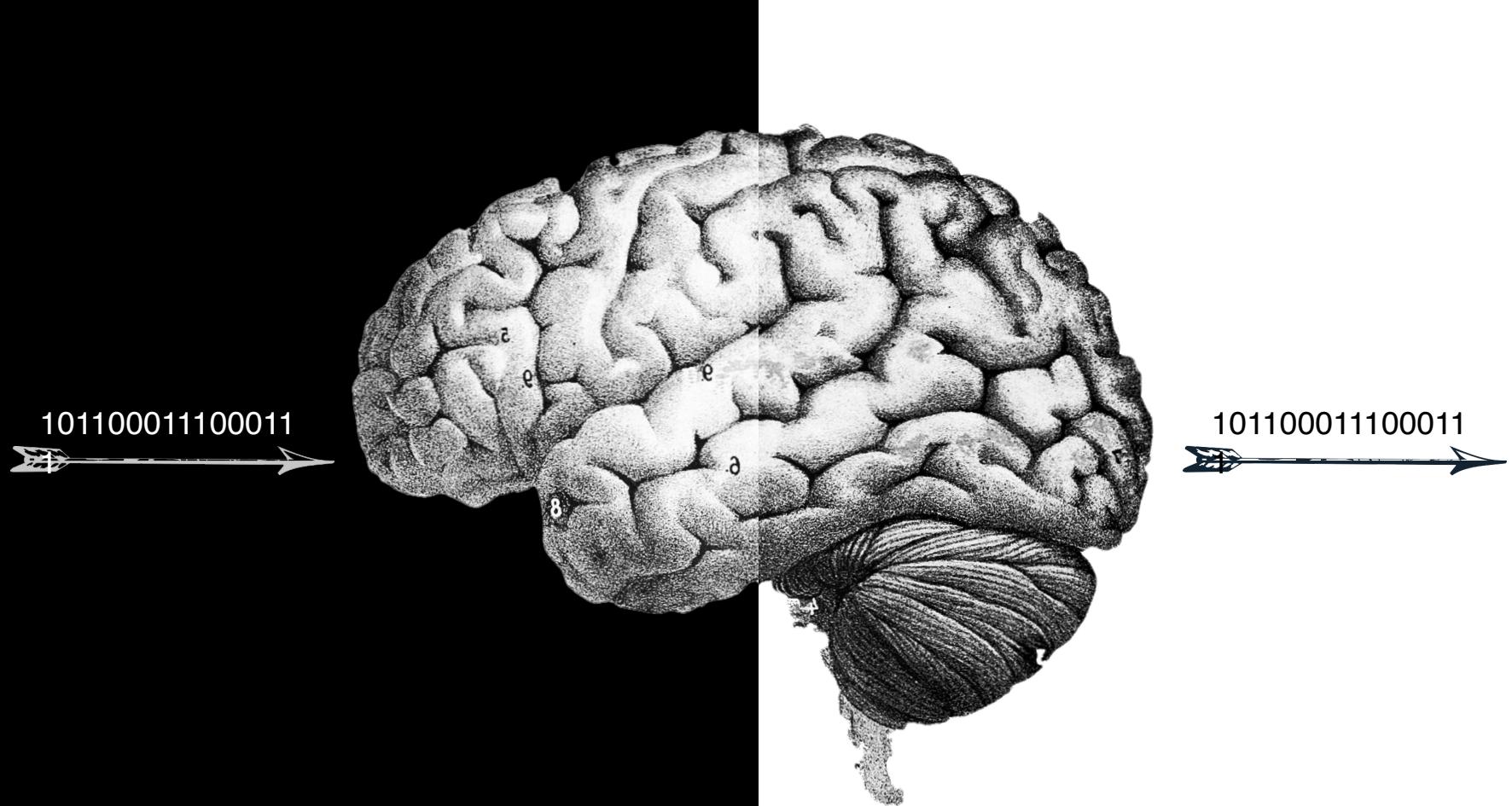


CC(=O)OCN(C)C

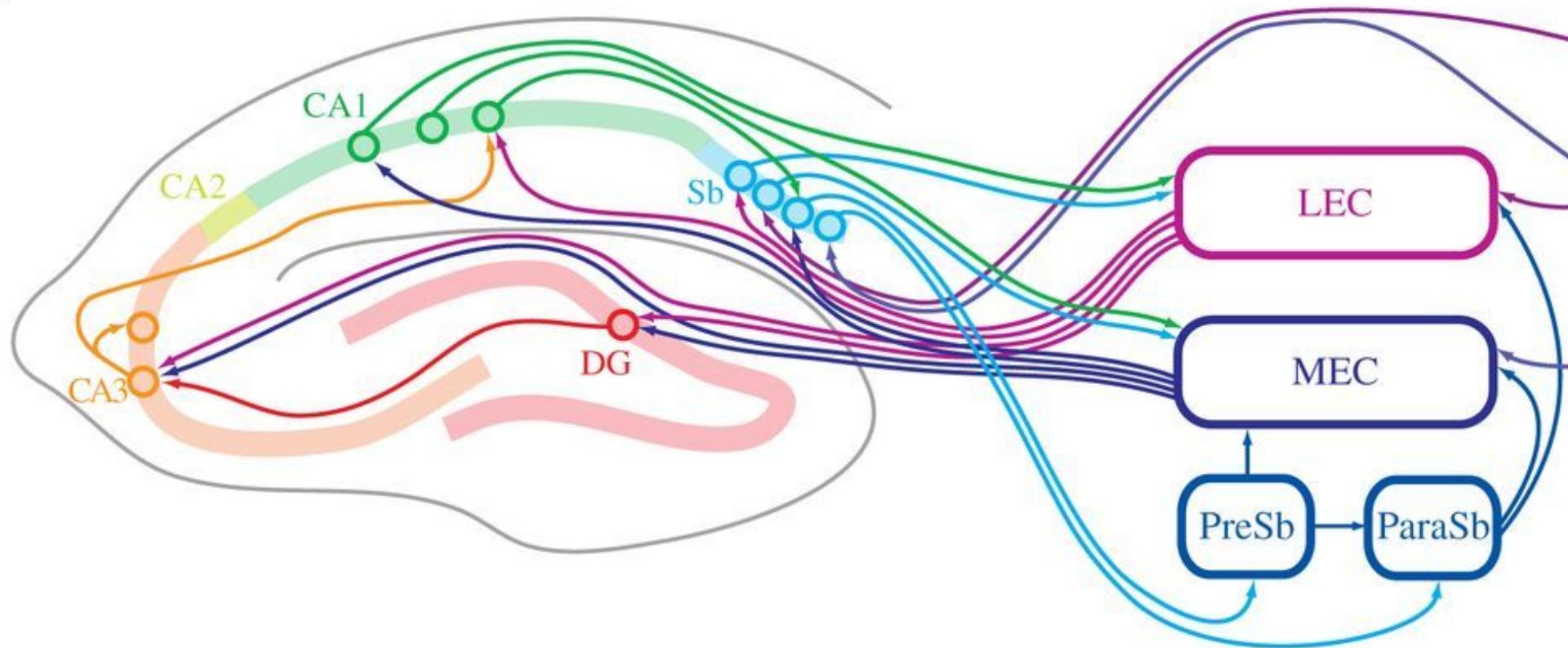
&  $\Theta$  mods hippocampal

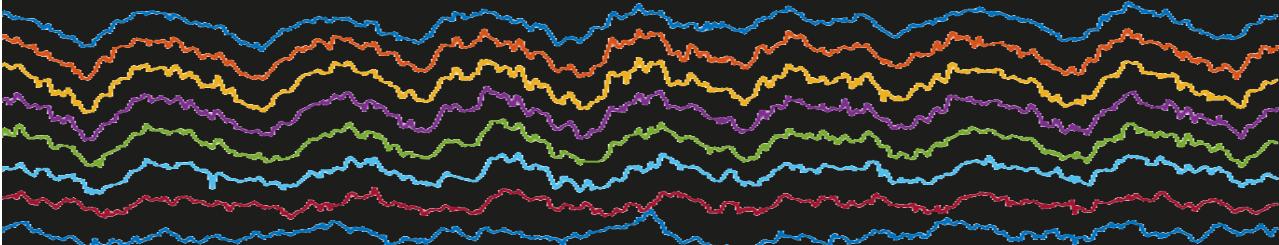
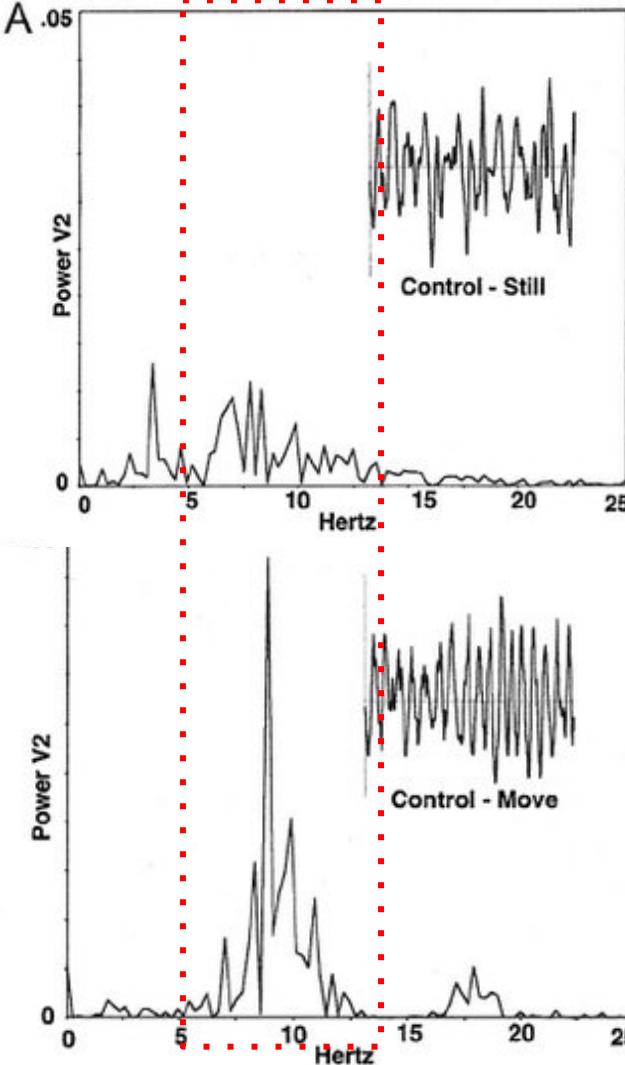
modes



