The uniquely human hippocampus? A high resolution perspective

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Case example

5.26pm I DO LIVE!!!!

Saturday 13
Week 2 · 13-352

7.46am I WAKE FOR THE FIRST ~~CONSCIOUS~~ TIME.
7.47am THIS ILLNESS HAS BEEN LIKE DEATH TILL NOW ALL SENSES WORK
— " — FIRST THOUGHT: I LOVE DARLING DEBORAH FOR EVER. OUR FATHER
7.51am FIRST CONSCIOUS STROLL.
8.07am I AM ~~TOTALLY~~ ~~PERFECTLY~~ AWAKE. 1ST TIME. B'FAST
8.31am NOW I AM ~~REALLY~~ ~~COMPLETELY~~ AWAKE (~~1ST TIME~~). PATIENCE
8.35am TIME TO SEE RELAXING TV.
9.06am NOW I AM ~~PERFECTLY~~, ~~OVERWHELMINGLY~~ AWAKE (~~1ST TIME~~). 2ND STROLL.
9.34am NOW I AM ~~SUPERLATIVELY~~ ~~ACTUALLY~~ AWAKE (~~1ST TIME~~). LOO CALLS.
~~9.40am~~ NOW I AM ~~MAGNIFICENTLY~~, ~~PERFECTLY~~ AWAKE (~~1ST TIME~~). AFTER 1ST STROLL.
9.54am I AM ~~COMPLETELY~~ AWAKE WITH ~~THE~~ CUP OF COFFEE. PATIENCE.
~~10.08am~~ NOW I AM ~~TOTALLY~~, ~~MAGNIFICENTLY~~ AWAKE (~~1ST TIME~~).
10.38am TIME FOR FIRST STROLL + ? TV.
11.01am I AM ~~REALLY~~ SUPERLATIVELY, PERFECTLY AWAKE (1ST TIME). PATIENCE
11.03am FIRST THOUGHT — I LOVE DARLING DEBORAH FOR ETERNITY (1ST TIME) —
11.15am FIRST ~~CONSCIOUS~~ WALK
~~11.26am~~ NOW I AM PERFECTLY, COMPLETELY AWAKE (1ST TIME). ~~CONSCIOUS~~ WALK
11.37am I RETURN AND AWAITING 1ST COFFEE, PATIENTLY AND THINKING OF DEBORAH
11.45am 1ST CUP OF COFFEE ARRIVES — I LIVE FULLY AWAKE & I TASTES SUPERLATIVE
12.31pm AFTER LUNCH I AM ~~REALLY PERFECTLY~~ AWAKE (1ST TIME). PATIENCE.
12.54pm TIME FOR ~~1ST CONSCIOUS~~ WALK
1.[illegible]pm I AM REALLY SUPERLATIVELY, COMPLETELY AWAKE (1ST TIME).

Hippocampal memory deficit

- Loss of the continuity of consciousness--lost in time
- Described by human attributes: self-awareness, conscious recollection, reference to specific episodes, “declarative” implies a language component

These aspects of amnesia seem tied to uniquely human abilities- yet the HC is an old structure and very similar to that of rodents.

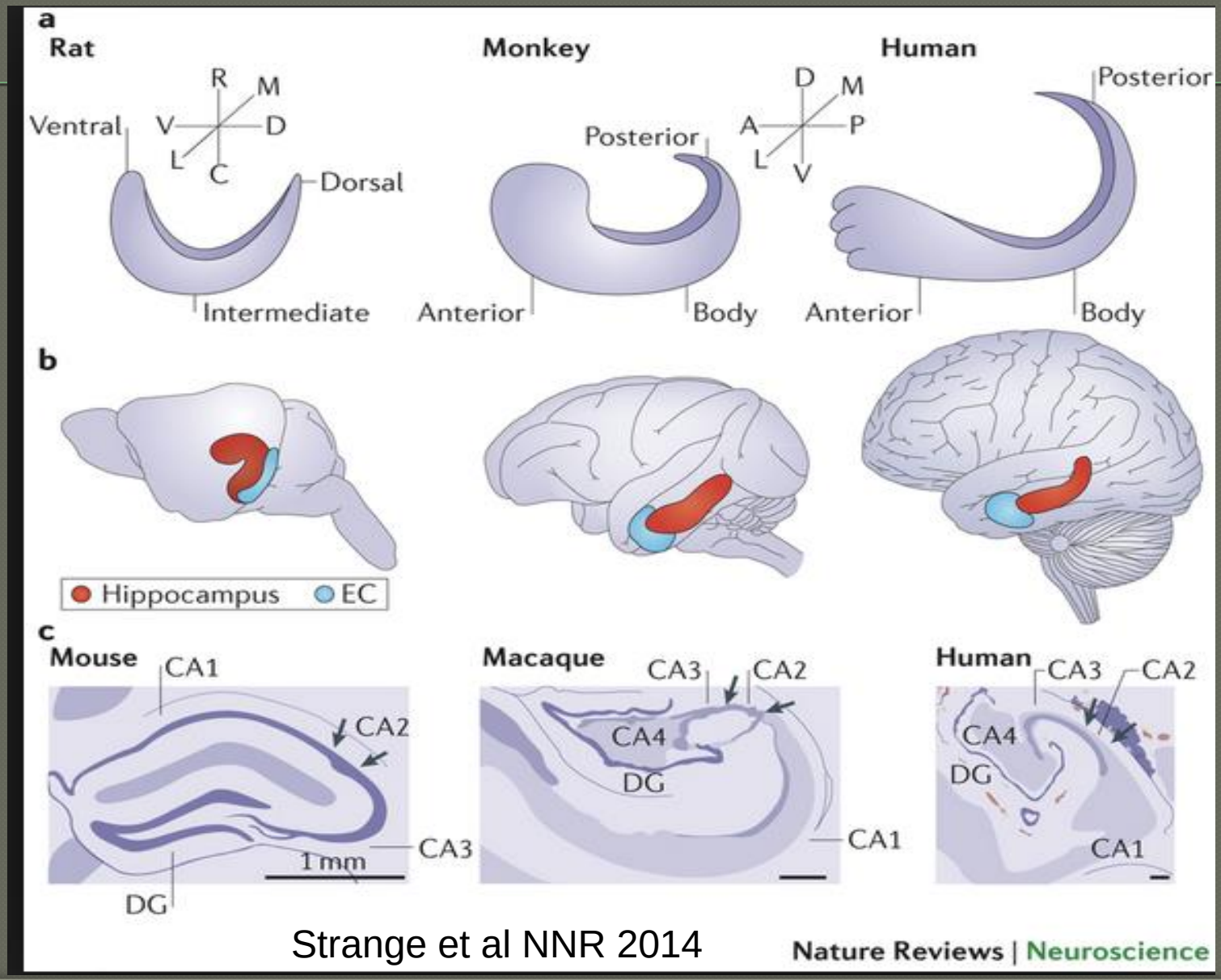
- Rodents: Novelty detection; navigation including cell-specific functions (place, grid, time cells); associative learning (food locations; fear acquisition)

Questions

- How can we reconcile the uniquely human characterization of episodic memory with rat HC function?
  - Hippocampal circuitry
  - High resolution fMRI of the human HC
  - Single unit recording in human HC
- If the HC is so critical to what makes us uniquely human, then why is the HC so vulnerable-encephalitis; anoxia; stress; seizures, aging?
  - These questions are not unrelated

