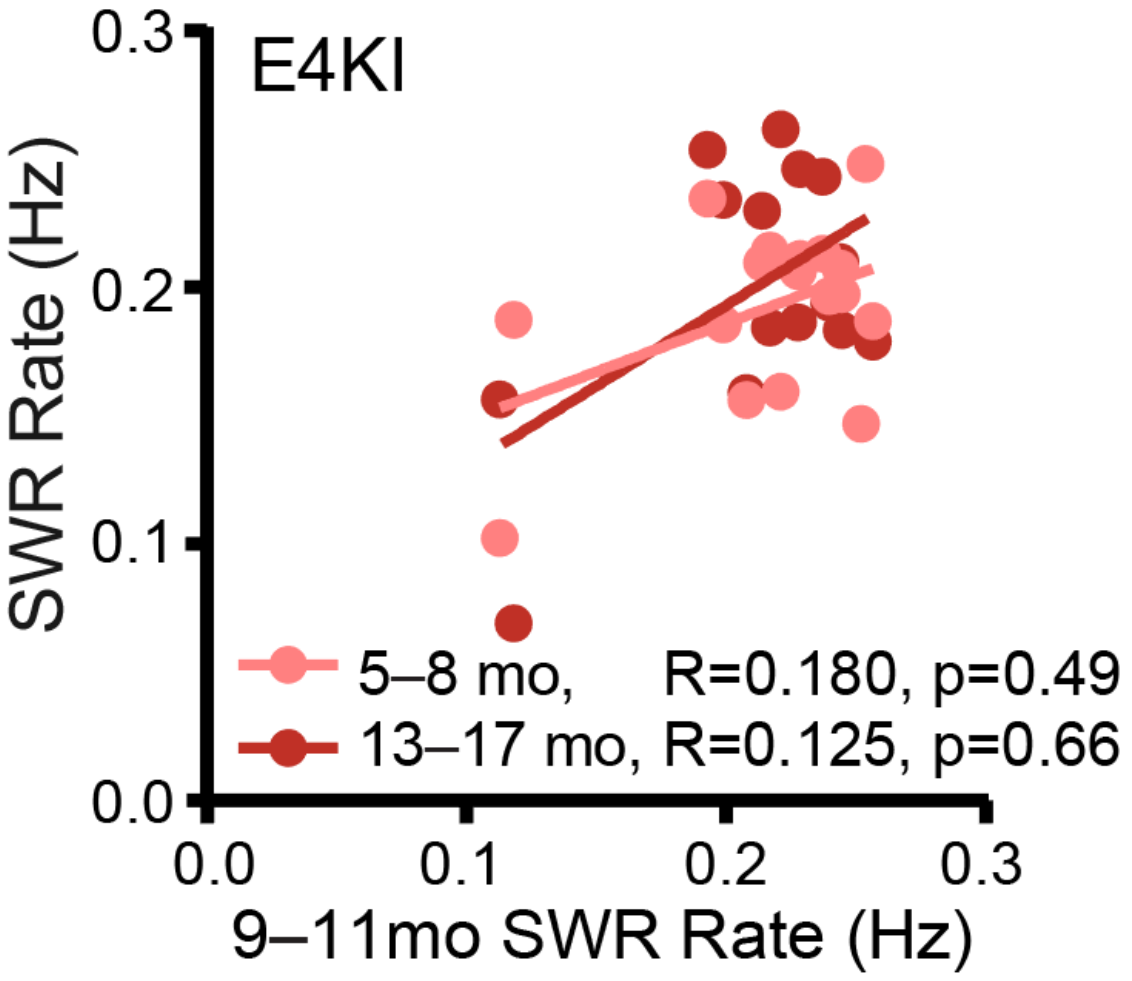




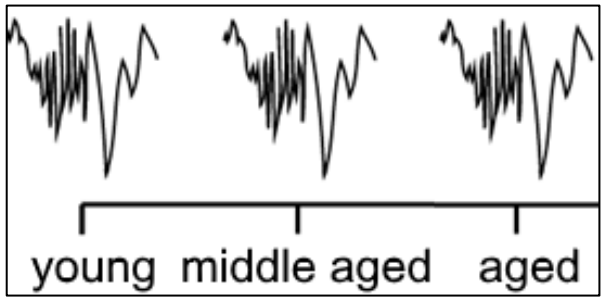
SWR Rate Is Not Significantly Correlated Over Aging