Encoding

Retrieval





## HPC/EC Theta Rhythms

6-12 Hz

Prominent during locomotion and REM sleep

Enhanced learning during theta

Cholinergic neurons show this rhythmic firing

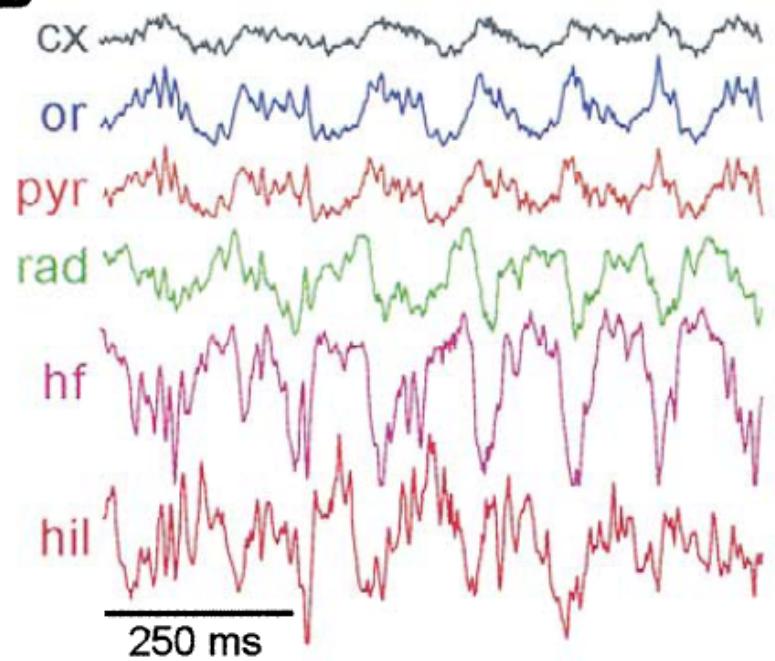
-> enhanced LTP mech?

No MS, no theta

Lesions impair T-Maze performance

LTP correlation



**B**

## HPC/EC Gamma Rhythms

Fast gamma (~65 - 120 Hz)

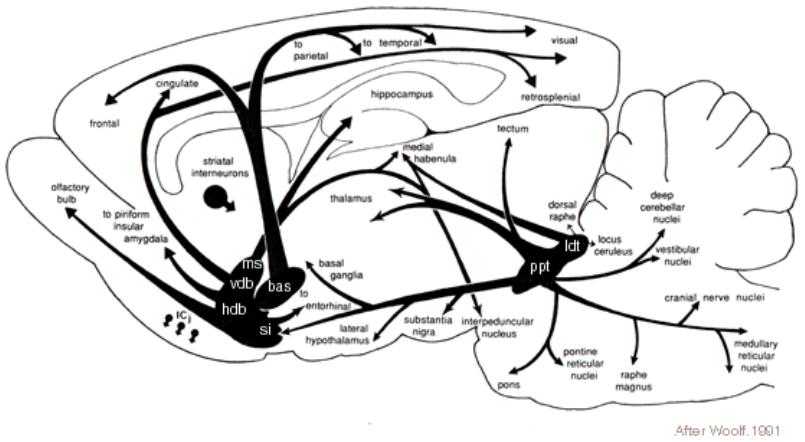
Can be correlated regionally:

Slow gamma (~30 - 65 Hz)

Fast Gamma = EC

Mid gamma?

Slow Gamma = CA3



## HPC/EC ACh

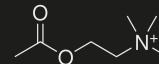
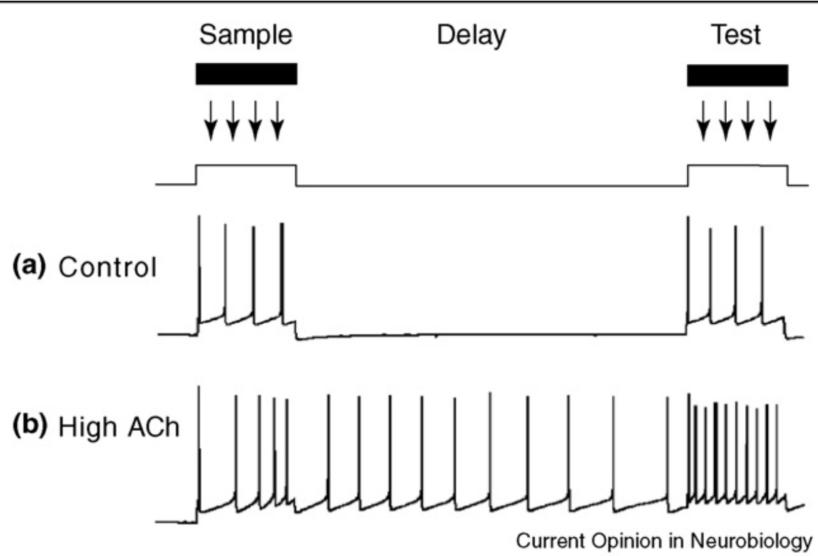
Medial septum projections via fornix

High levels correlate with alertness

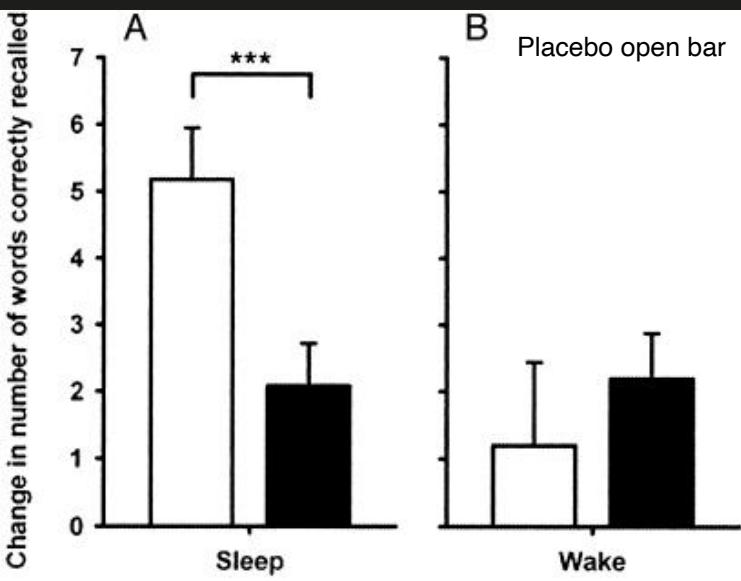
-> ACh sleep levels are  $\sim\frac{1}{3}$  of waking

Persistent activation of neurons

-> Enhances LTP  $\sim 30\%$



hasselmo 2006;



## HPC/EC ACh Evidence

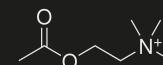
Donepezil for Alzheimer's

Blocking effects encoding (but not recall)

-> scopolamine

-> ↑ACh impairs consolidation

-> ↓ACh improves consolidation



hasselmo 2006; rasch et al. 2006; atri 2004

(a) High ACh

(b) Low ACh

Input

Nicotinic  
enhancement

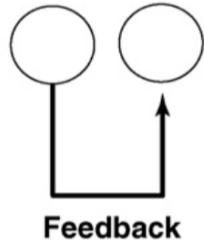
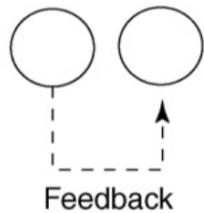
Input

HPC/EC ACh

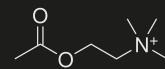
Suppress feedback mechanisms (CA3)