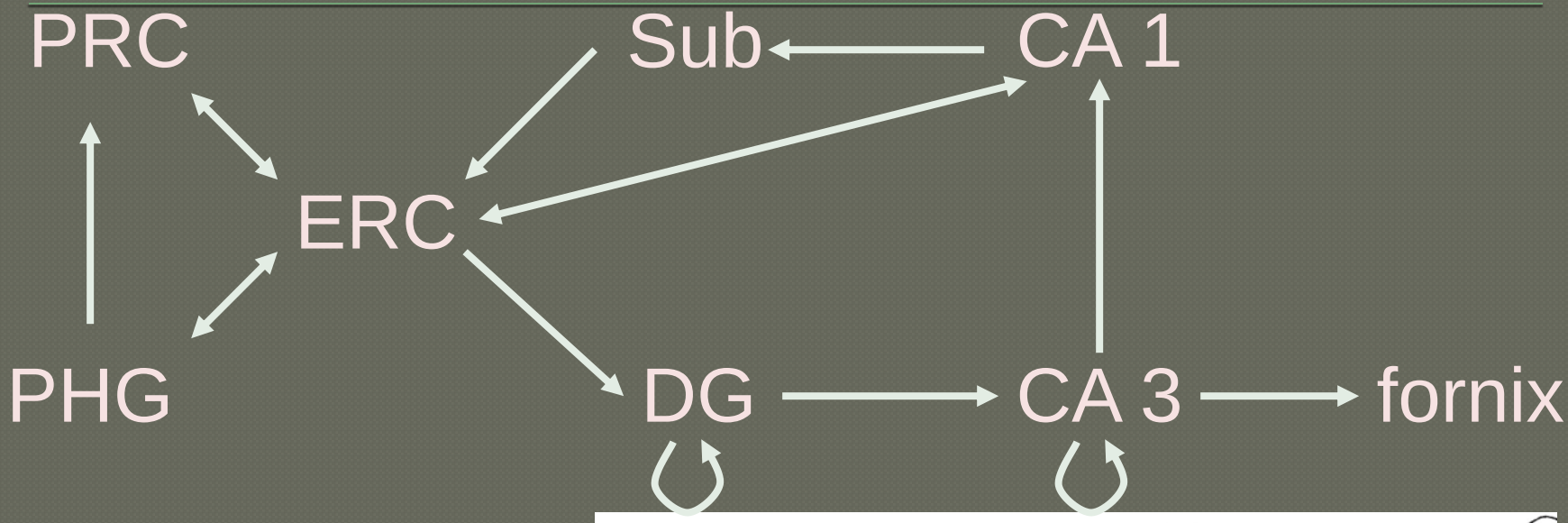
Hippocampal Circuitry

Architecture of the HC

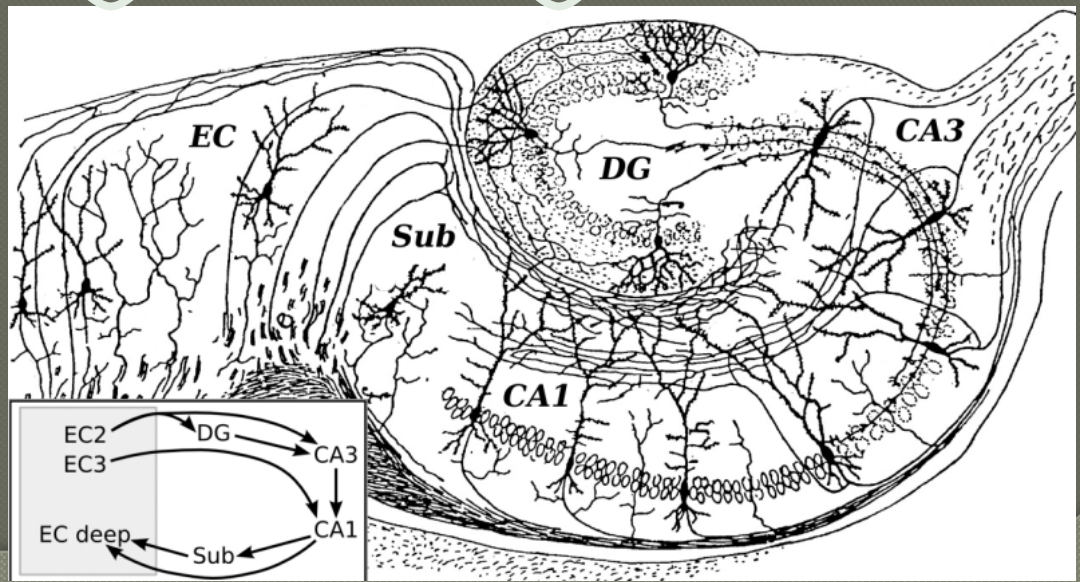


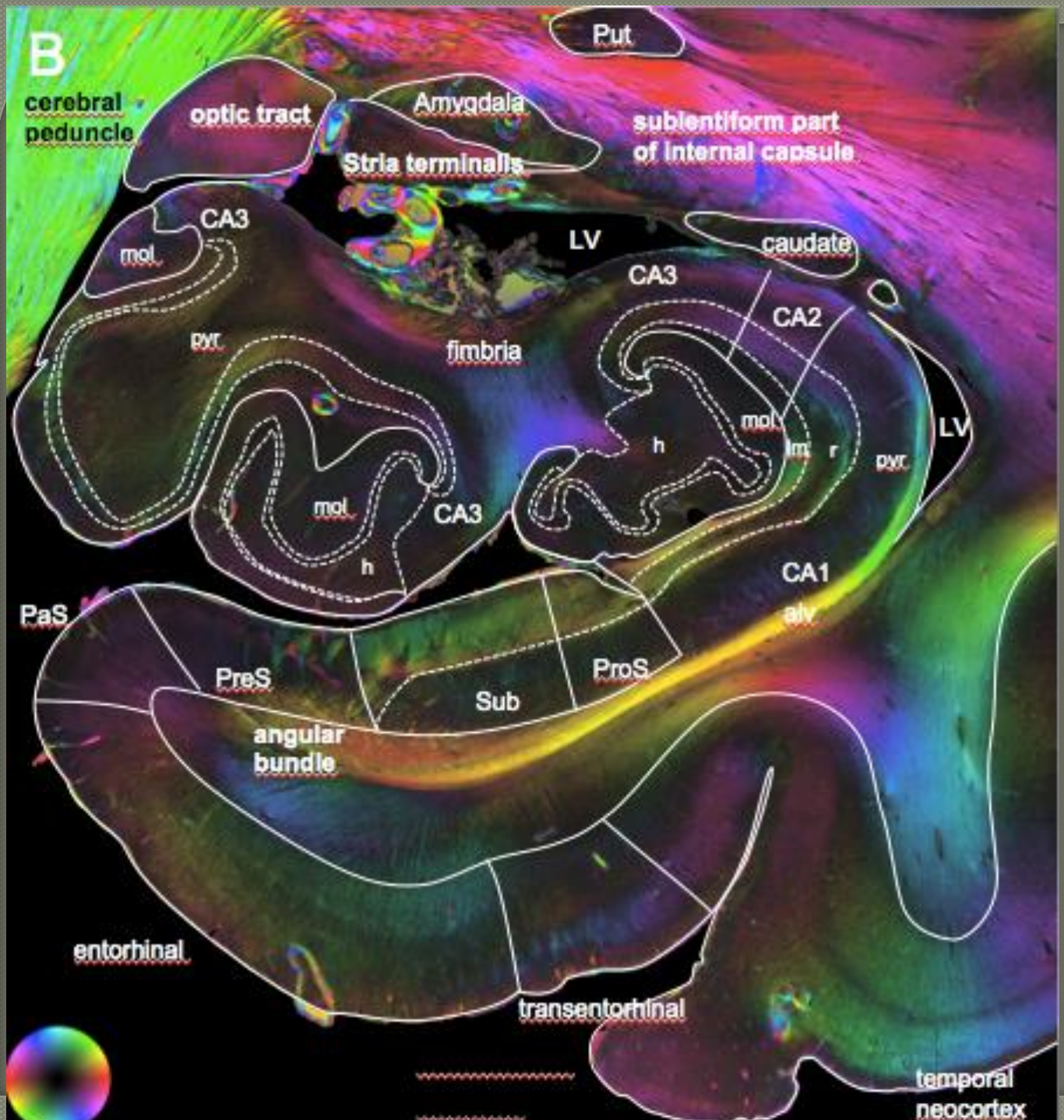
Strange et al NNR 2014

Hippocampal anatomy suggests functional heterogeneity



Based on tracer studies in monkeys, rats, and the cat.