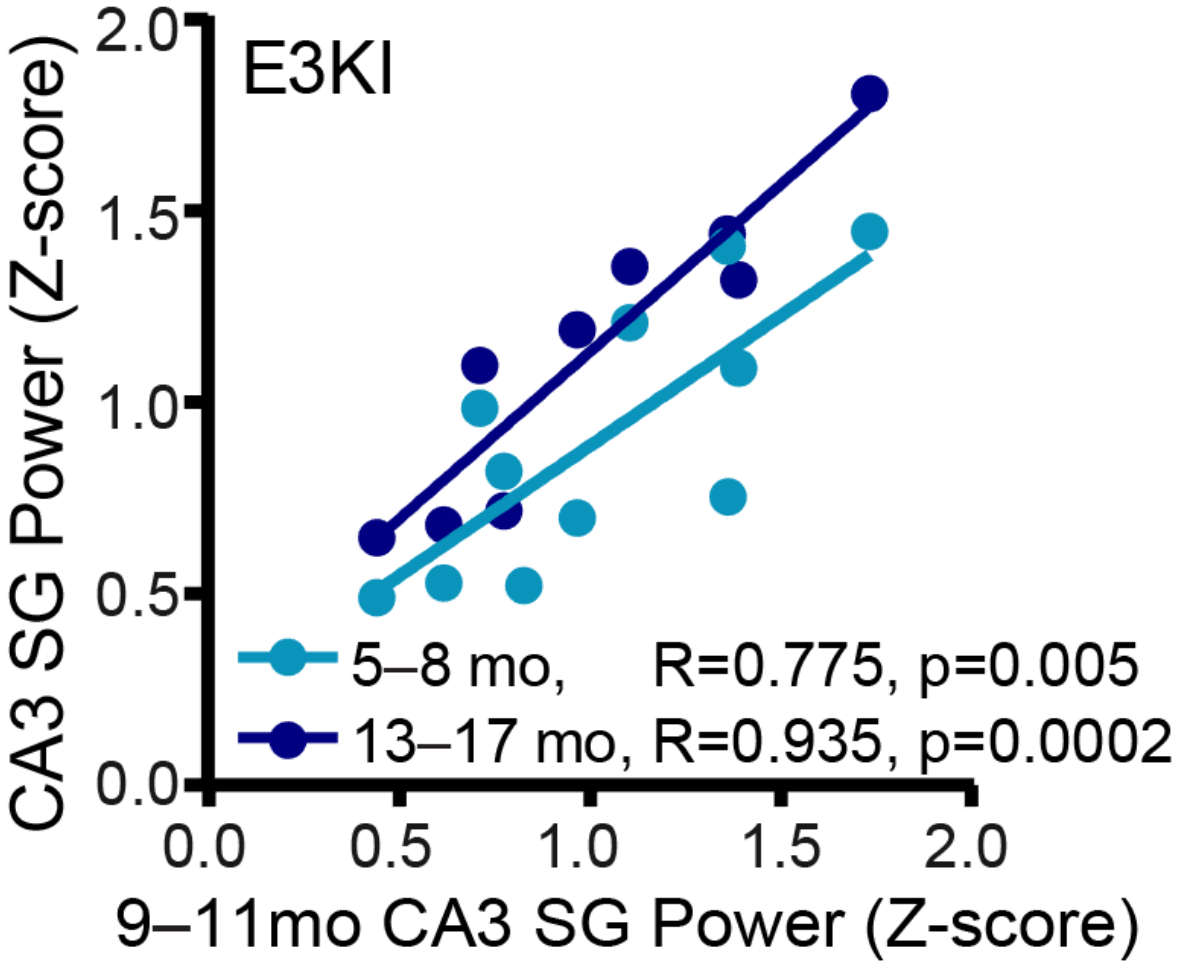


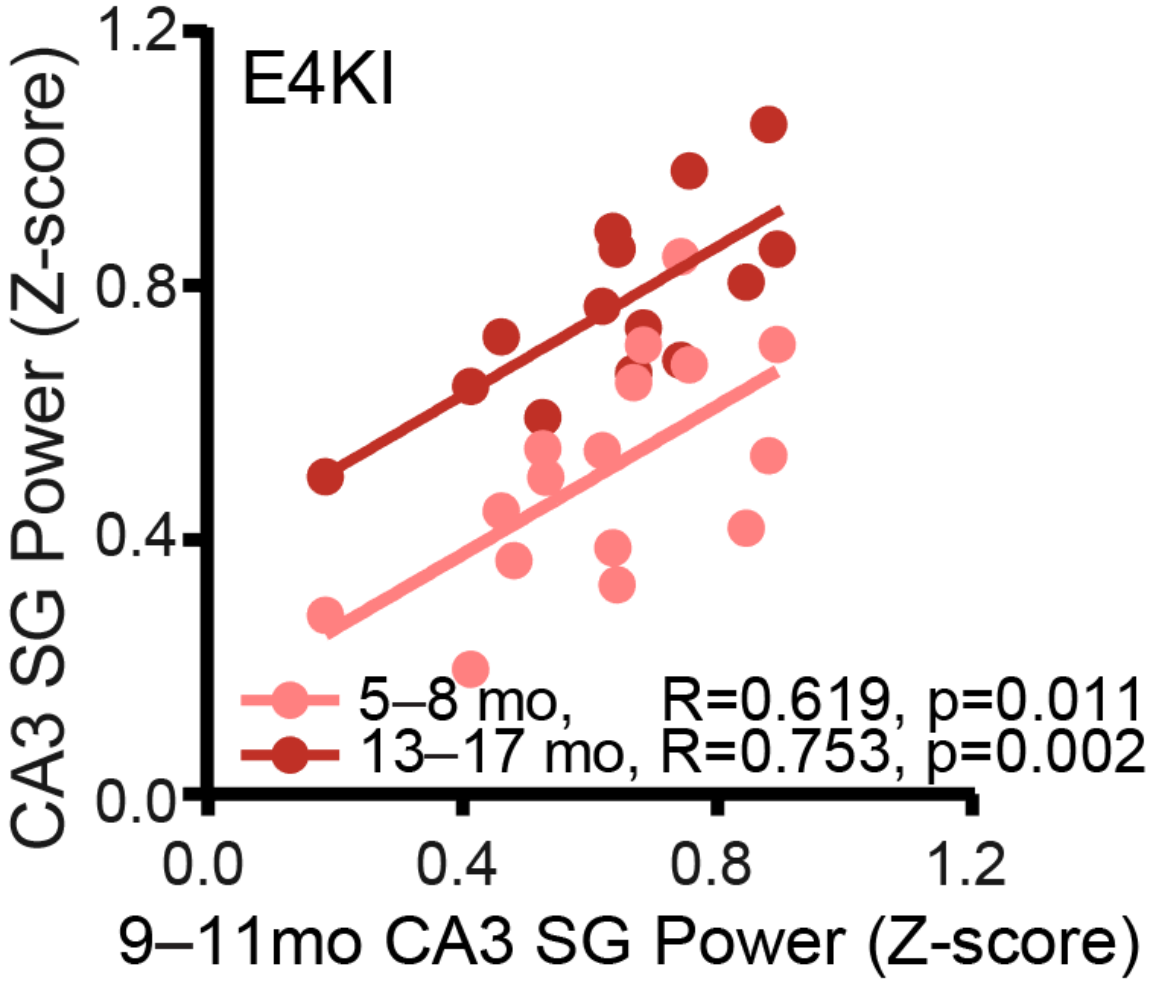




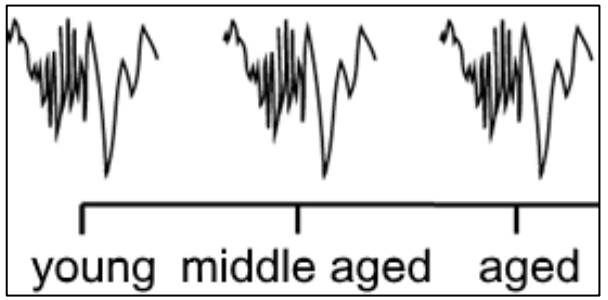
SWR-Associated CA3 SG Power Is Significantly Correlated Over Aging

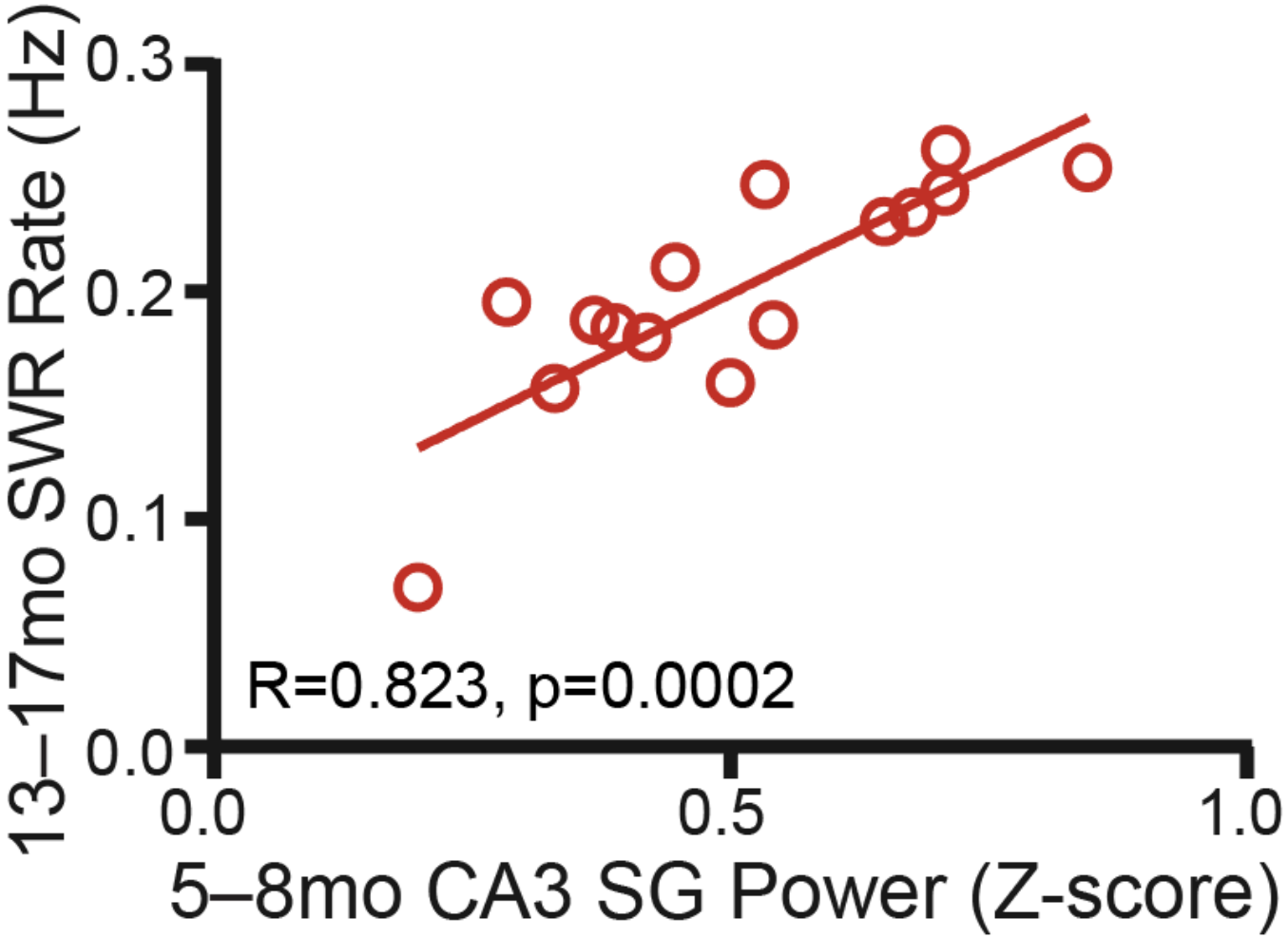




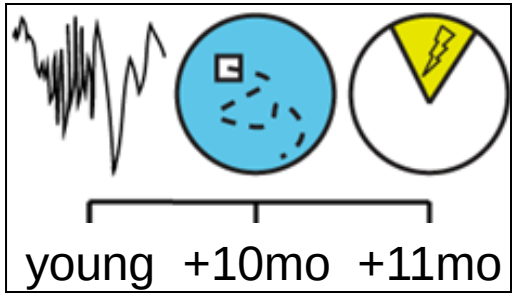


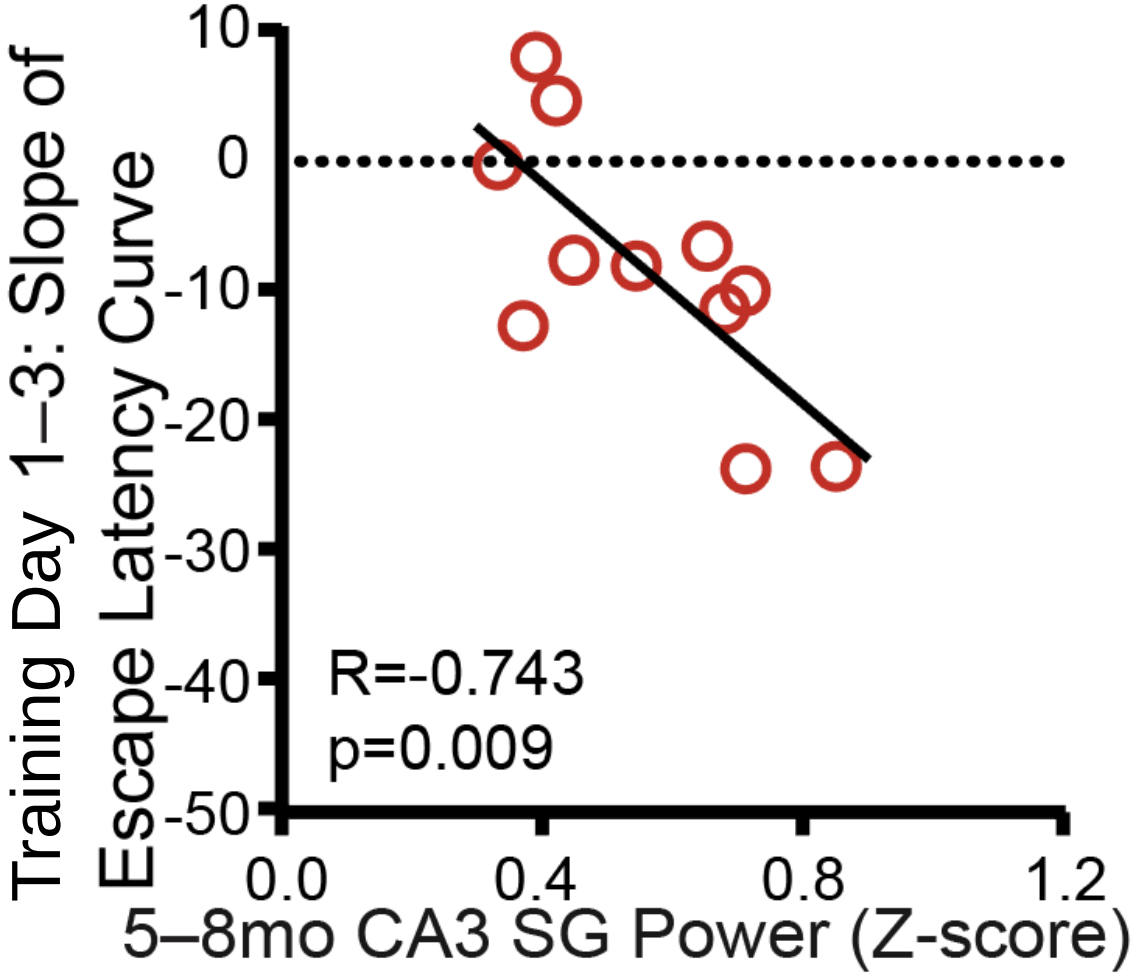
SWR-Associated CA3 SG Power at Younger Ages Predict SWR Rate at Older Ages