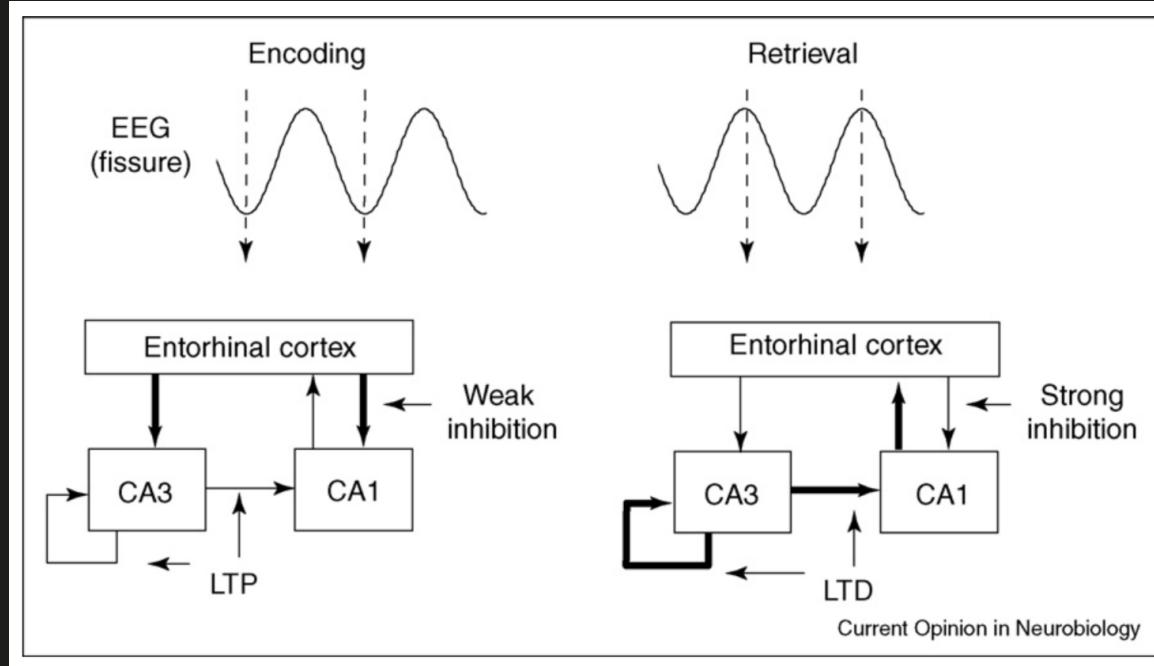
Effect found throughout the brain

Muscarinic  
suppression



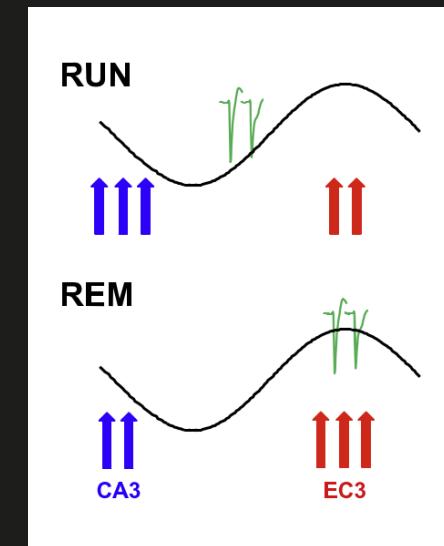
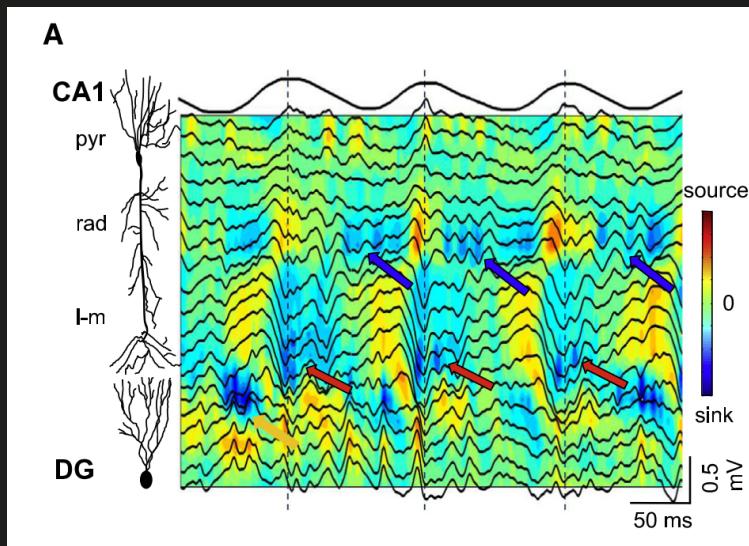
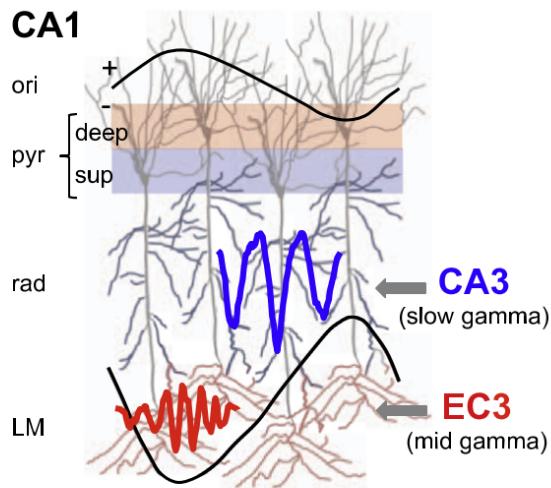
Current Opinion in Neurobiology





## HPC/EC Theta Model

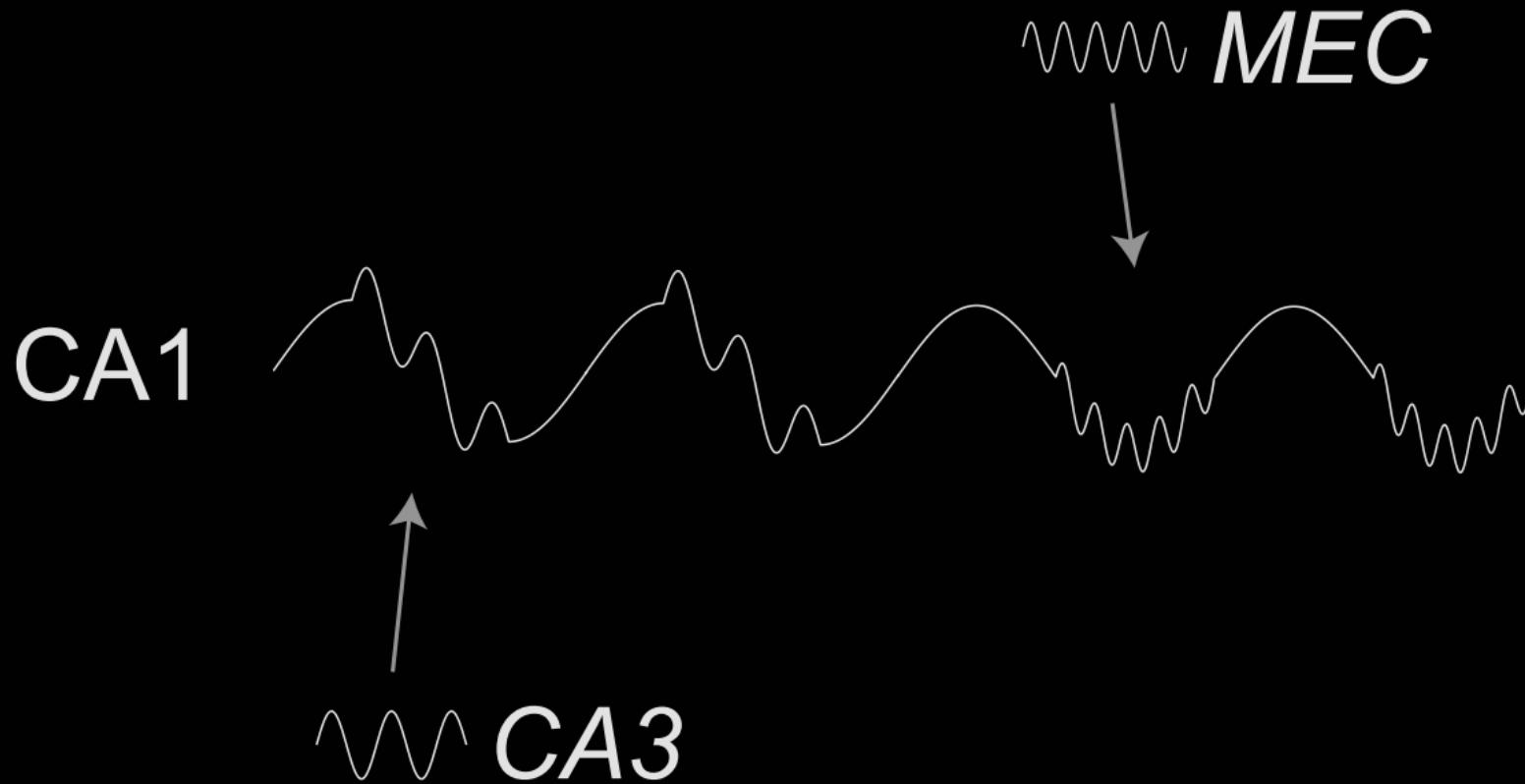
# In vivo evidence of E/R in hippocampus?



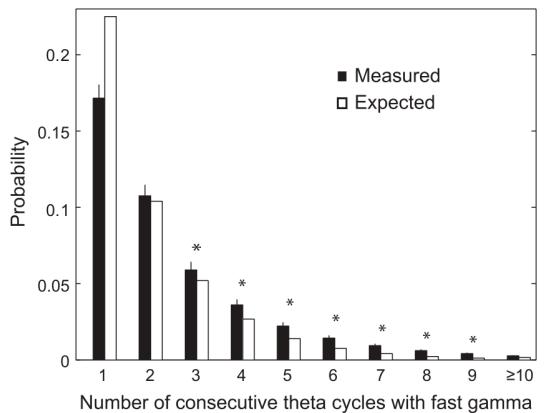
Recording from CA1 and CA3 or CA1 and EC, specific gamma epochs from each region can be correlated with different phases of theta

Slow gamma CA3 (40 -60 Hz) & Fast gamma EC3 (60 - 120 Hz)

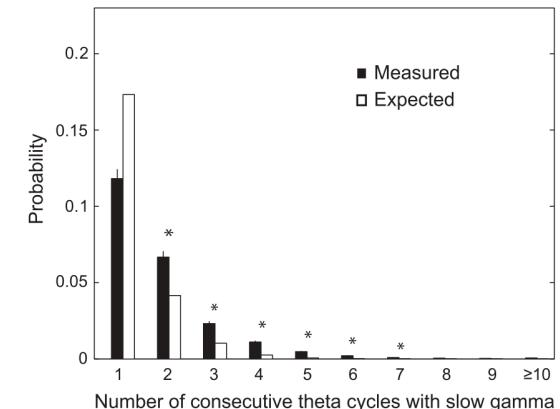
In vivo evidence?



## Fast gamma



## Slow gamma



# Problems

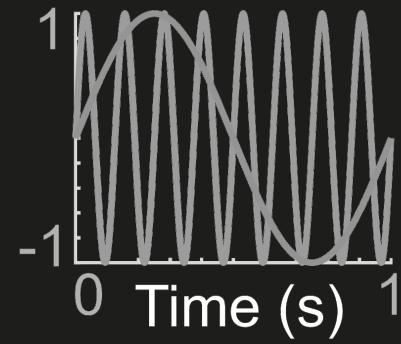
Similar mechs, different time scales: 10's of ms vs 100's of ms

theta model predicts that ENC and RET occur on each cycle

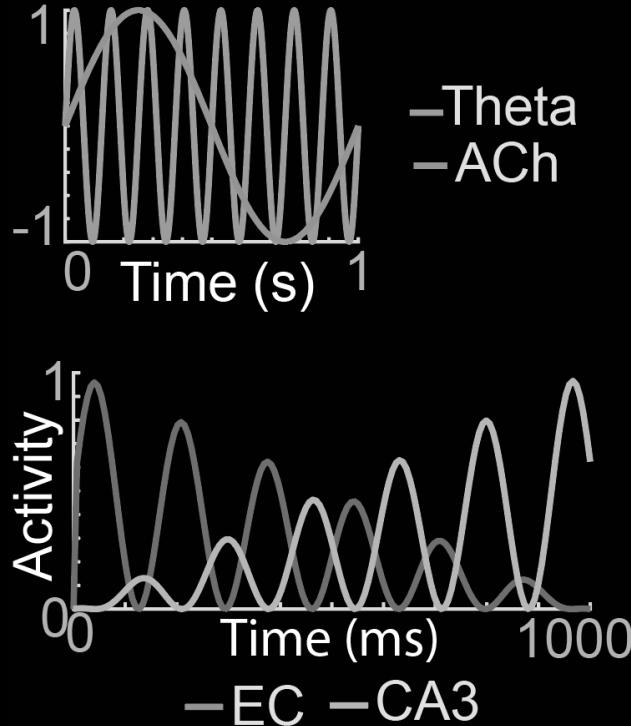
- > colgin data disagree
- > also CA3 on descending phase, not peak

MS mechanism?