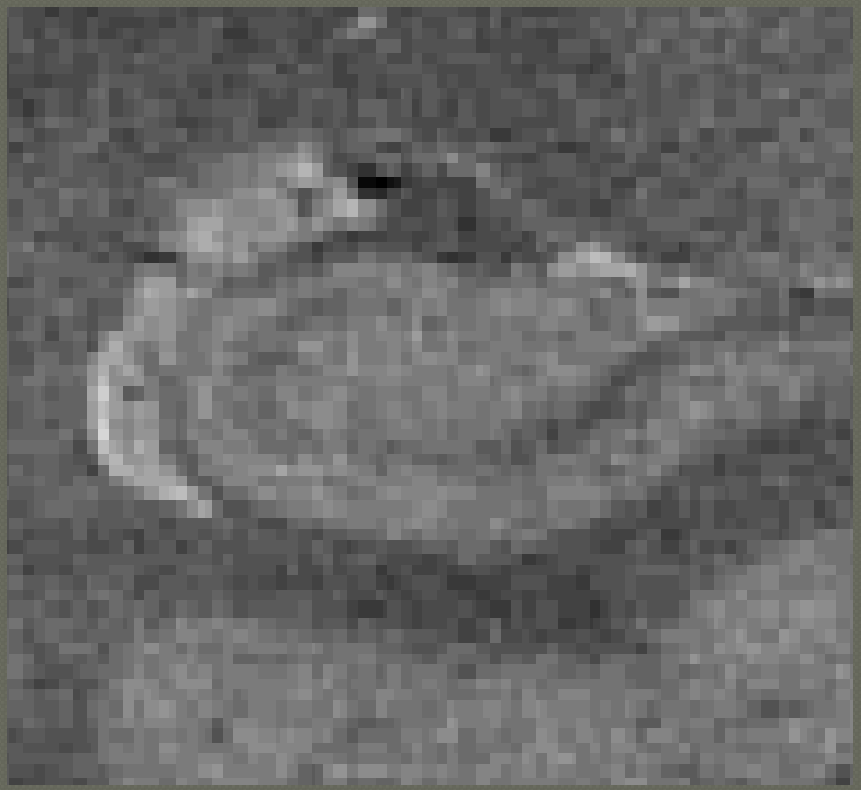
Michael Zeineh, MD. Ph.D.
Asst. Professor, Stanford

Cerebral Cortex, 2016

Using fMRI to examine hippocampal function

- Challenges
  - Functional heterogeneity within HC sub-regions -insufficient spatial resolution to resolve
  - HC has an oddly rolled architecture- “Jelly roll”

The hippocampus as Cinnabon



Smaller- need high resolution to visualize sub-regions
Unrolled- see functional patterns more readily

Little heterogeneity on long axis

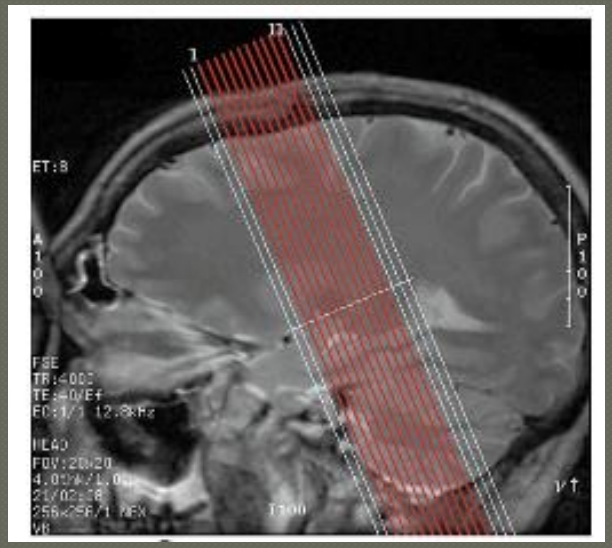
Little heterogeneity on long axis

Segmentation and Unfolding of the Hippocampal Complex

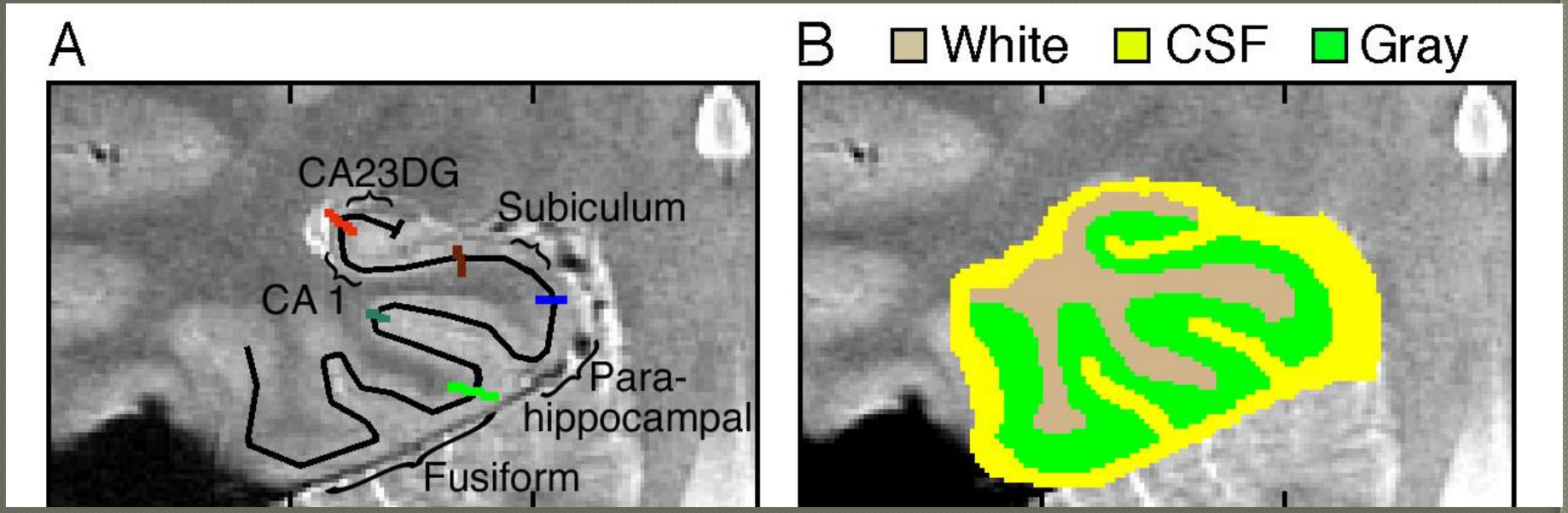
Michael Zeineh, MD, Ph.D.
Stanford University

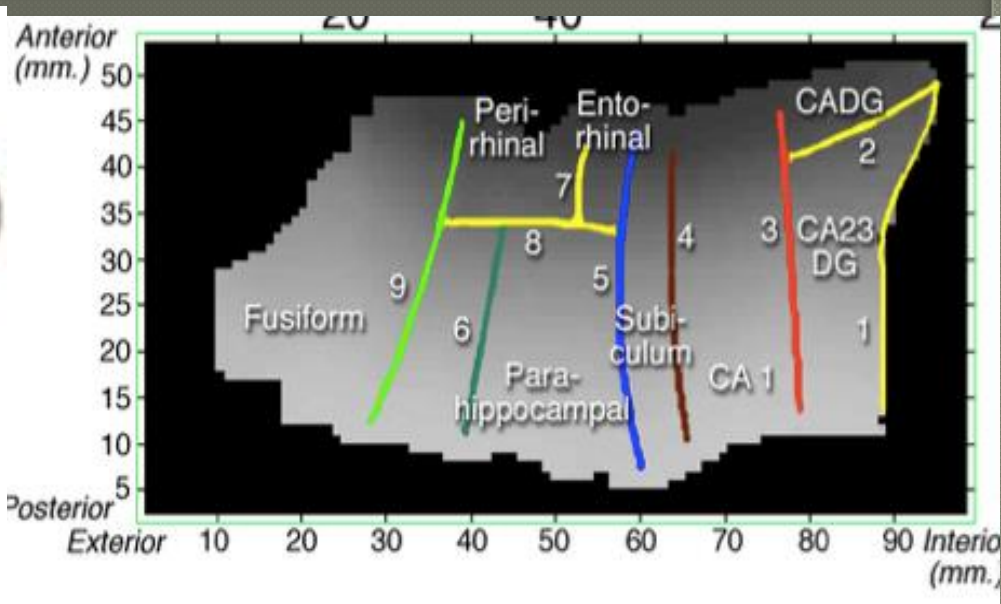
Unfolding methods

- T2 FSE pulse sequence: high gray–white contrast, high in-plane resolution, and low susceptibility artifact.
- Voxel size 0.391 x 0.391 x 3.00 mm thickness
- Perpendicular to HC long axis