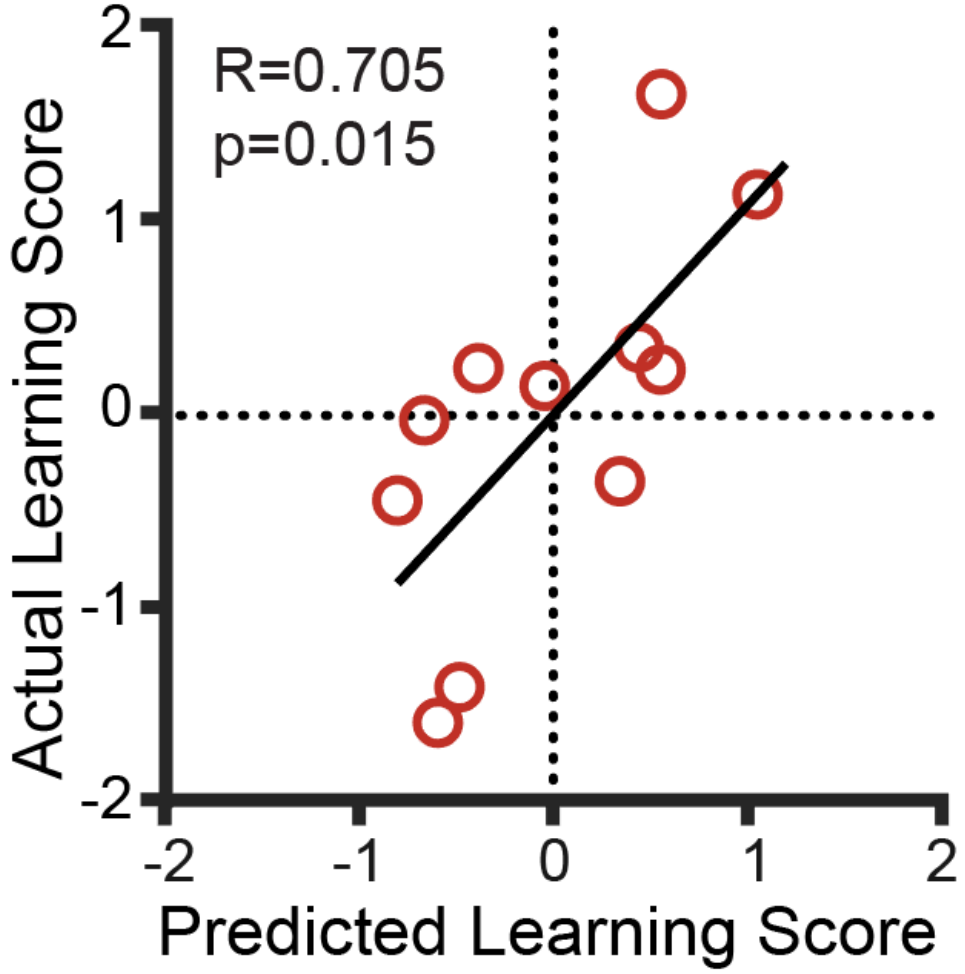




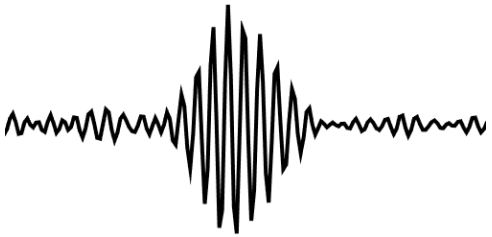
SWR-Associated CA3 SG Power Deficits at Younger Ages Predict Learning Impairment at Older Ages







Conclusions: Part 1



Ripple Rate

# of consolidation events

- predicts learning speed impairments

Slow Gamma Power

Coordination of consolidation

- predicts memory precision impairments
- predicts learning speed impairments 10-11 months before the task

Potential Applications

Use ripple deficits as a biomarker to…

- Test if drug candidates repair the brain before the onset of memory impairment
- Predict whether someone will develop Alzheimer’s disease to begin early interventions