OLM story?

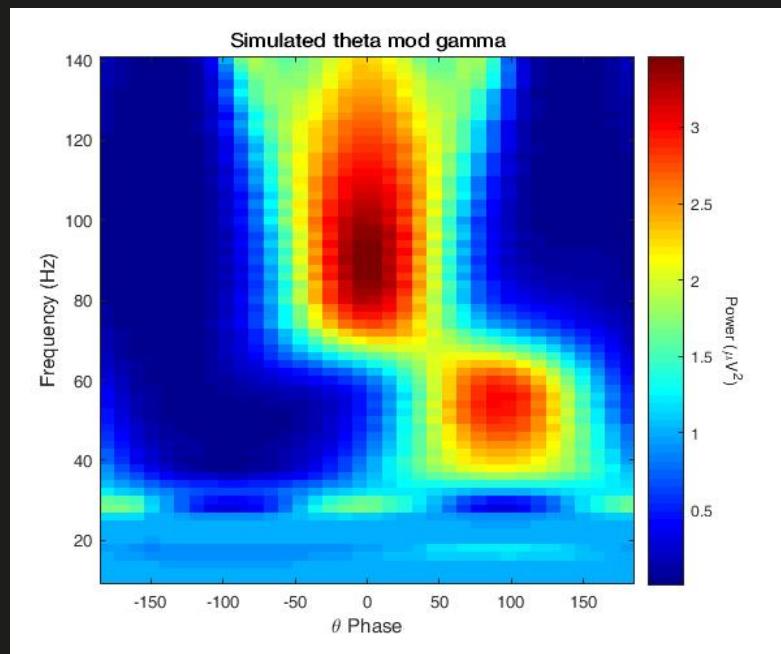
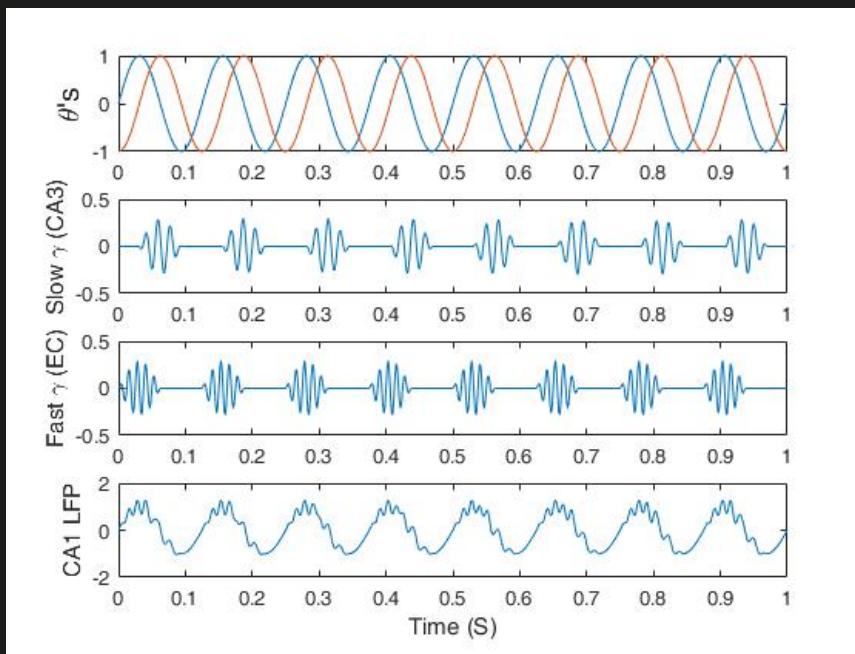


## Possible explanation



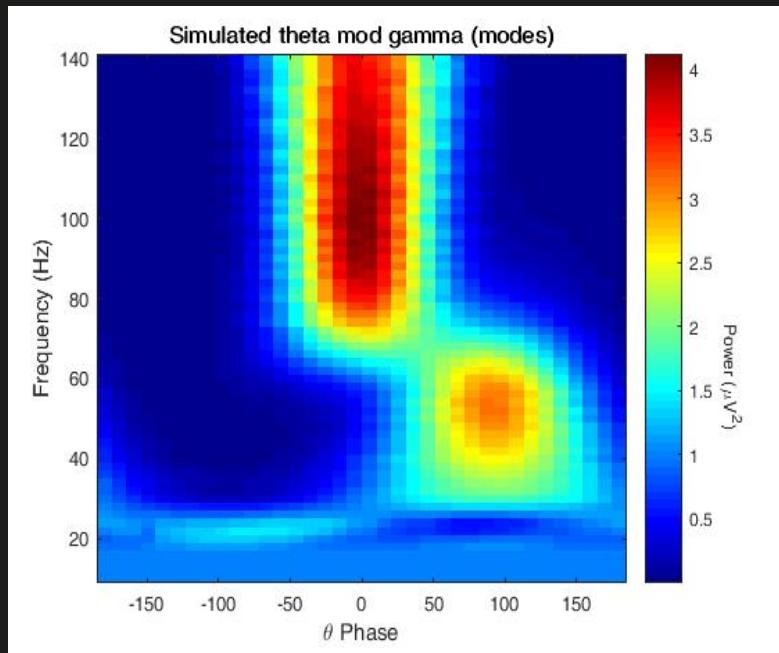
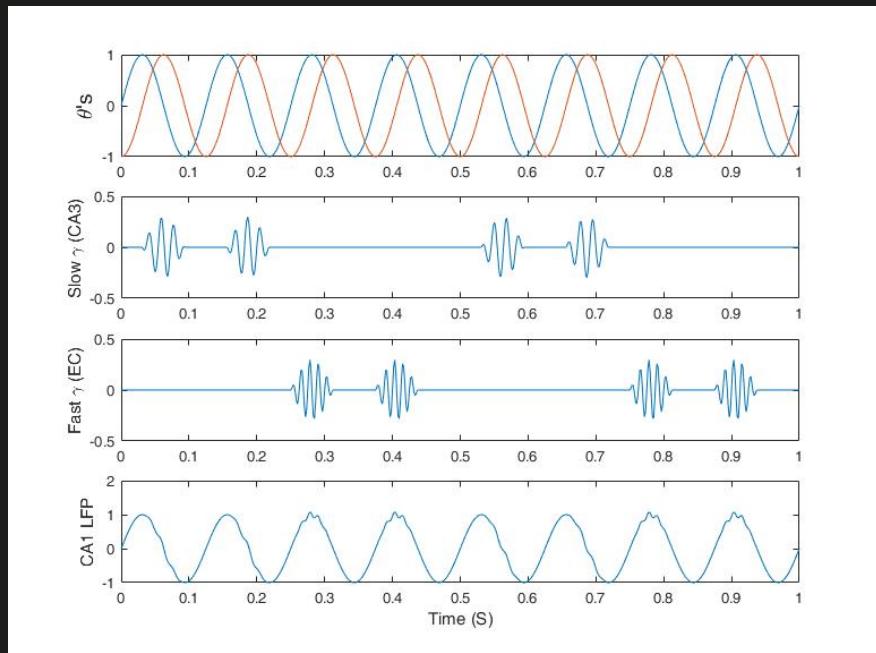
Hypothesis: That EC and CA3 dynamics which constitute the gamma oscillations observed are governed by Ach

# Possible explanation



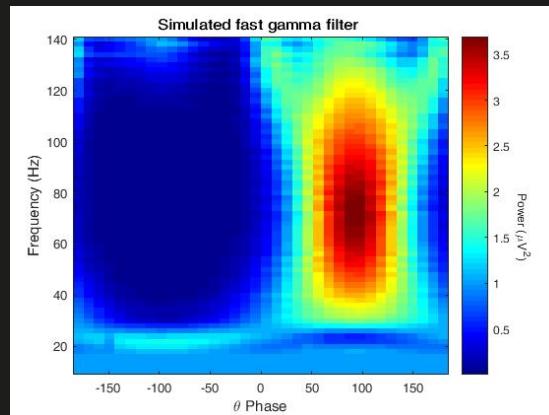
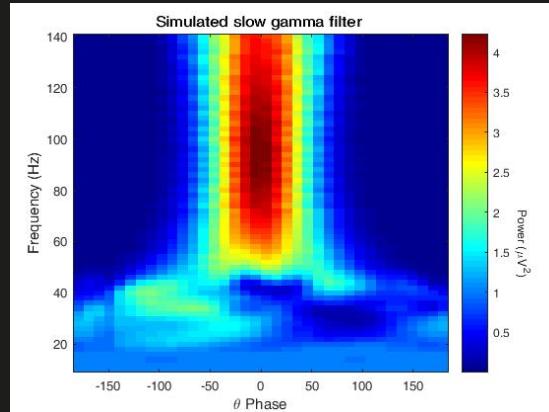
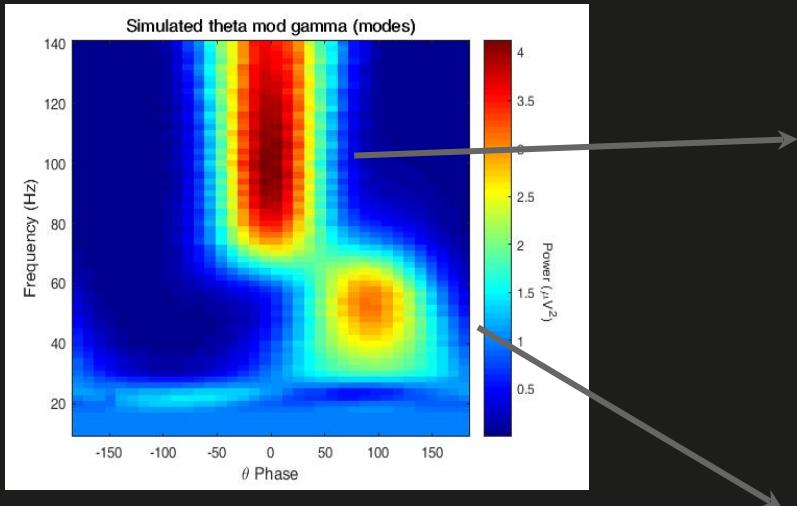
Theta Model Prediction

# Possible explanation



Modes Model Prediction

# Possible explanation



Filter for cycles with only high gamma  
or low gamma present

Plot whole cycle



A fluorescence micrograph showing two distinct brain regions highlighted by white outlines against a dark blue background. The upper region is labeled 'CA1' and the lower region is labeled 'CA3'. The background shows a dense network of blue-stained cellular structures.