Solution: Higher resolution, HC unfolding

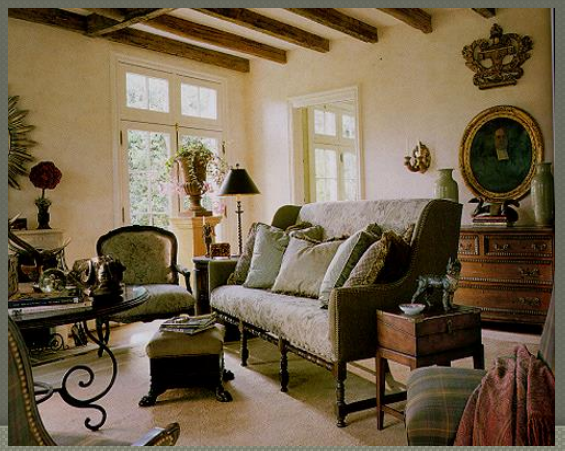




High Resolution fMRI of the Human Hippocampus

Novelty encoding

- Rodent data show HC response to novelty
- Evidence of sub-regional heterogeneity in dentate, CA3- where the reverberating circuits are located



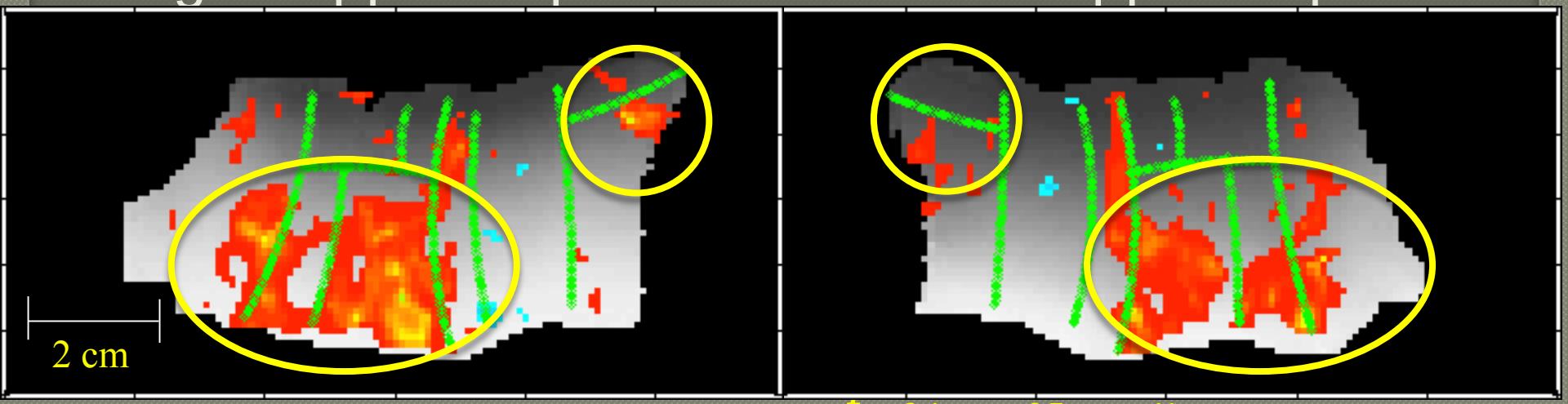
Functional methods

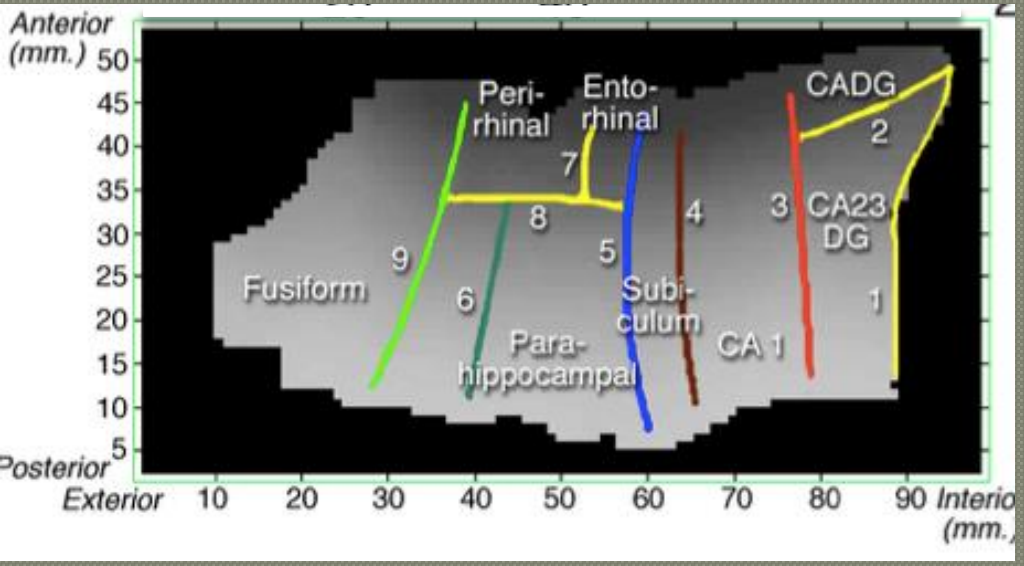
- 3-Tesla
- EPI GE TR=3400 ms, TE= 30 ms, FOV 20, 128x128, 11slices, 3 mm thick, 0 mm spacing: 1.5 mm voxel size in-plane
- Normalized each block against neighboring blocks to account for drift
- Simple contrast of new vs. old blocks
- Extracted times series from each region in the flat map

Flat maps averaged across subjects

Right Hippocampus

Left Hippocampus





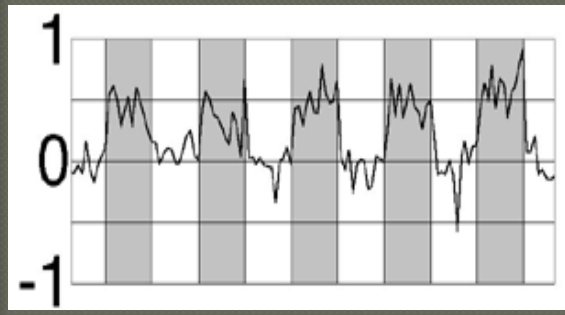
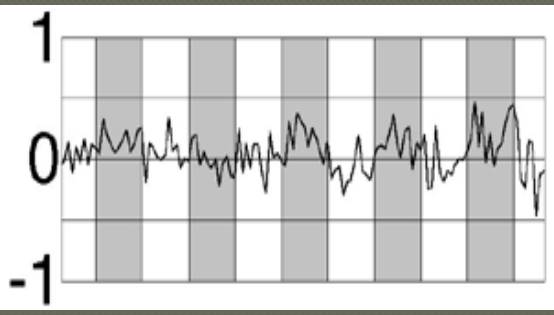
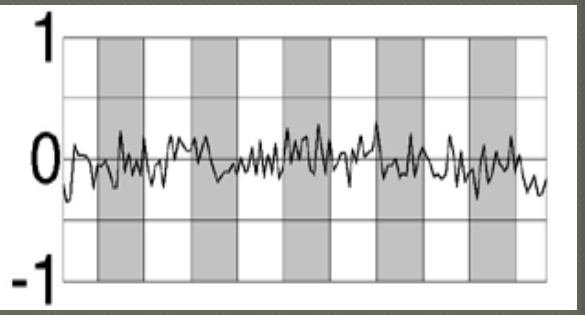
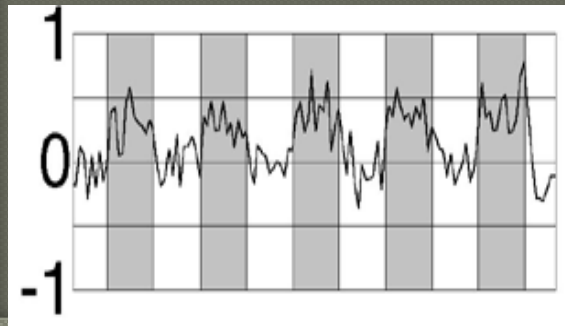
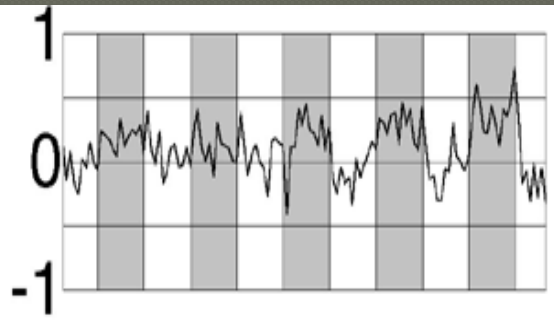
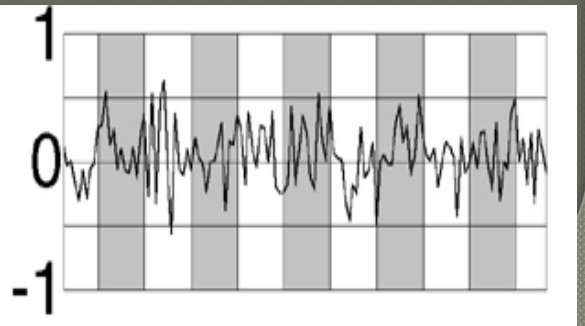
Anterior CA3/DG