Outline

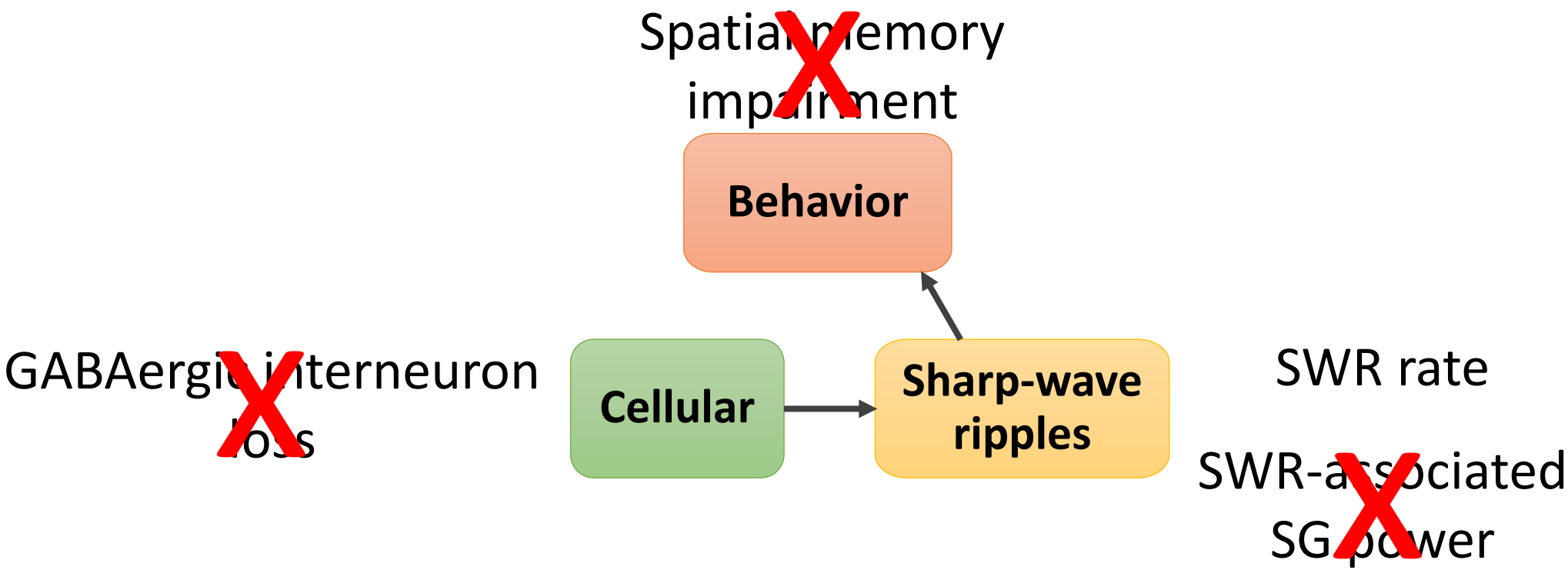
Background

1. Alzheimer's disease and Apolipoprotein (apo) E4
2. Hippocampal sharp-wave ripples

Results

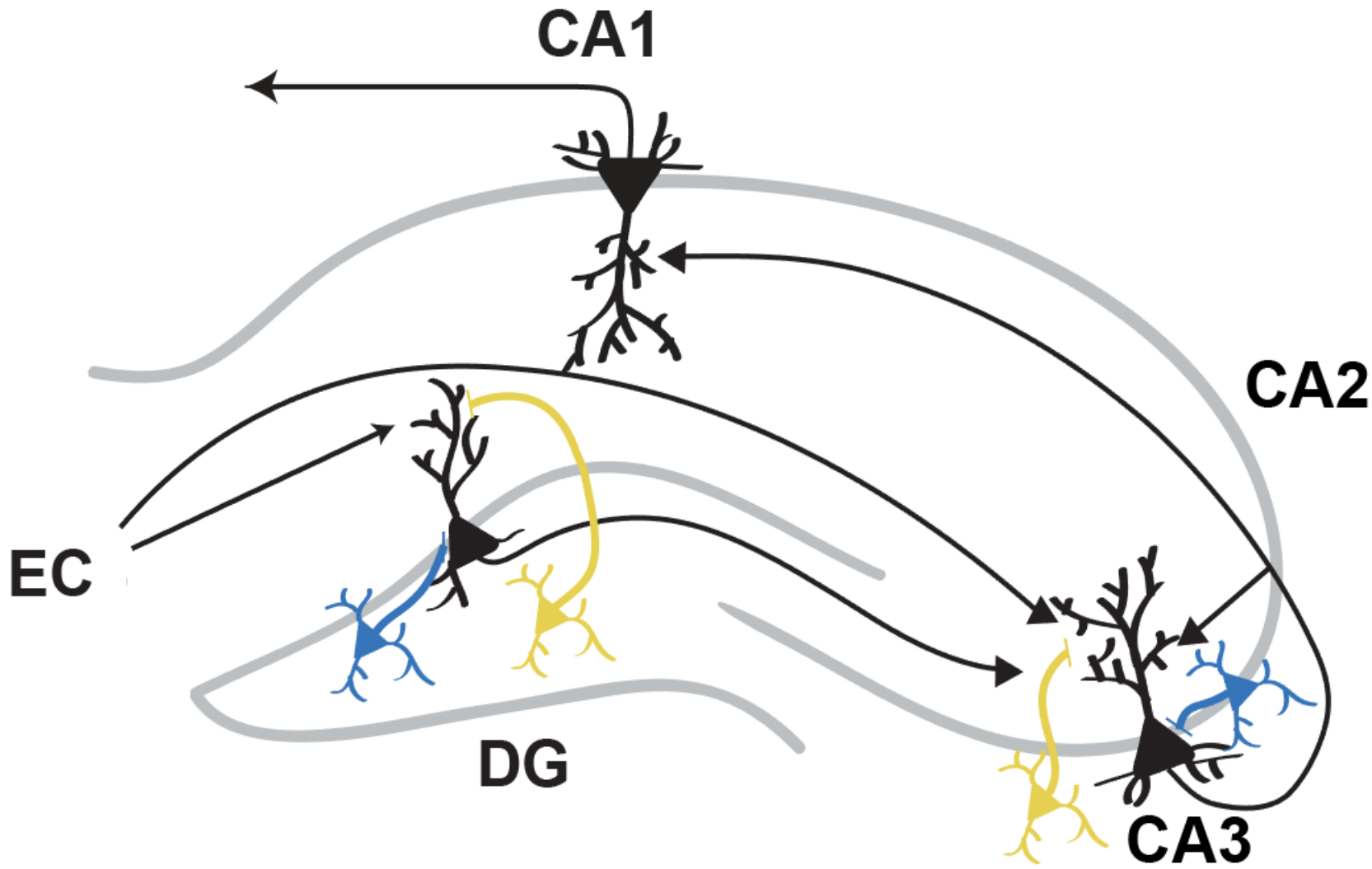
1. Early hippocampal sharp-wave ripple deficits predict later learning and memory impairments in an Alzheimer's disease mouse model
2. Hippocampal GABAergic interneurons bidirectionally modulate sharp-wave ripples

Deleting ApoE4 from GABAergic Interneurons Prevents ApoE4-induced Deficits



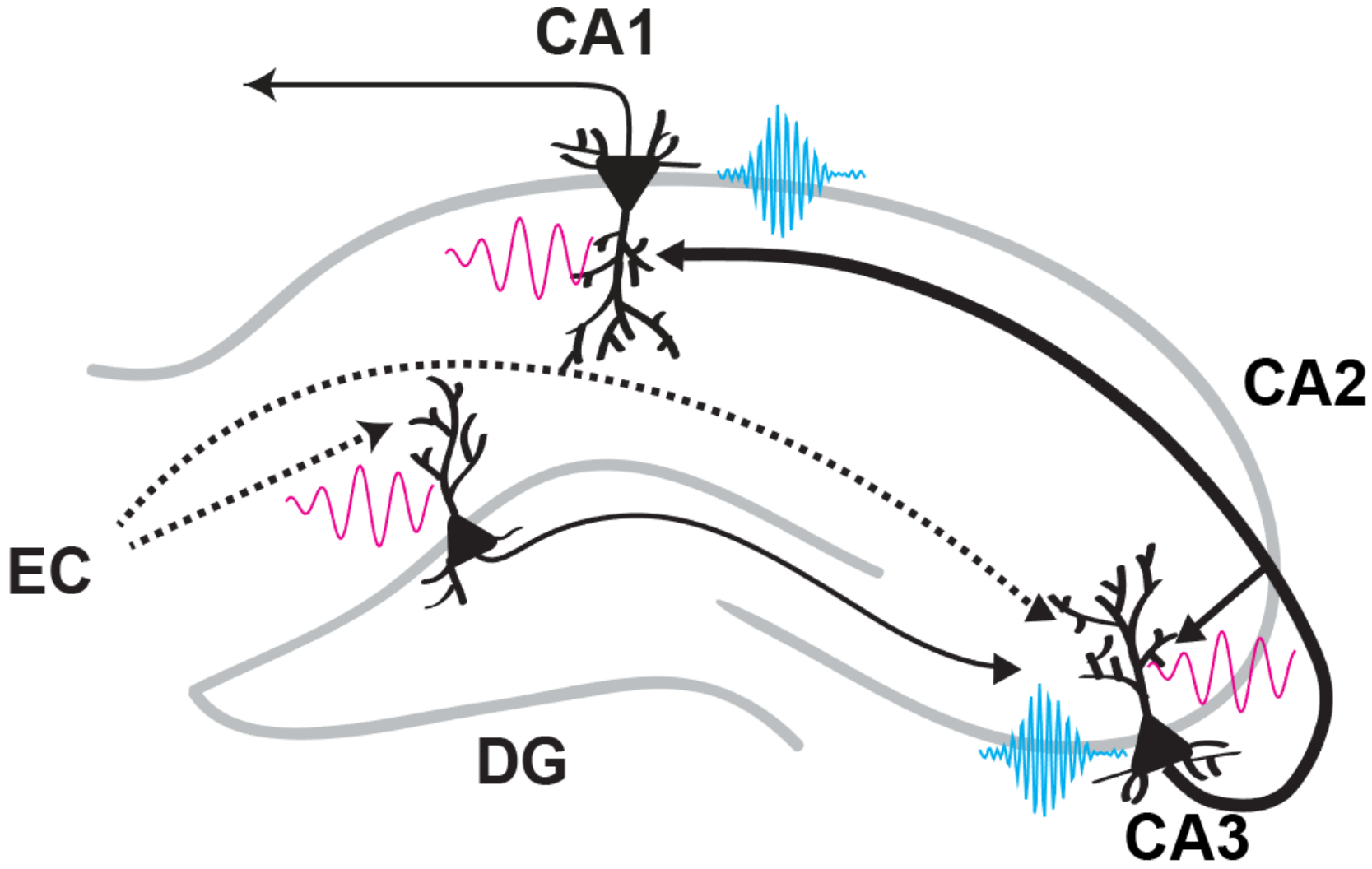
(Knoferle et al, 2014; Gillespie et al, 2016)

CA3 and Dentate Gyrus (DG) Interneurons Are Critical for Memory



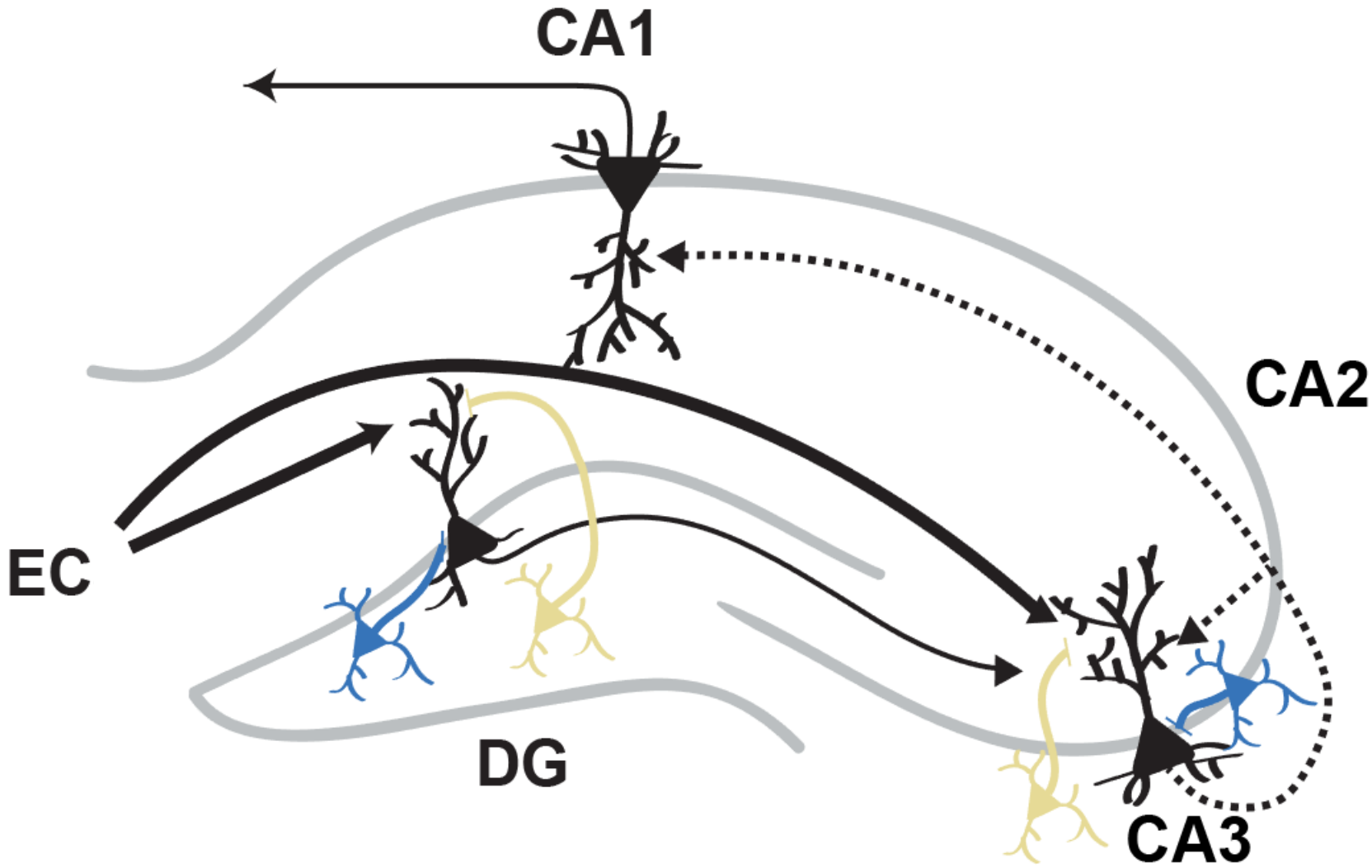
(Najm*, Jones*, & Huang, 2019)