CA1

(EC)

CA3

CA1

(MS)

(EC)

CA3

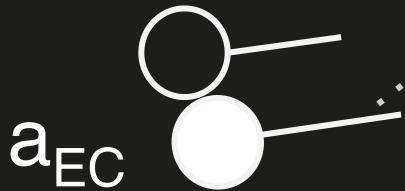
(MS)

CA1

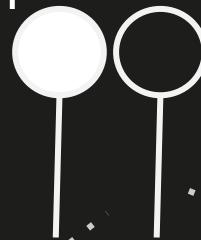
(EC)

CA3

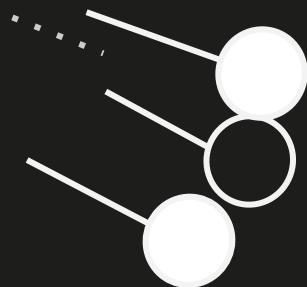
(MS)



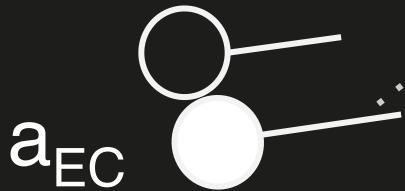
$a_{CA1}$



$a_{CA3}$



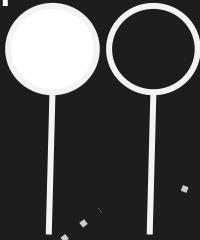
(MS)



$a_{EC}$

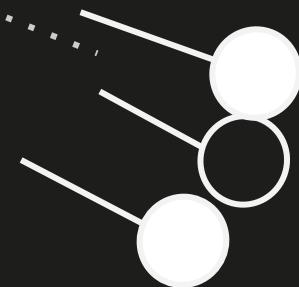
$W_{EC}$

$a_{CA1}$



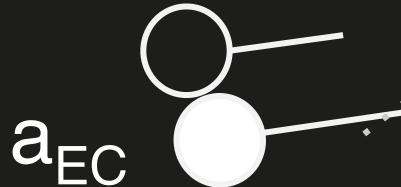
$W_{CA3}$

$a_{CA3}$



(MS)

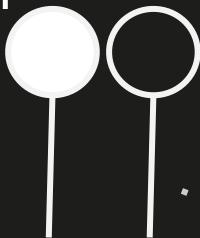
$\Theta_{EC}$



$a_{EC}$

$W_{EC}$

$a_{CA1}$



3

$\Theta_{LTP}$



$a_{CA3}$

$W_{CA3}$

## The theta model

$$a_{CA1}(t) = \theta_{EC}(t)W_{EC}a_{EC}(t) + \theta_{CA3}(t)W_{CA3}(t)a_{CA3}(t)$$

$$W_{CA3}(t+n) = W_{CA3}(t) + \sum \int_t^{t+n} \theta_{LTP} a_{CA1}(t) a_{CA3}(t)^T dt$$

## The theta model

$$\theta_{LTP}(t) = \sin(t + \phi_{LTP})$$

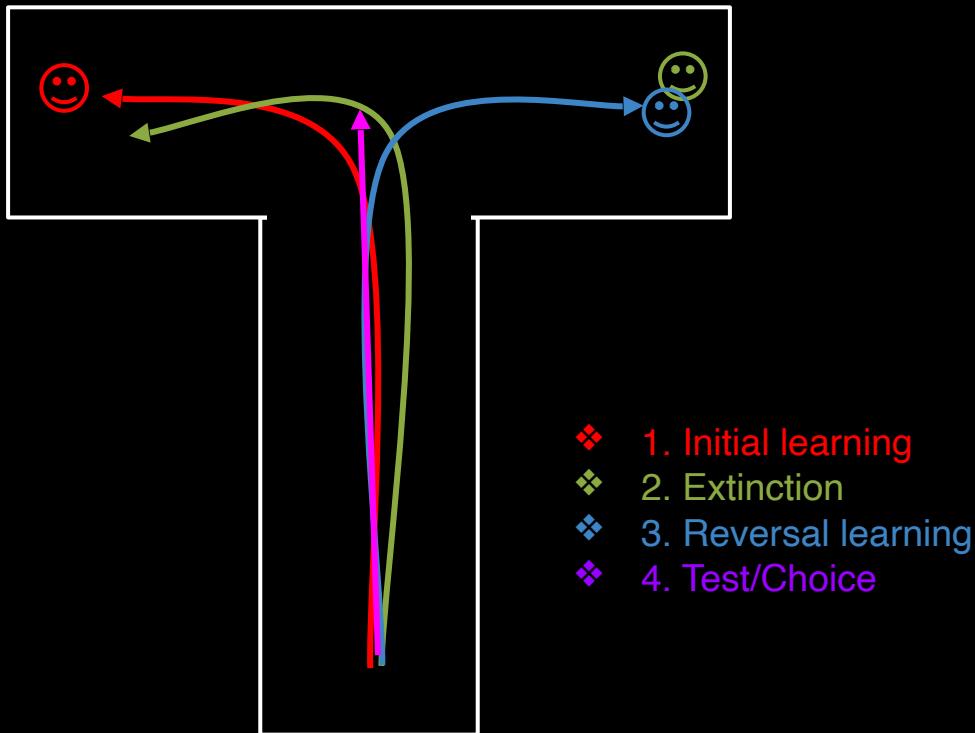
$$\theta_{EC}(t) = (X/2) \sin(t + \phi_{EC}) + (1 - X/2), (0 < X < 1)$$

$$\theta_{CA3}(t) = (X/2) \sin(t + \phi_{CA3}) + (1 - X/2), (0 < X < 1)$$

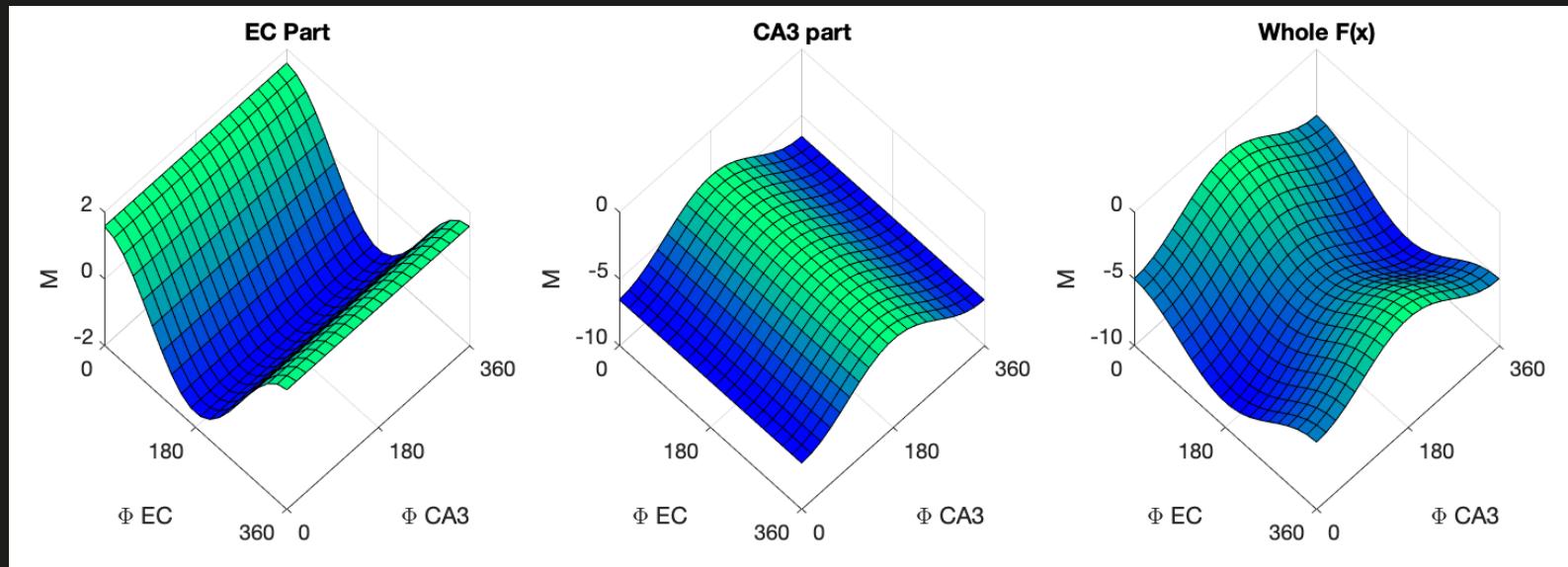
$$a_{CA1}(t) = \theta_{EC}(t)W_{ECA}a_{EC}(t) + \theta_{CA3}(t)W_{CA3}(t)a_{CA3}(t)$$

$$W_{CA3}(t+n) = W_{CA3}(t) + \sum \int_t^{t+n} \theta_{LTP} a_{CA1}(t) a_{CA3}(t)^T dt$$

# Model Task

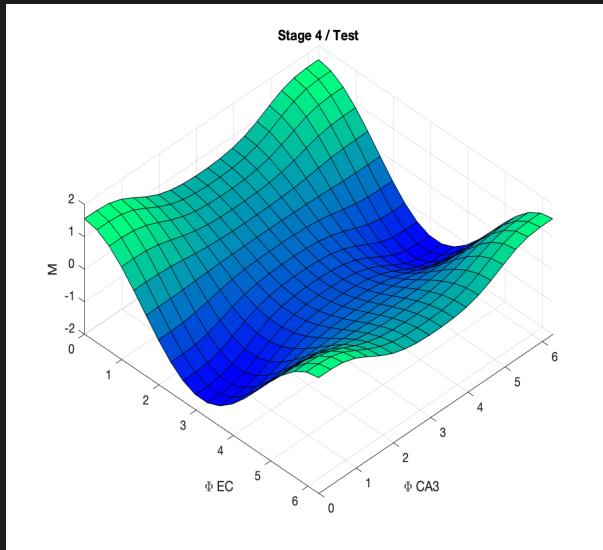


## theta model performance (analytical)



$$M = (I/2)\pi \cos(\phi_{LTP} - \phi_{EC}) - K - (I/2)\pi \cos(\phi_{LTP} - \phi_{CA3})$$