Subiculum

PHC place area

Medial Fusiform object areas

activity patterns in HC sub-regions

Sustained	Late Activation	No Activation
Parahippocampal	CA 2, 3, DG	CA 1
		
Fusiform	Subiculum	Entorhinal
		

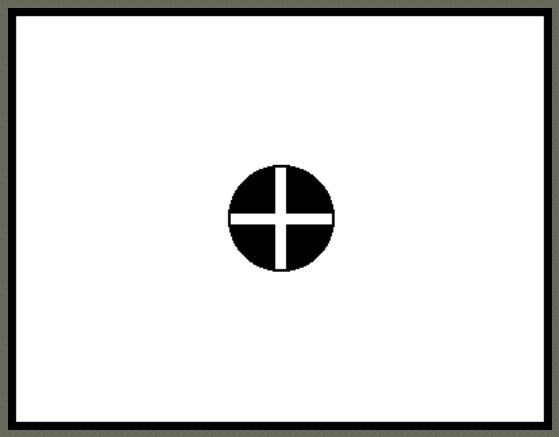
Learning associations

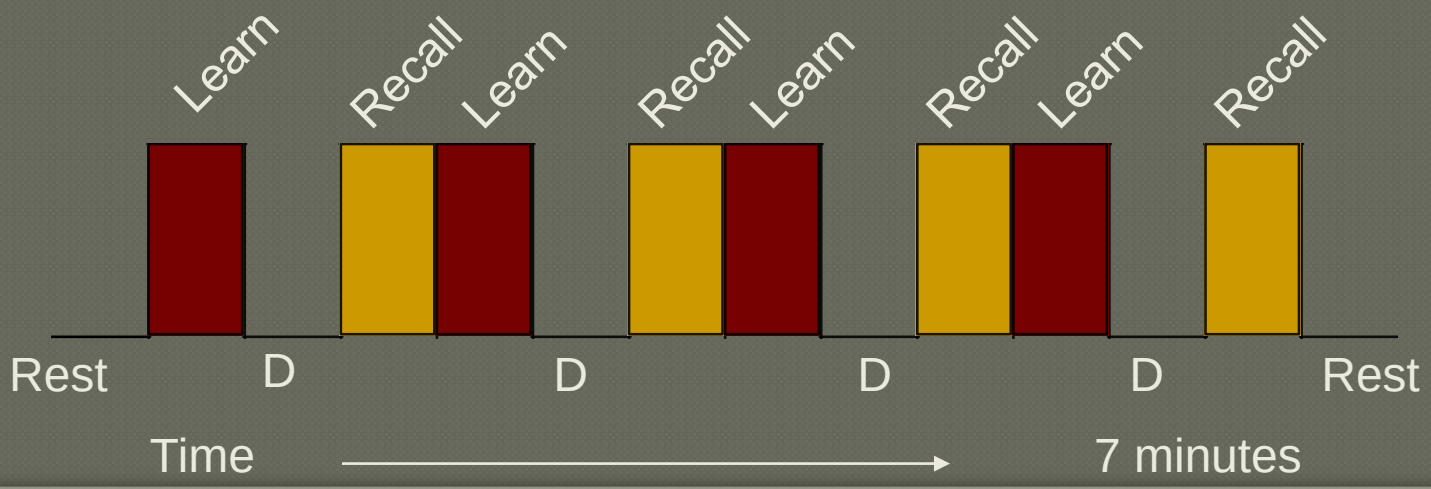
Zeineh et al, Science, 2003

Learn Face-Name Pair

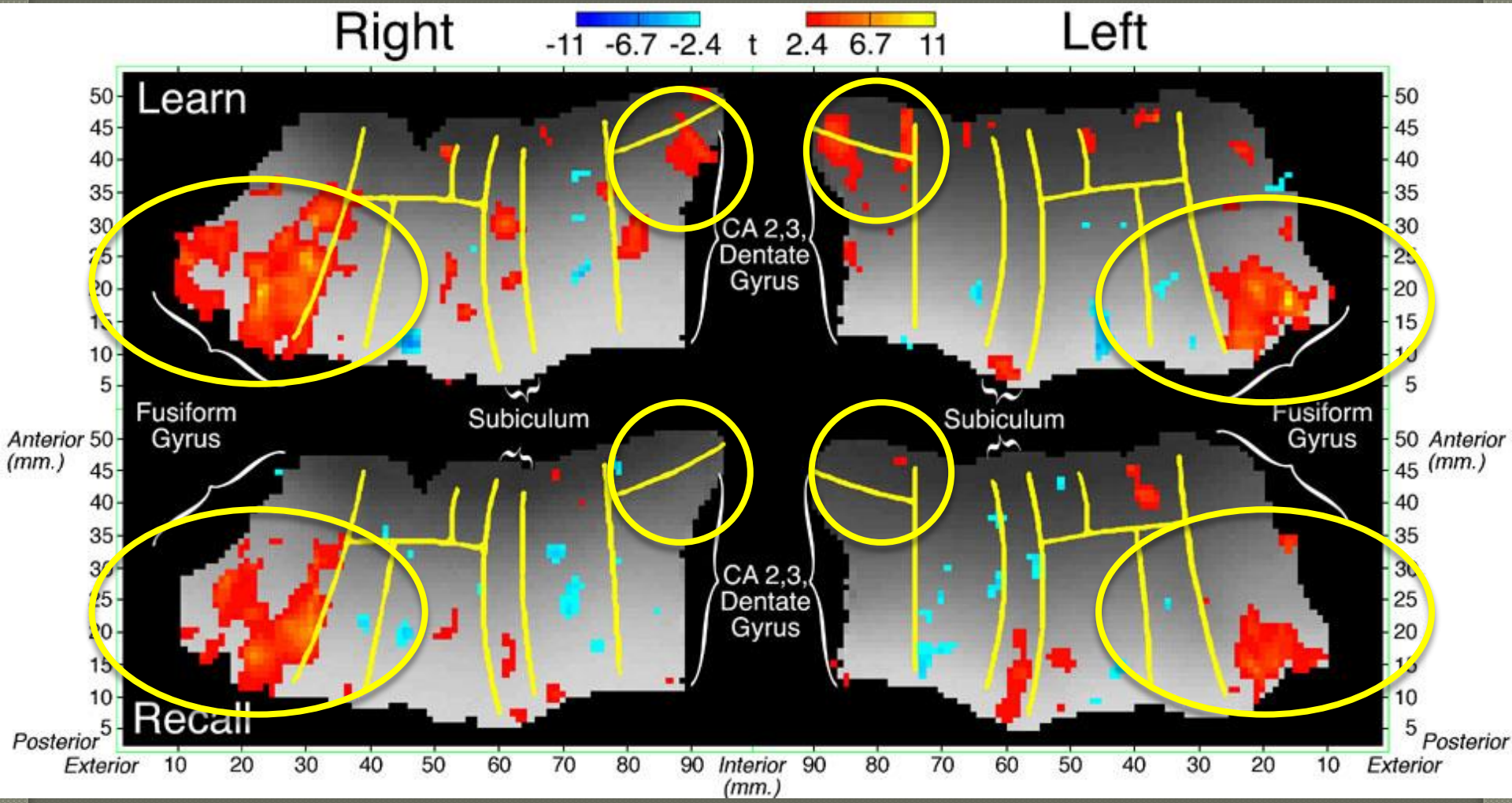
Covert Name Recall

Distractor



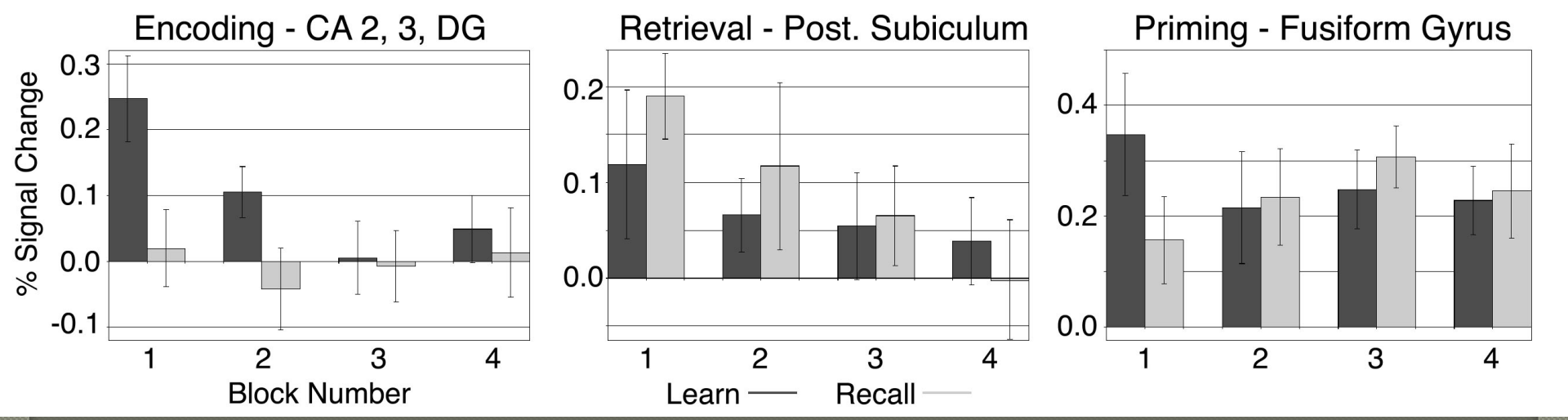


Results



1. Inside HC, dissociation between encoding (CA23/DG) and retrieval (subiculum)
2. Outside of HC- process independent but content specific activation (face area)