Hippocampal Oscillatory Activity Organizes Encoding, Retrieval, & Consolidation, and is Driven By External vs Internal Inputs

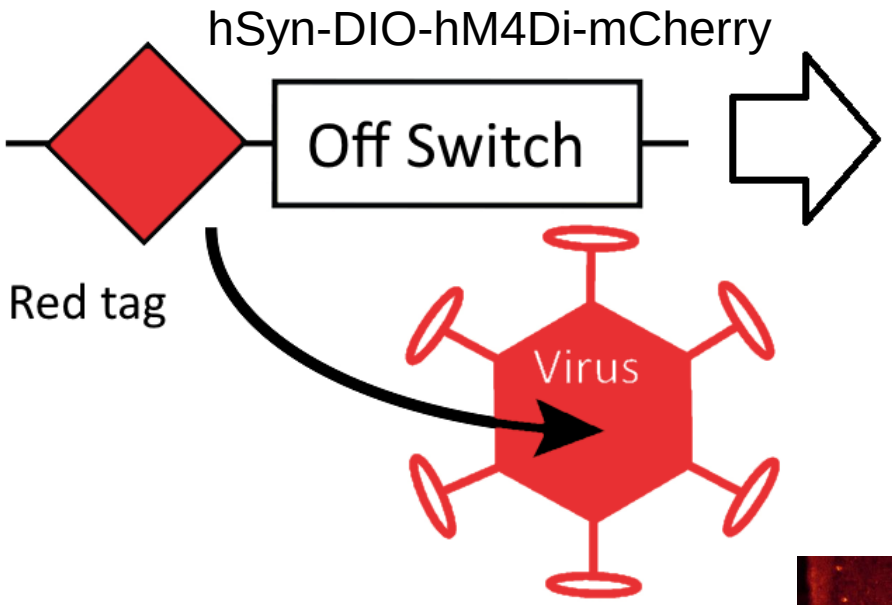


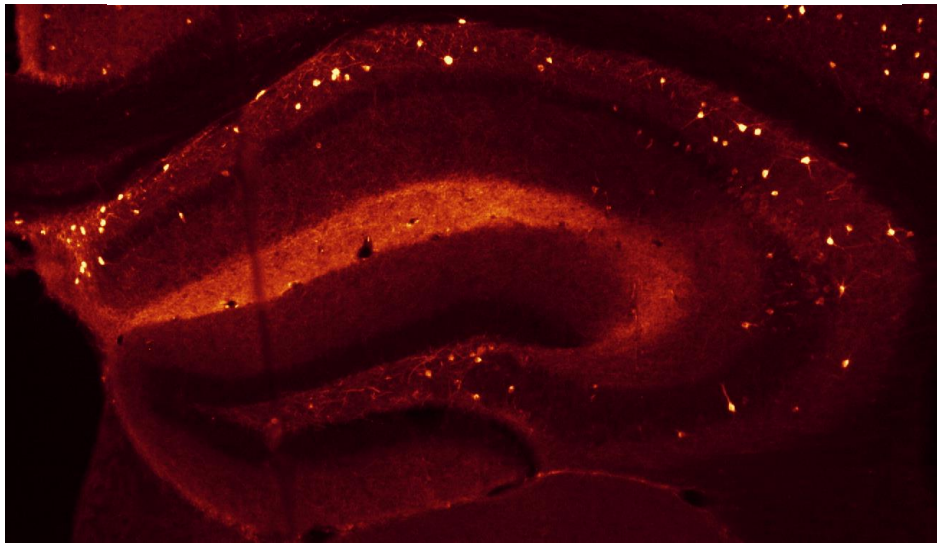
Parvalbumin (PV+) and Somatostatin (SST+) Interneurons Gate Different Parts of Input/Output Transformations

PV+ and SST+ Interneurons CA3 + DG Might Gate Internal vs External Inputs



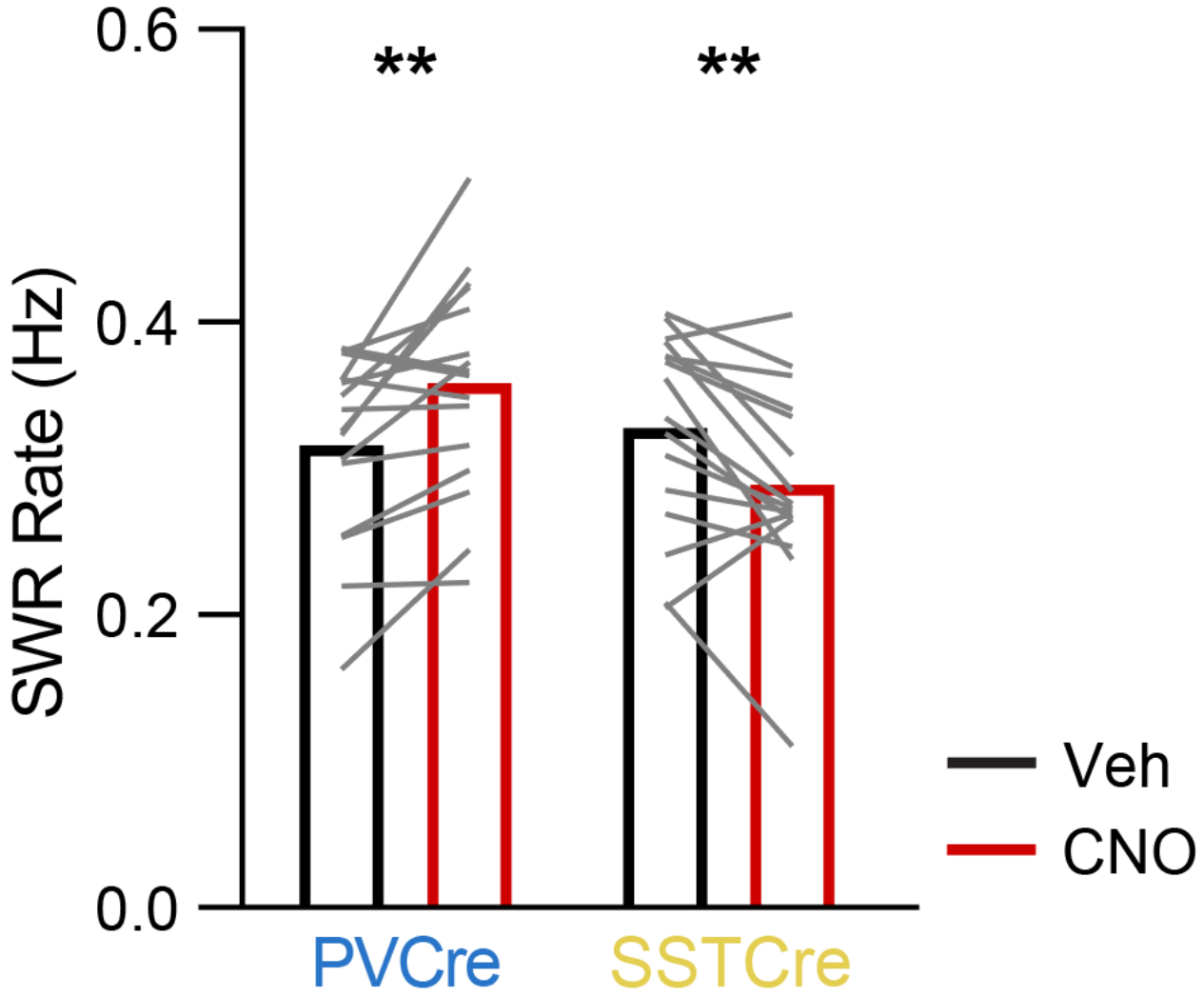
Experimental Design: Chemogenetic Suppression of PV+ and SST+ DG and CA3 Interneurons