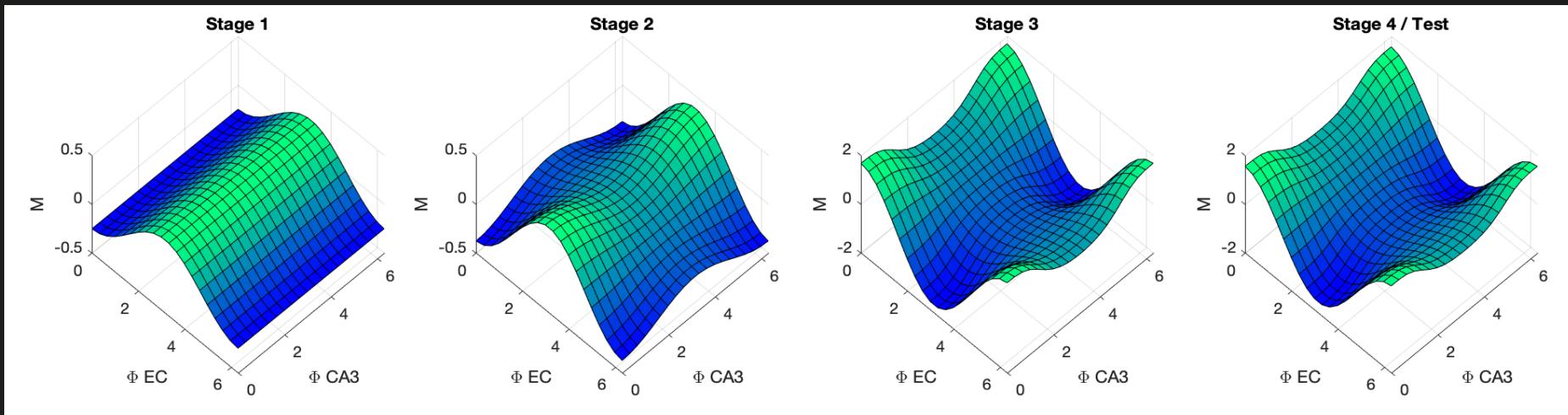
## theta model performance (computational)



Similar, but output is not the same

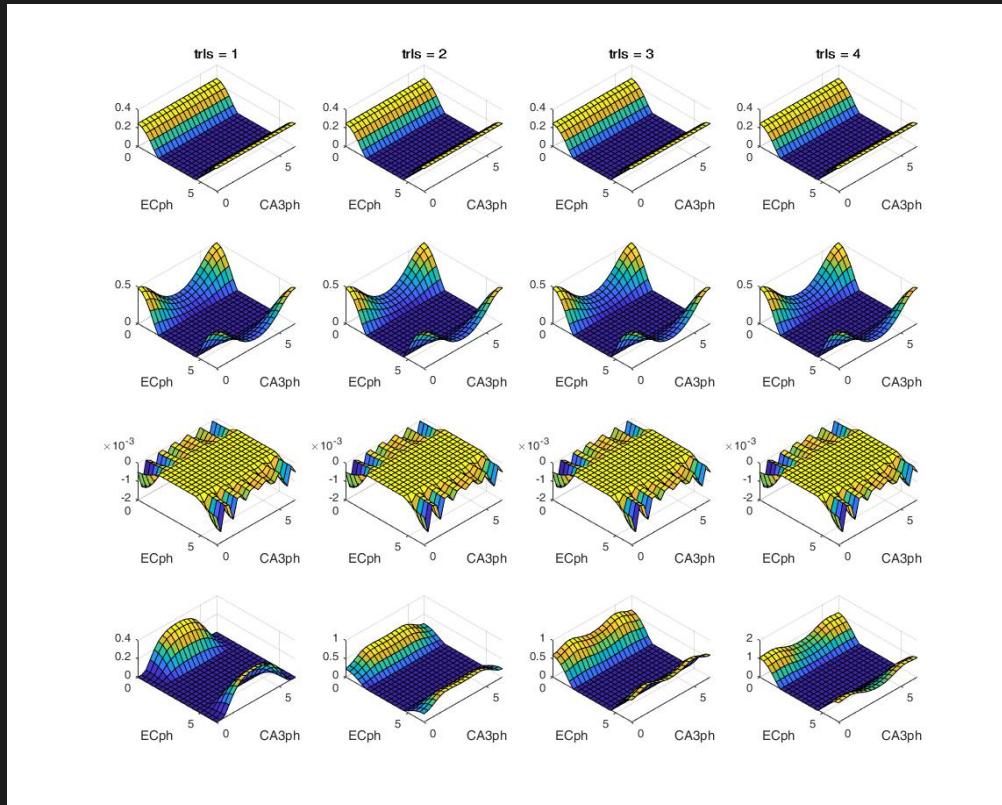
Analytical solution may not suffice

## theta model performance (computational)



Breaking the metric down by task aids understanding

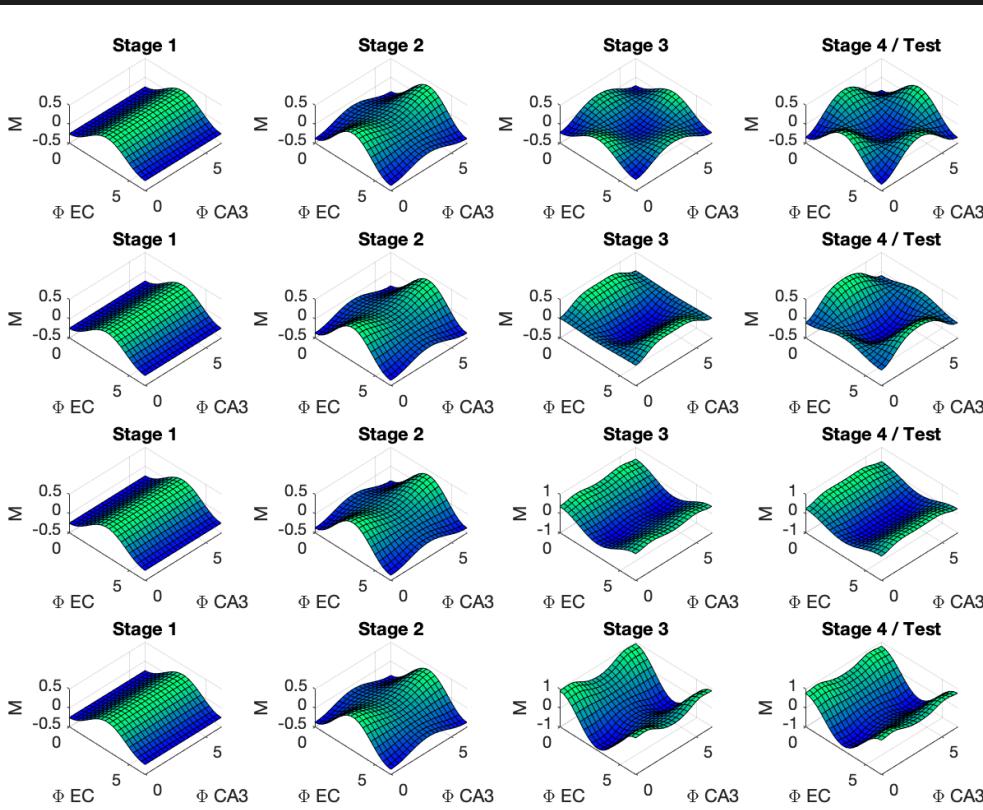
# theta model performance (computational)



Is it a coding bug? Probably not\*

\*But it is coding

# theta model performance (computational)



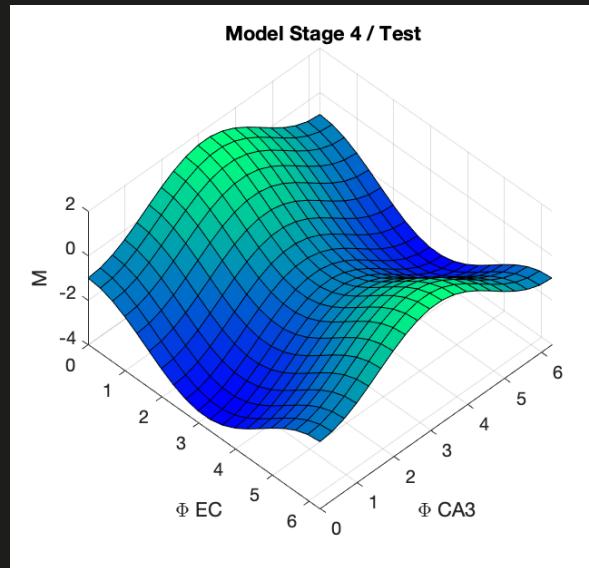
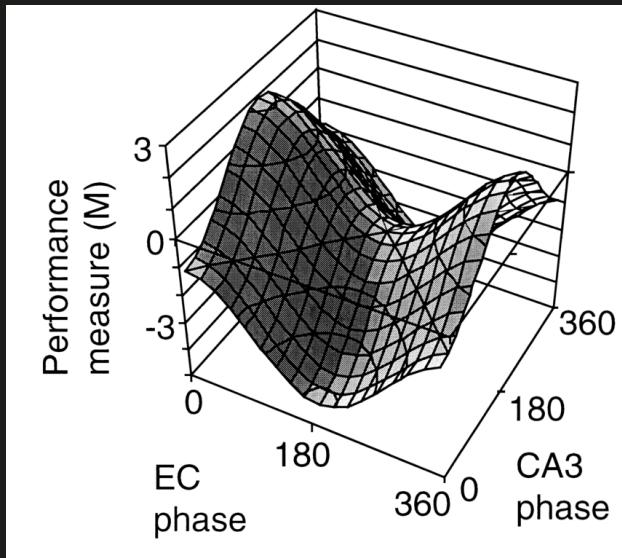
Trial iteration drastically alters dynamics

(Highly unstable)