Time series



Learn

Recall

Anterior/posterior and regional dissociations

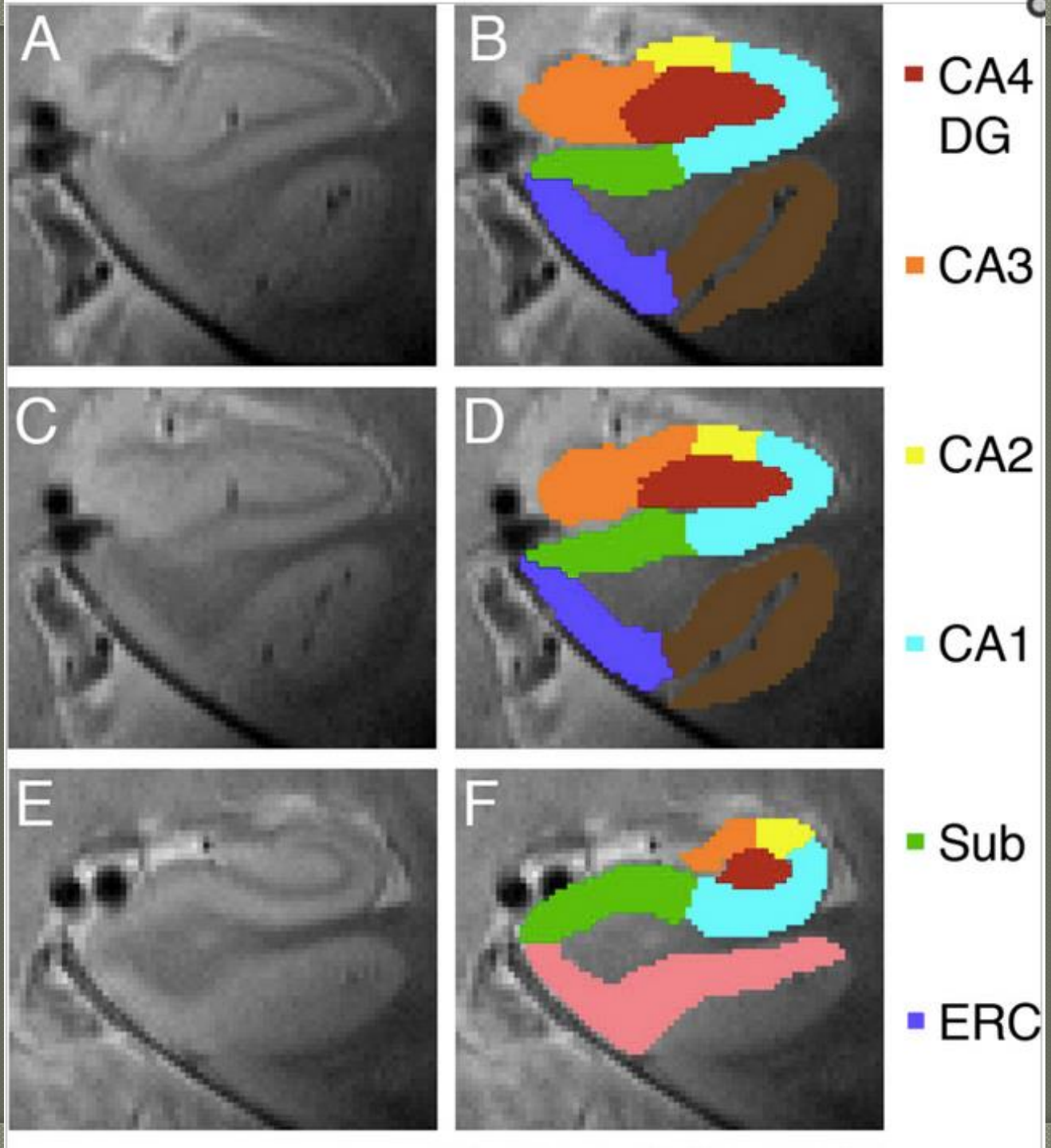
Encoding: Anterior CA23DG

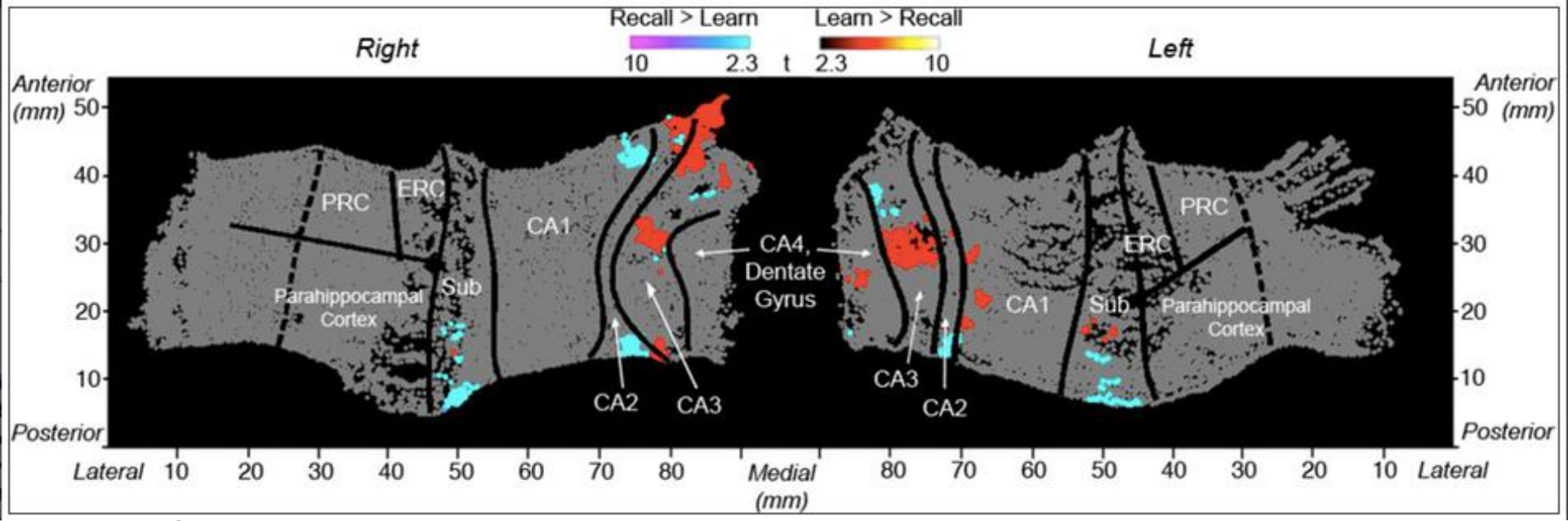
Retrieval: Posterior subiculum- encoding to a lesser extent

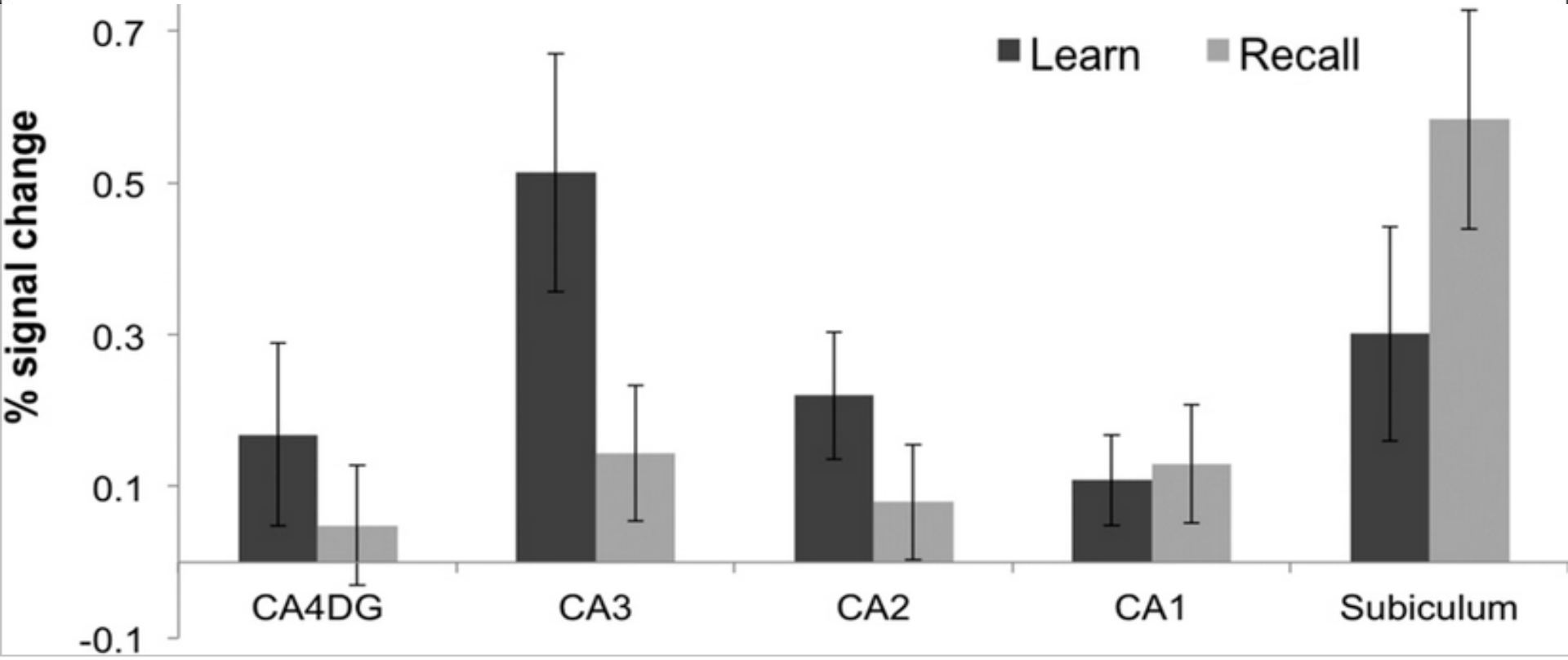
Differentiating CA3/DG with 7 T

- Suthana et al, Turner lab at Leipzig
- Reduced fMRI voxel size to 1x1x2 mm
- Differentiate DG from CA2,3
- Similar face-name encoding/retrieval paradigm

Nanthia Suthana, Ph.D.
Asst. Prof, UCLA


A
B
C
D
E
F
CA4
DG
CA3
CA2
CA1
Sub
ERC


Recall > Learn
Learn > Recall
10
2.3
t
2.3
10
Right
Left
Anterior (mm)
Posterior
Lateral
Medial (mm)
PRC
ERC
CA1
Parahippocampal Cortex
Sub
CA4, Dentate Gyrus
CA2