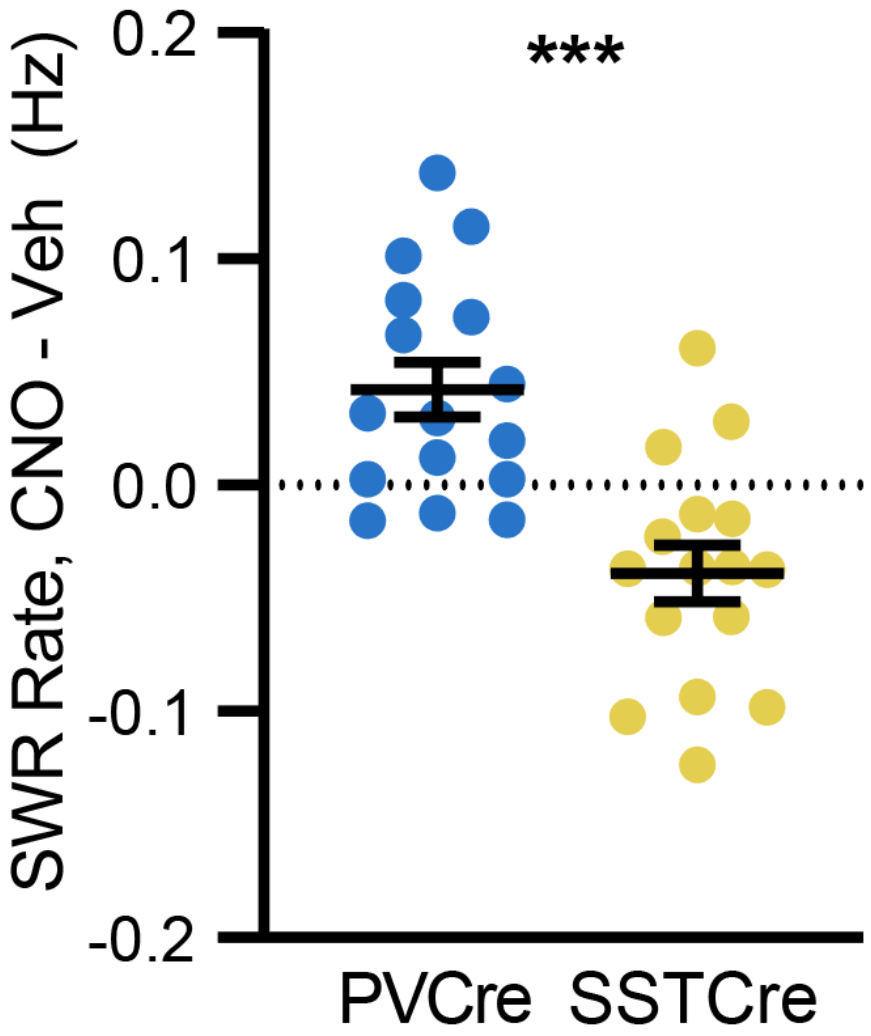




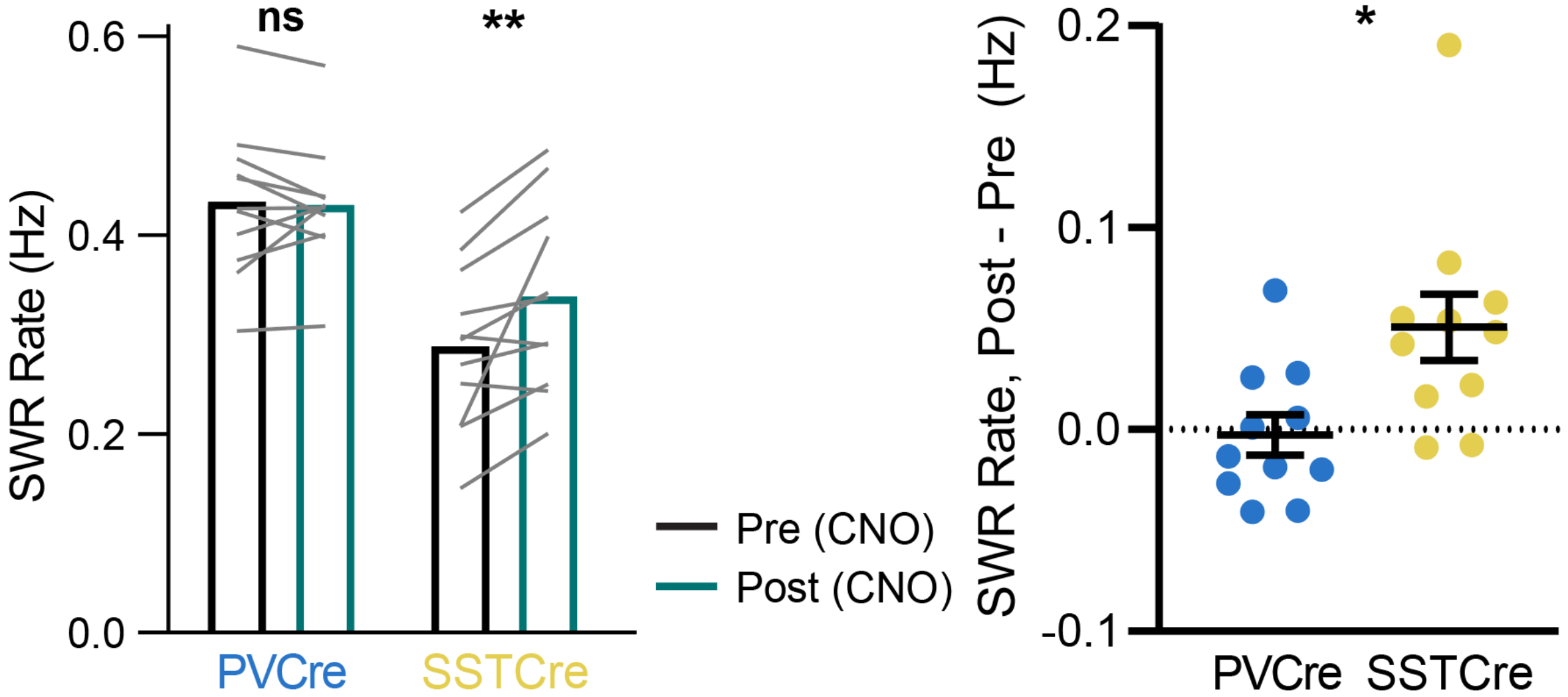
(Adapted from Neuwrite San Diego)