In its current form, may not be meant to be solved dynamically

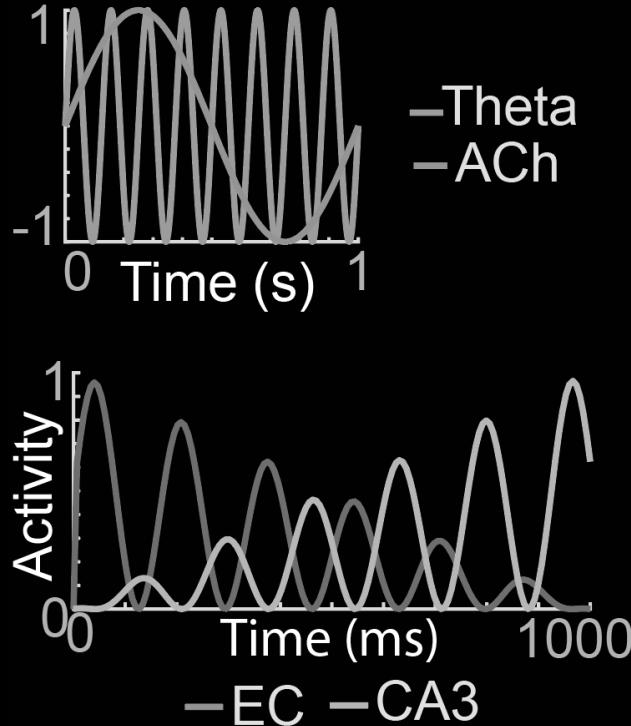
(Each row increased trial count)

# The theta model



Adding weights at the end solves the model

## Possible explanation



Hypothesis: That EC and CA3 dynamics which constitute the gamma oscillations observed are governed by Ach

(MS)

$a_{CA1}$

$W_{CA3}$

$\Theta_{LTP}$

$W_{EC}$

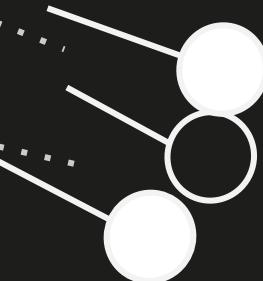
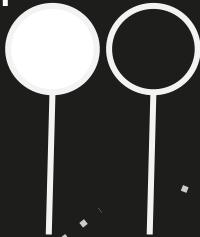
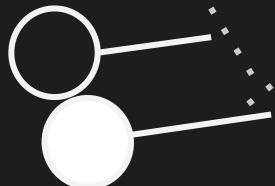
$a_{EC}$

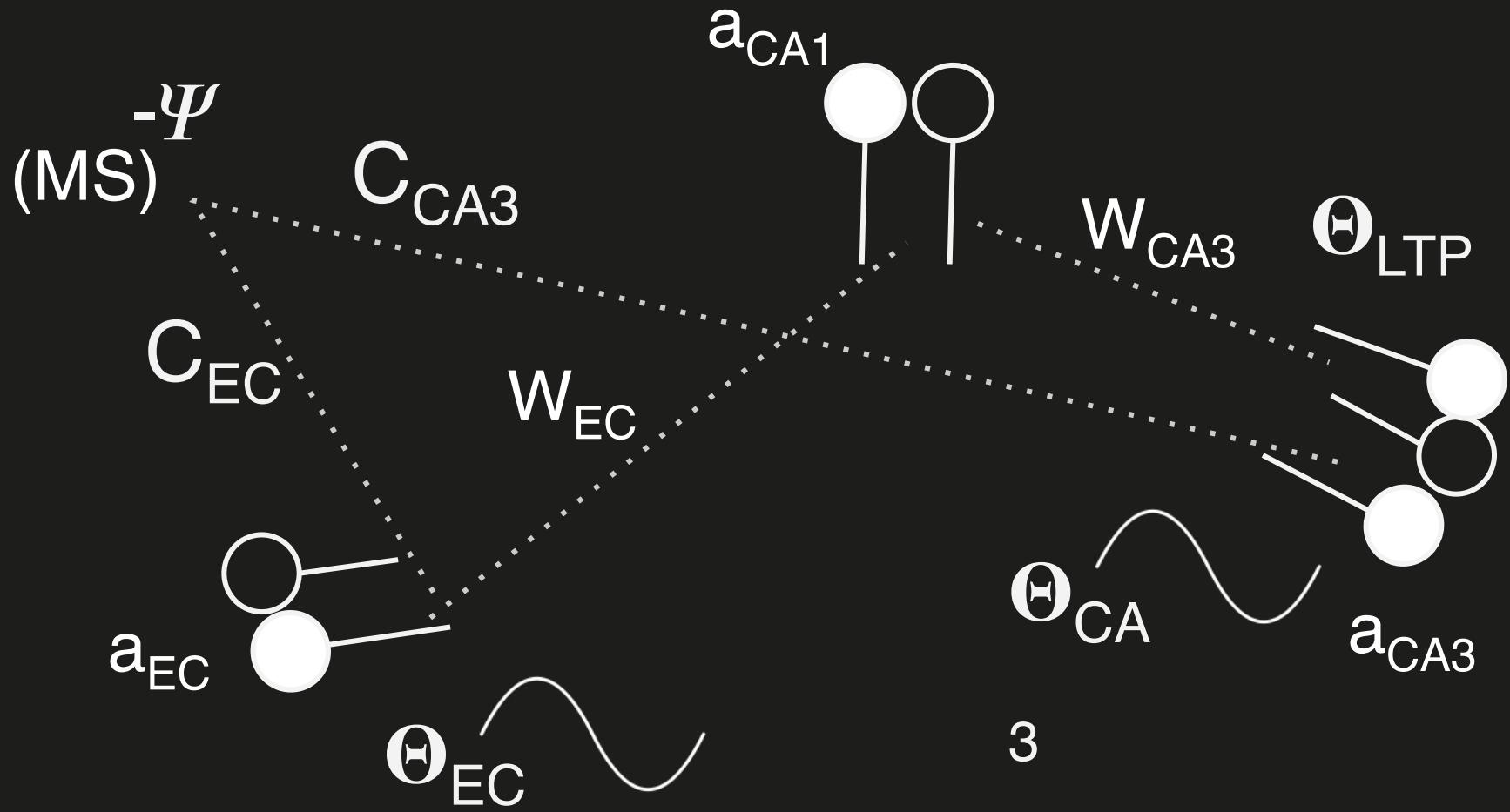
3

$\Theta_{CA}$

$a_{CA3}$

$\Theta_{EC}$





## The theta model

$$a_{CA1}(t) = \theta_{EC}(t)W_{EC}a_{EC}(t) + \theta_{CA3}(t)W_{CA3}(t)a_{CA3}(t)$$

$$W_{CA3}(t+n) = W_{CA3}(t) + \sum \int_t^{t+n} \theta_{LTP} a_{CA1}(t) a_{CA3}(t)^T dt$$

## The theta+ACh model

$$syn_{EC}(t) = (1 - \Psi(t) * C_{EC})\theta_{EC}(t)W_{EC}a_{EC}(t)$$

$$syn_{CA3}(t) = (1 - \Psi(t) * C_{CA3})\theta_{CA3}(t)W_{CA3}a_{CA3}(t)$$

$$a_{CA1}(t) = syn_{EC}(t) + syn_{CA3}(t)$$

$$\psi(t) = \frac{1}{1 + e^{-t}}$$

$$\theta_{LTP}(t) = \sin(t + \phi_{LTP})$$

$$\theta_{EC}(t) = (X/2) \sin(t + \phi_{EC}) + (1 - X/2), (0 < X < 1)$$

$$\theta_{CA3}(t) = (X/2) \sin(t + \phi_{CA3}) + (1 - X/2), (0 < X < 1)$$

## The theta+ACh model

$$syn_{EC}(t) = (1 - \Psi(t) * C_{EC})\theta_{EC}(t)W_{EC}a_{EC}(t)$$

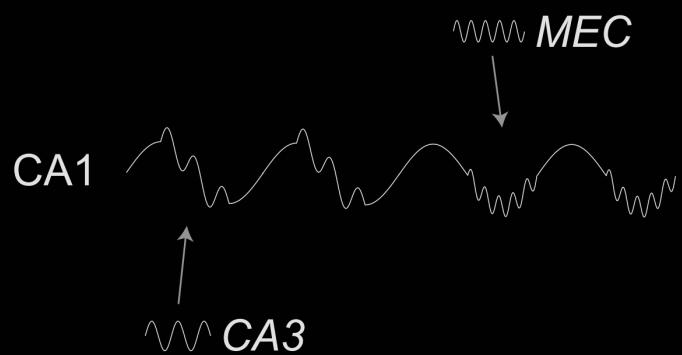
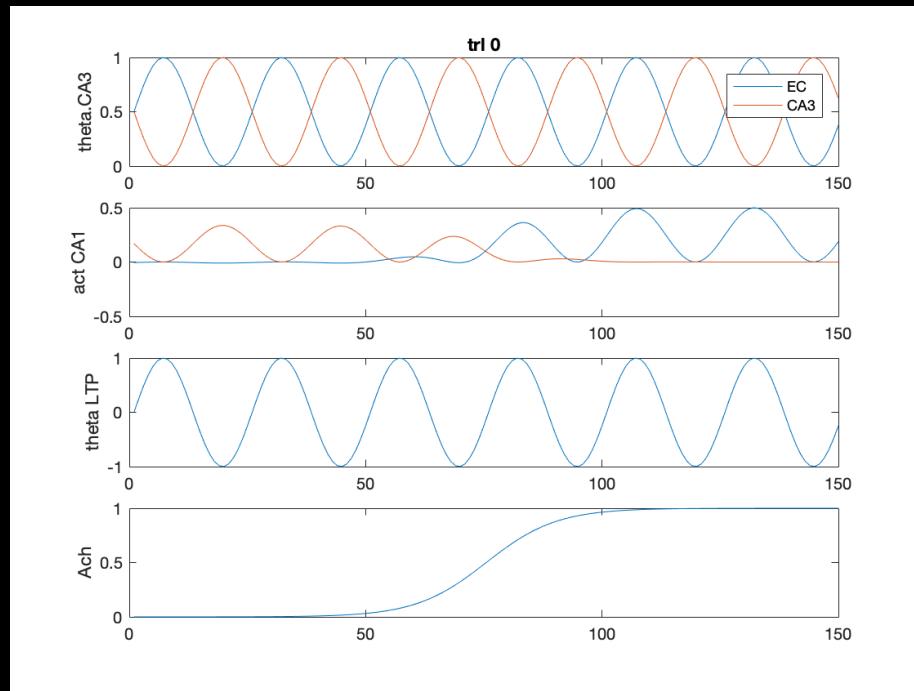
$$syn_{CA3}(t) = (1 - \Psi(t) * C_{CA3})\theta_{CA3}(t)W_{CA3}a_{CA3}(t)$$