CA3


% signal change
Learn
Recall
0.7
0.5
0.3
0.1
-0.1
CA4DG
CA3
CA2
CA1
Subiculum

Conscious recollection of episodes in humans

Remembering vs. Knowing

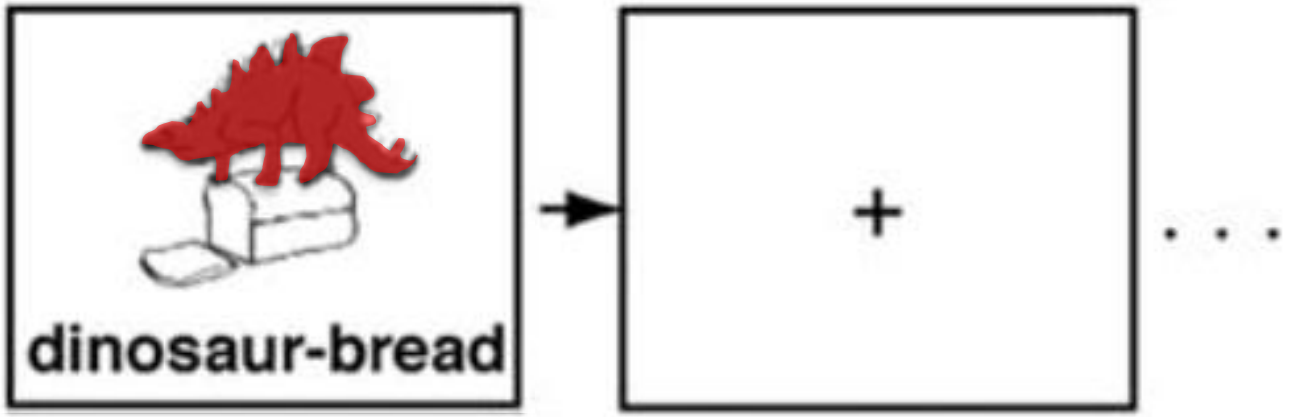
- (R) Remember - re-experience the encoding event at the time of recall, true episodic memory
  - Can provide explicit details of learning episode
- (K) - Know - the feeling of familiarity that you've seen something before, but not remembering the exact encoding event
  - Not implicit because it is conscious
- Both are declarative memories

Conscious recollection

- Eldridge (Knowlton lab) used remember- know paradigm and measured fMRI during encoding and retrieval of object-object or object-word pairs
- Event related design