Suppressing DG + CA3 Interneurons Bidirectionally Modulates SWR Rate

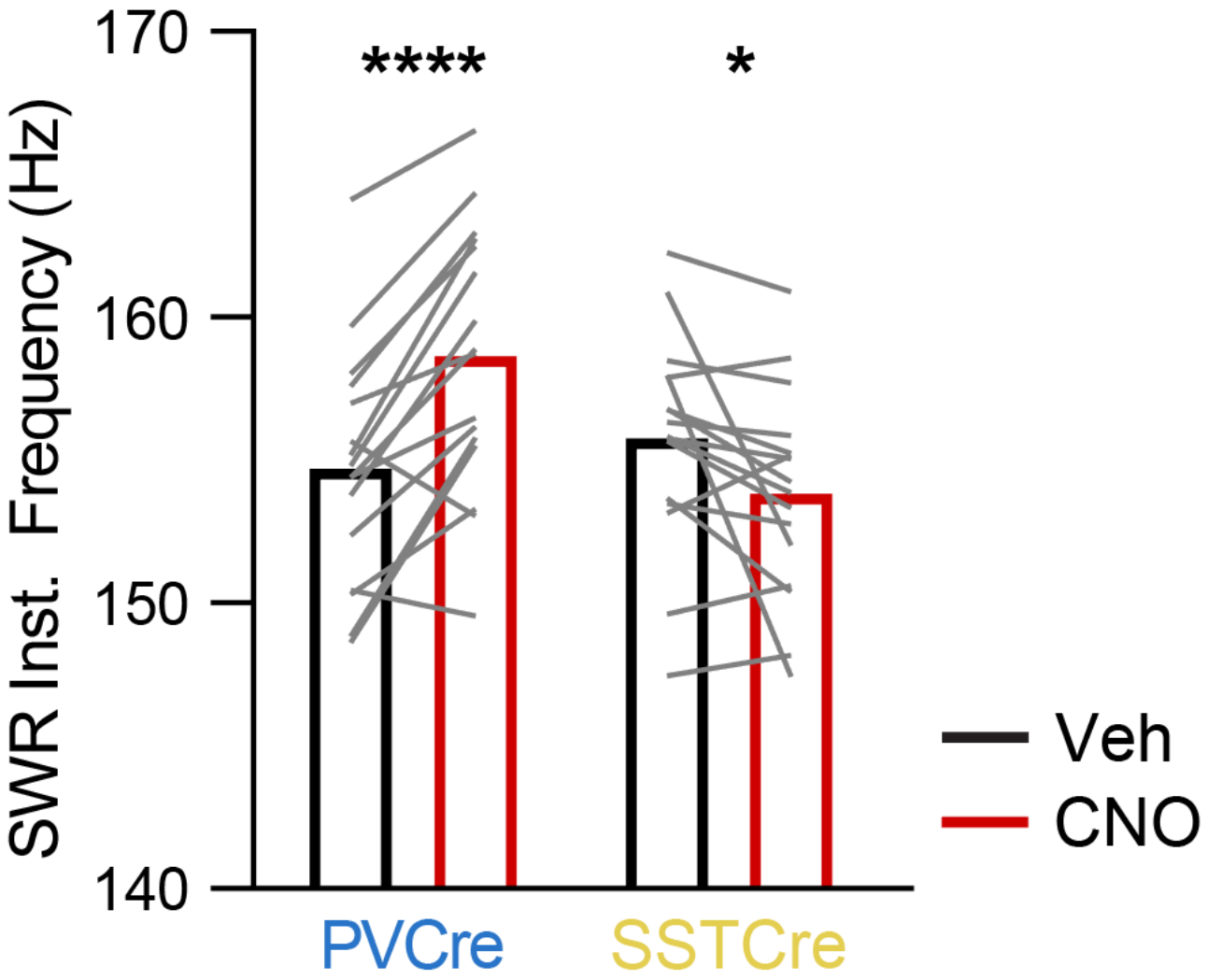


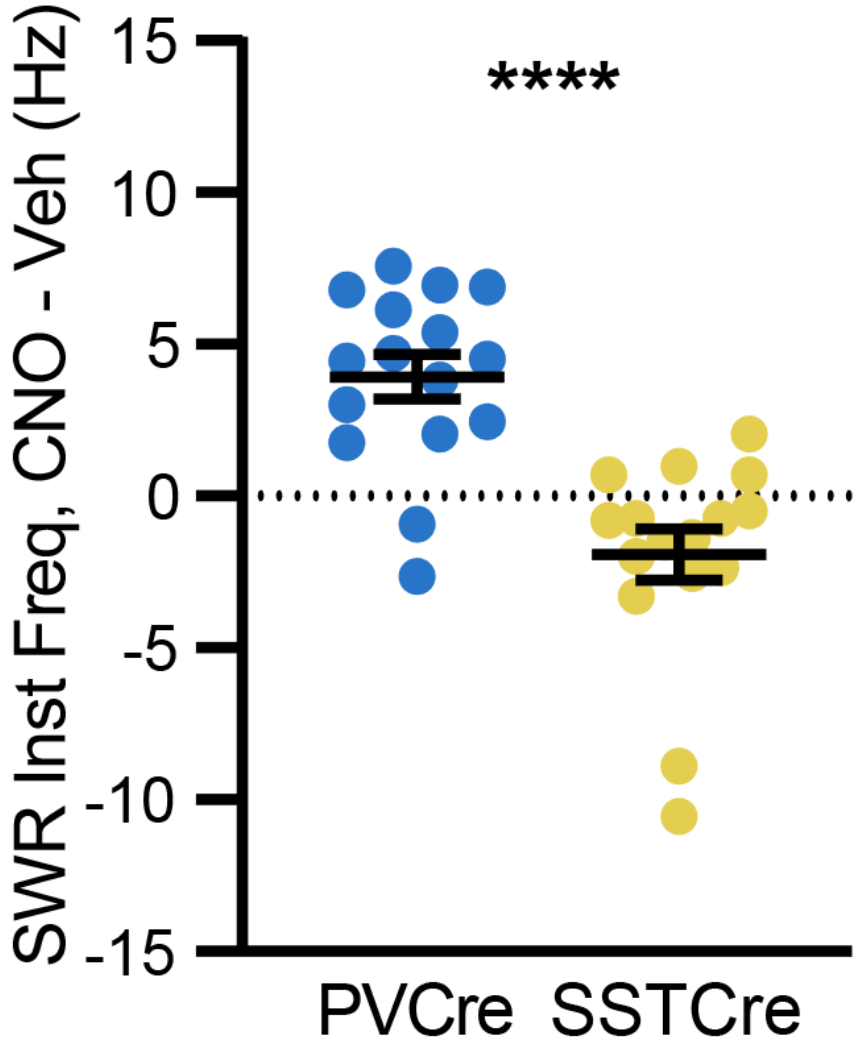


Suppressing PV+ Interneurons Prevents Learning-Induced SWR Rate Increase

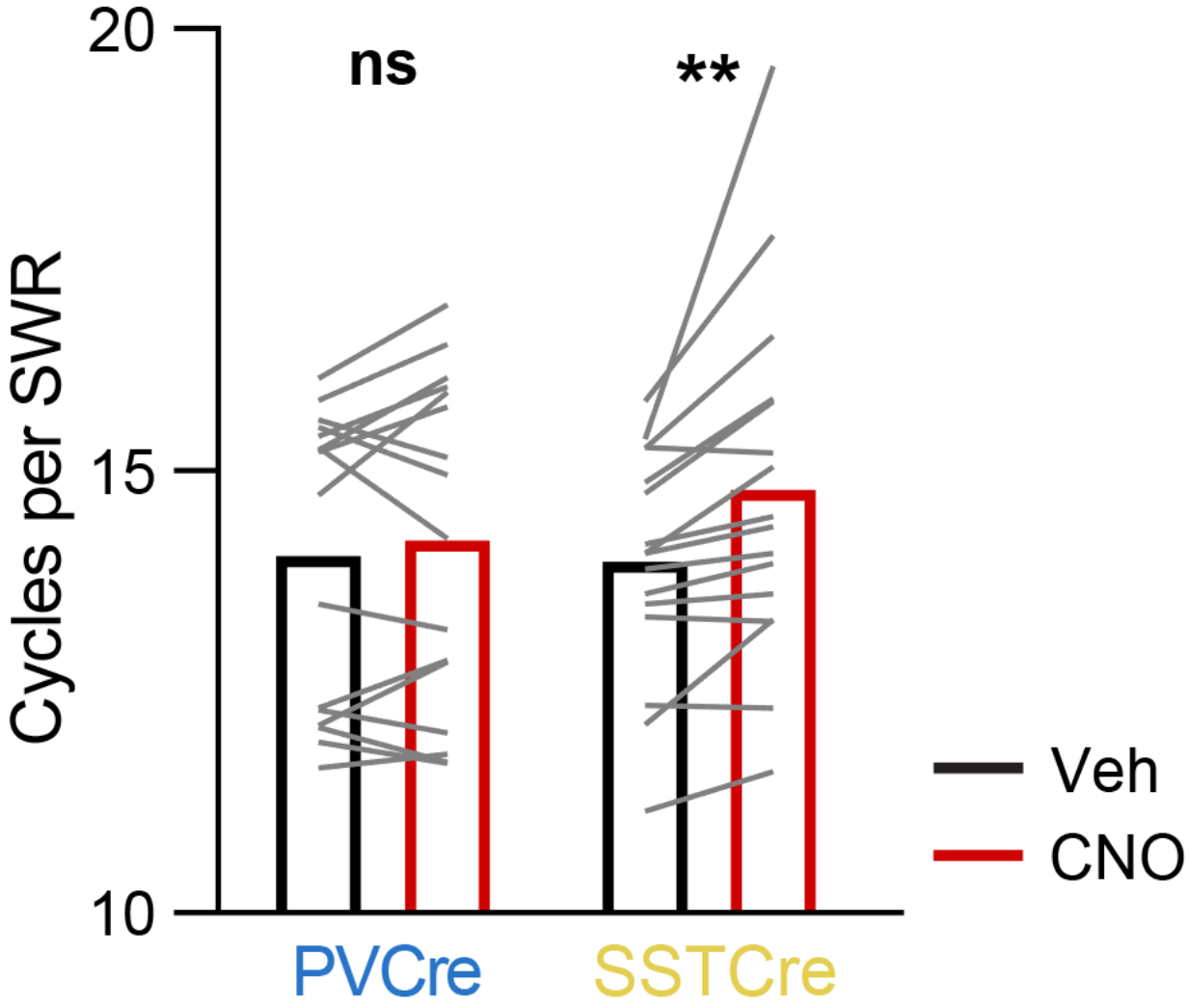


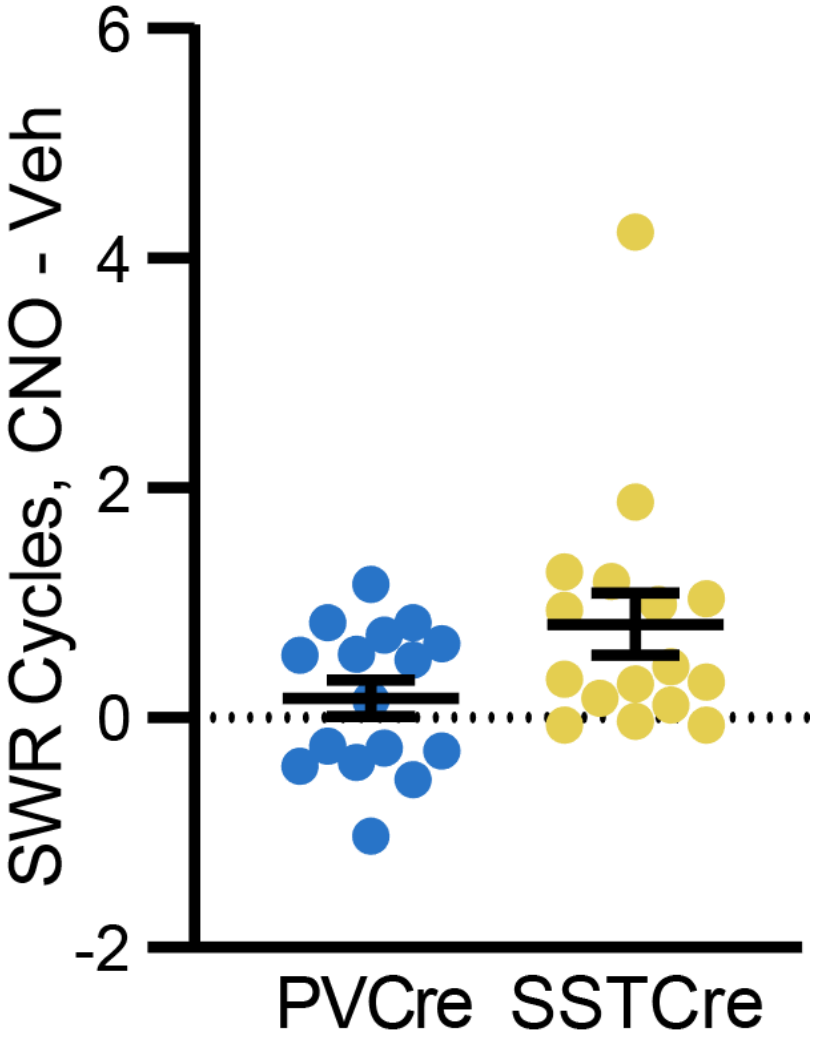
Suppressing DG + CA3 Interneurons Bidirectionally Modulates SWR Frequency