$$a_{CA1}(t) = syn_{EC}(t) + syn_{CA3}(t)$$

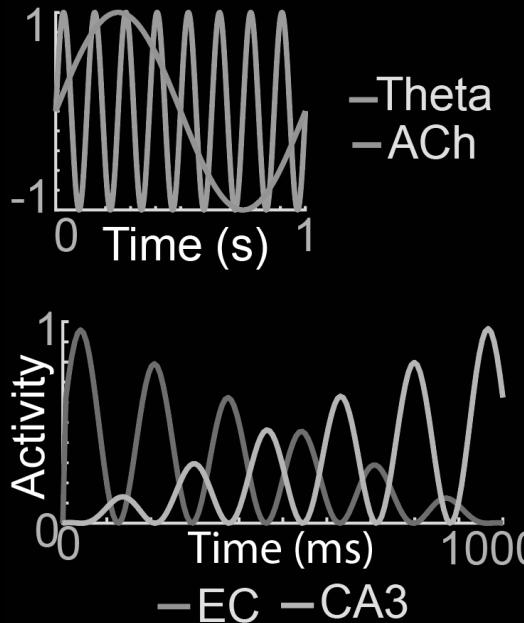
$$\psi(t) = \frac{1}{1 + e^{-t}}$$

$$W_{CA3}(t+n) = W_{CA3}(t) + \sum \int_t^{t+n} \theta_{LTP} a_{CA1}(t) a_{CA3}(t)^T dt$$

# The theta+ACh model



## ACh mods modes?

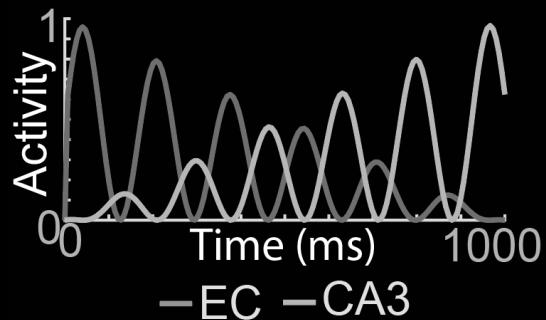
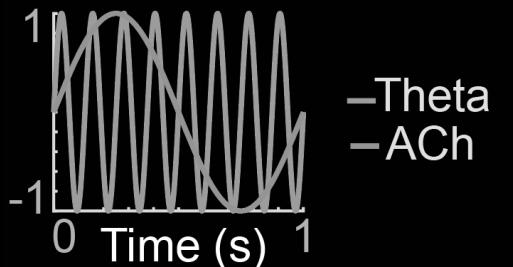


Hypothesis: That EC and CA3 dynamics which constitute the gamma oscillations observed are governed by Ach

Maybe. But in the simplest form it is only purely theoretical.

A different source of inhibition, interneurons, OLM cells could be a primary target for analysis

## Some final thoughts



Hypothesis: That EC and CA3 dynamics which constitute the gamma oscillations observed are governed by Ach

Bonus finding: Hasselmo et al. may not be viable as a dynamical systems model

ACh may play a role in E/R dynamics and mode switching. However more work needs to be done.

# Some final thoughts



Thank you

Dr. Ehren Newman, Dr. Josh Brown, Dr. John  
Beggs

All my past professors in and out of the classroom  
on and off campus

Family, Friends

The rats

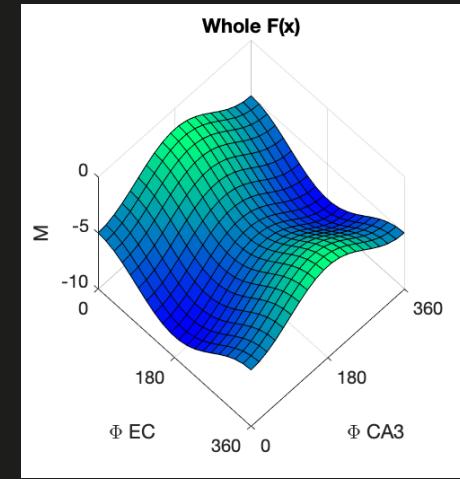
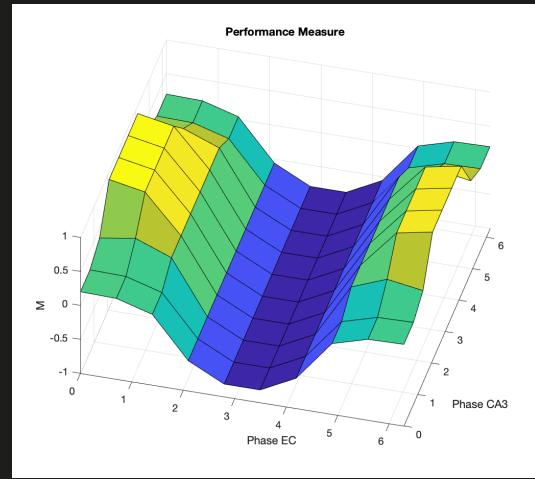
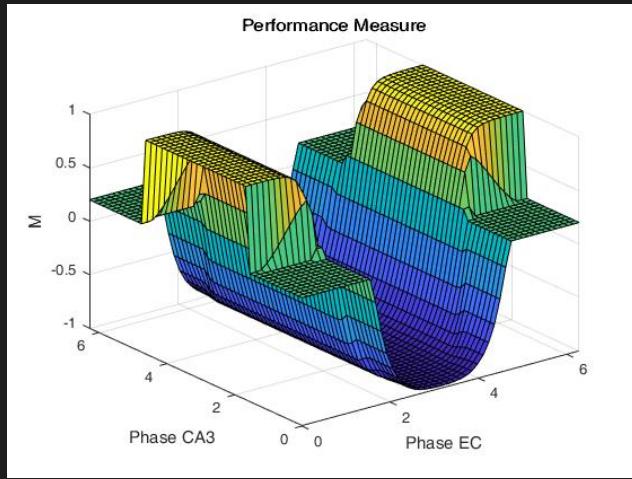
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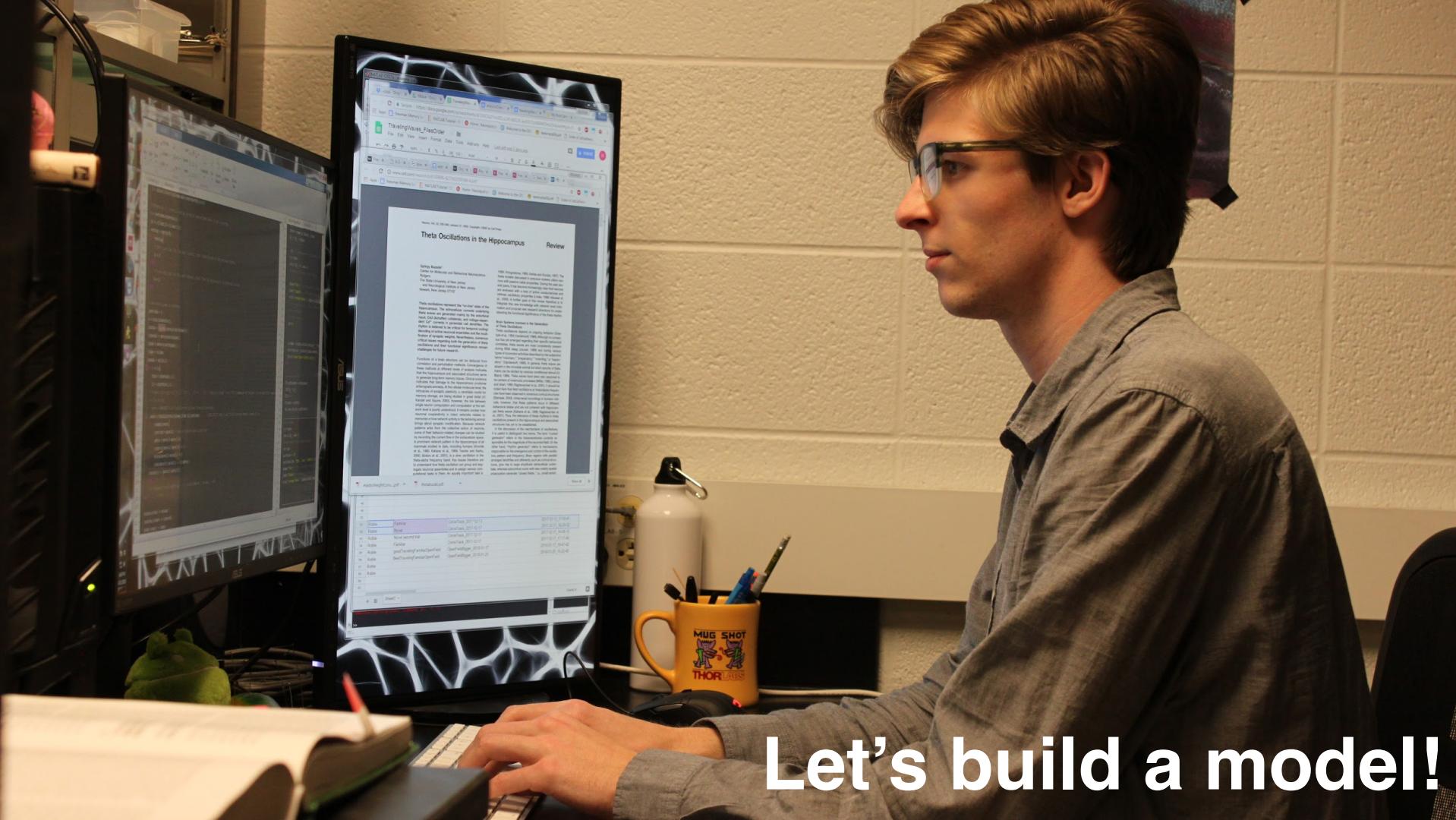
CA3

EC



# Iterations of knowledge





Let's build a model!