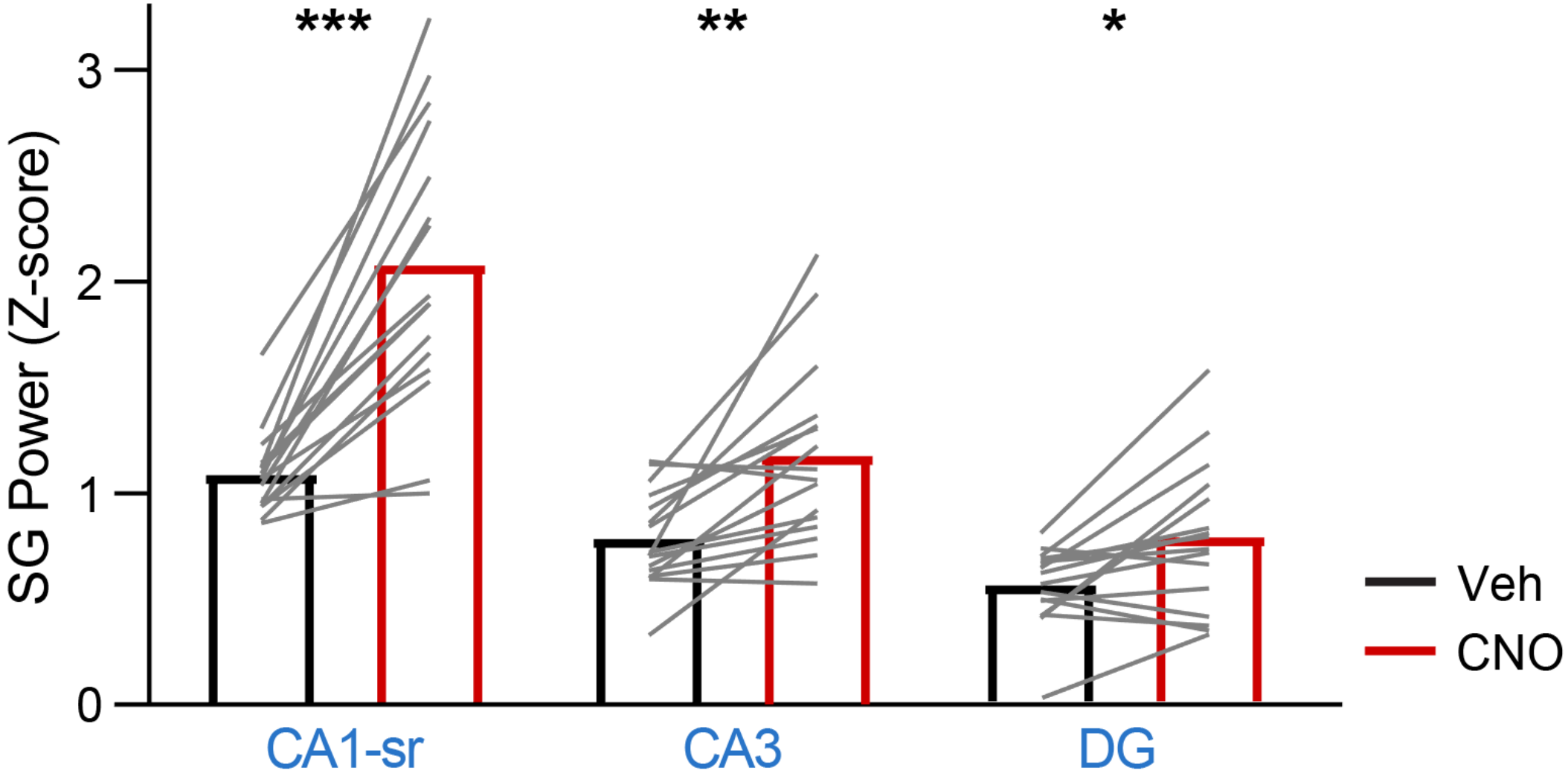


Suppressing SST+ Interneurons Increases Cycles per SWR





Suppressing PV+ Interneurons Increases SWR-Associated SG Power Throughout the Hippocampus



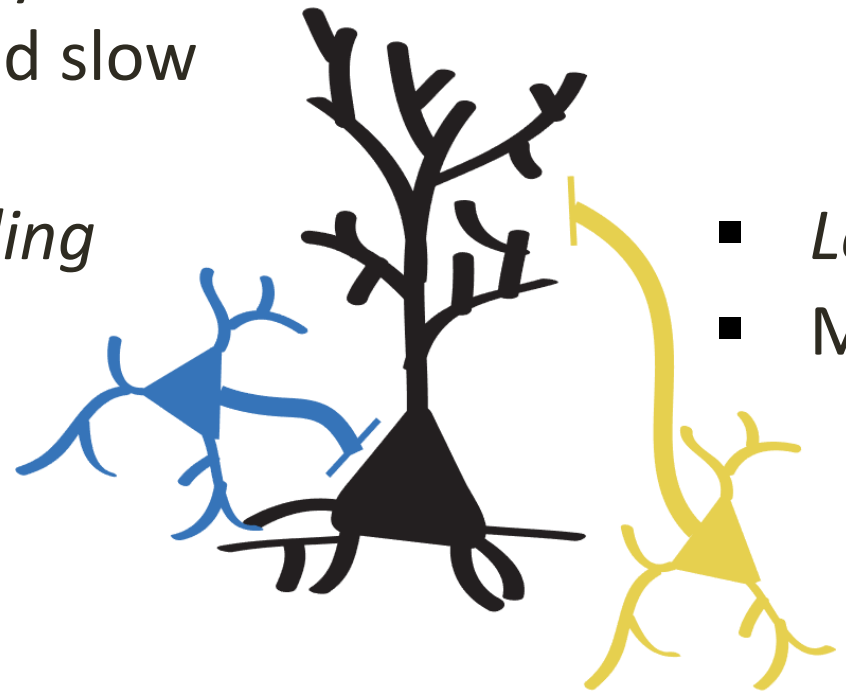
Conclusions: Part 2

Suppress PV+ Interneurons

- More SWRs with no learning increase
- Faster SWR frequency
- More SWR-associated slow gamma power
- *More CA3-CA1 coupling*

Suppress SST+ Interneurons

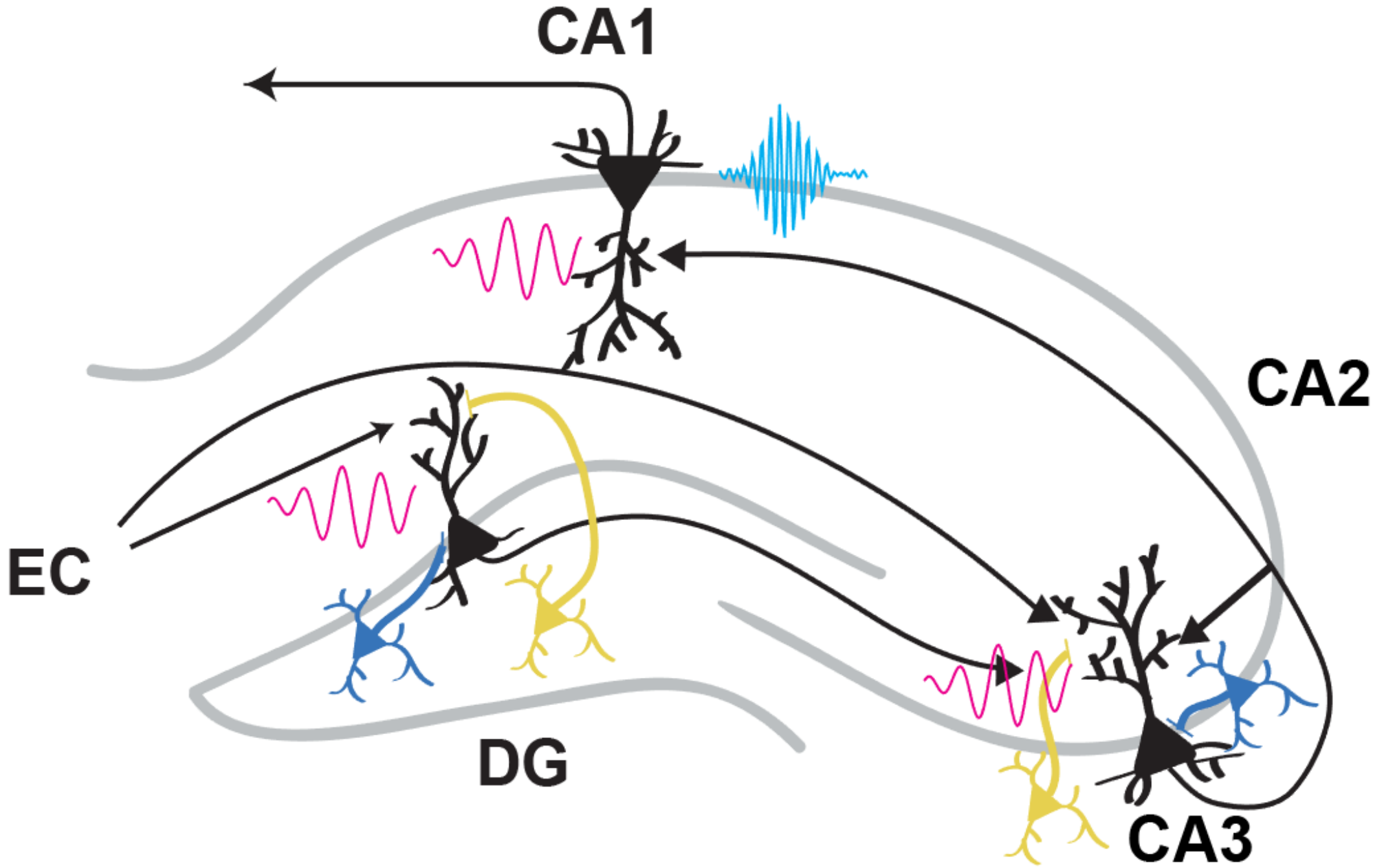
- Fewer SWRs
- Longer SWRs
- *Less CA3-CA1 coupling*
- Matches E4KI phenotypes



Suppress Both → PV effect dominates

Future Directions

- Are these features differently modulated in awake SWRs?
- How do PV+ and SST+ interneurons modulate hippocampal oscillatory activity during movement (theta and associated gamma)?
- Are these effects related to learning performance?


CA1
CA2
EC
DG
CA3

Questions?