Laura Eldridge Furmanski

Remember - know task



5 seconds

12.5 seconds

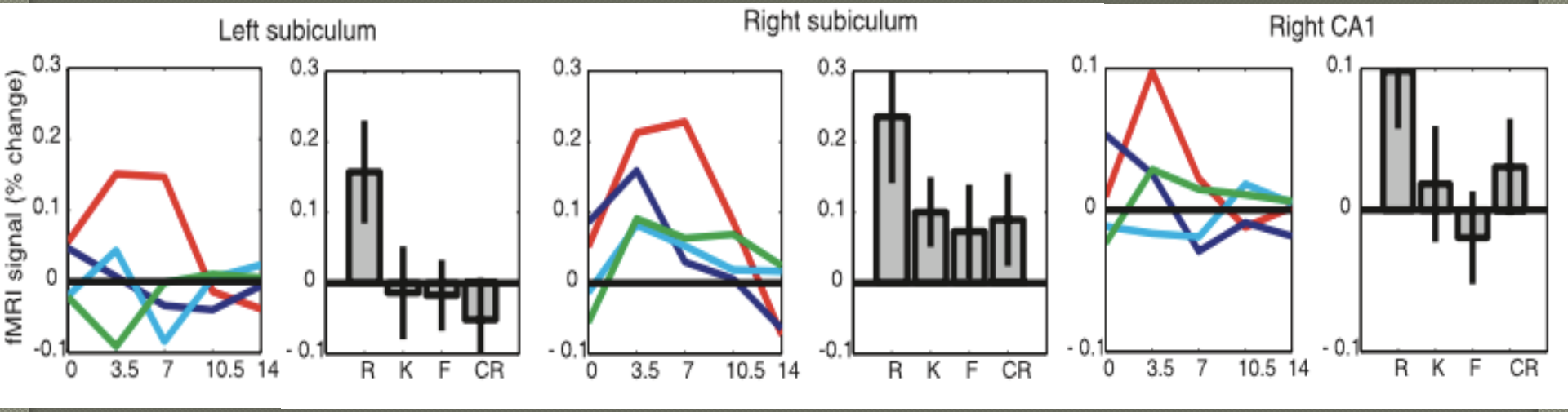
3 seconds

2 seconds

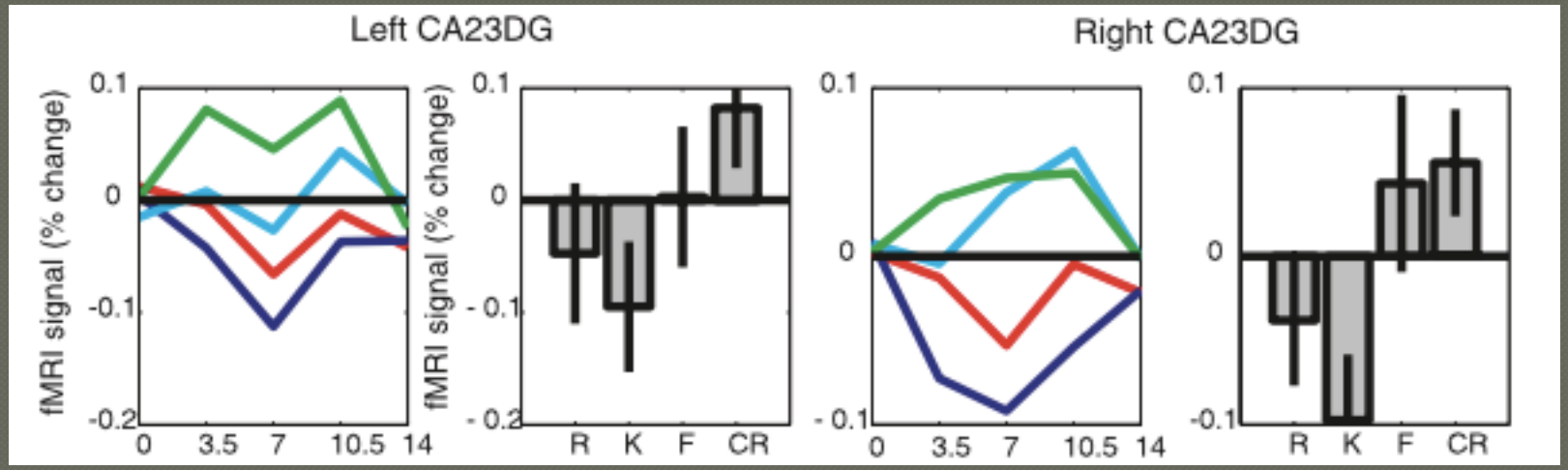
12.5 seconds

Retrieval

Remember Know Forgotten Correct Rejections

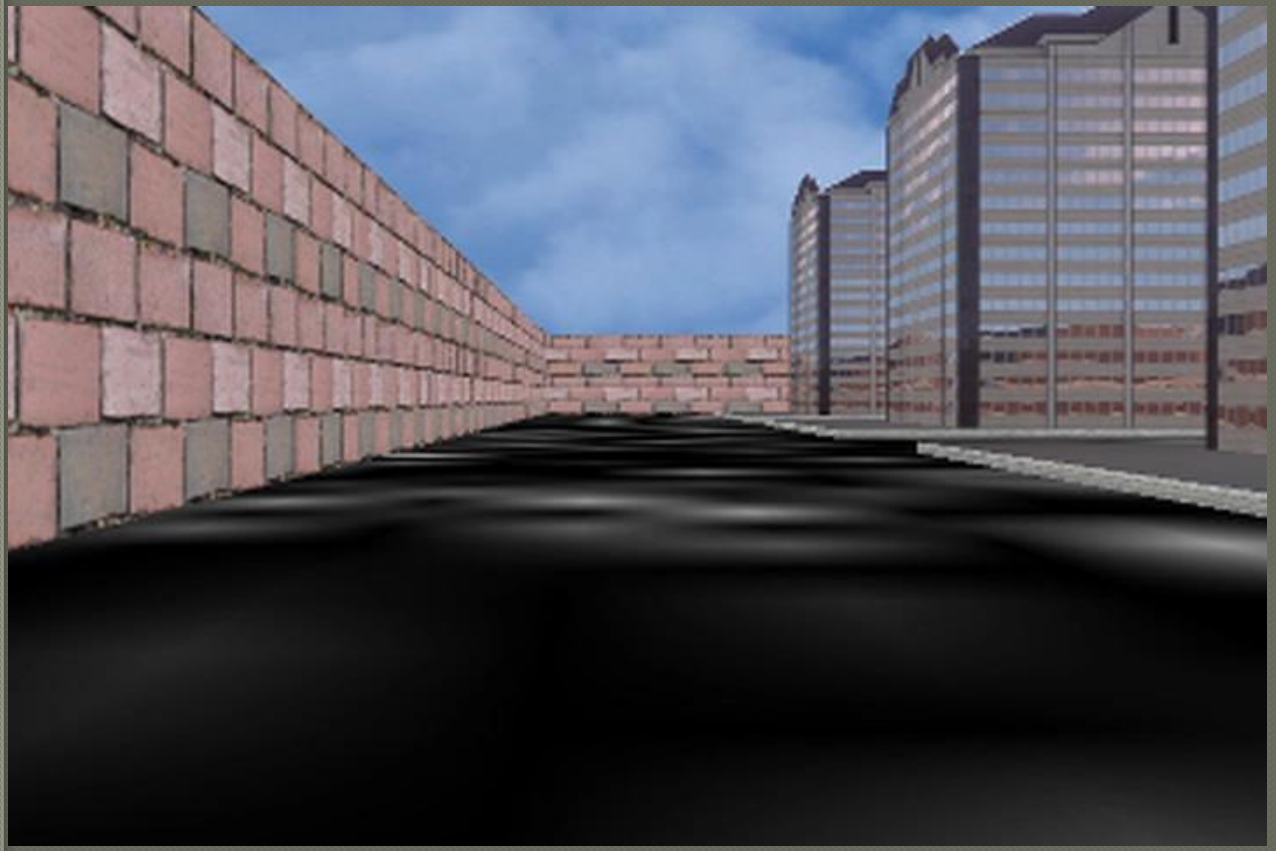


Subiculum and R CA-1 Increases for Remember trials compared to all others



Left CA3/DG: increases for Novel items (CR) - Right CA3/DG: Novel and Forgotten

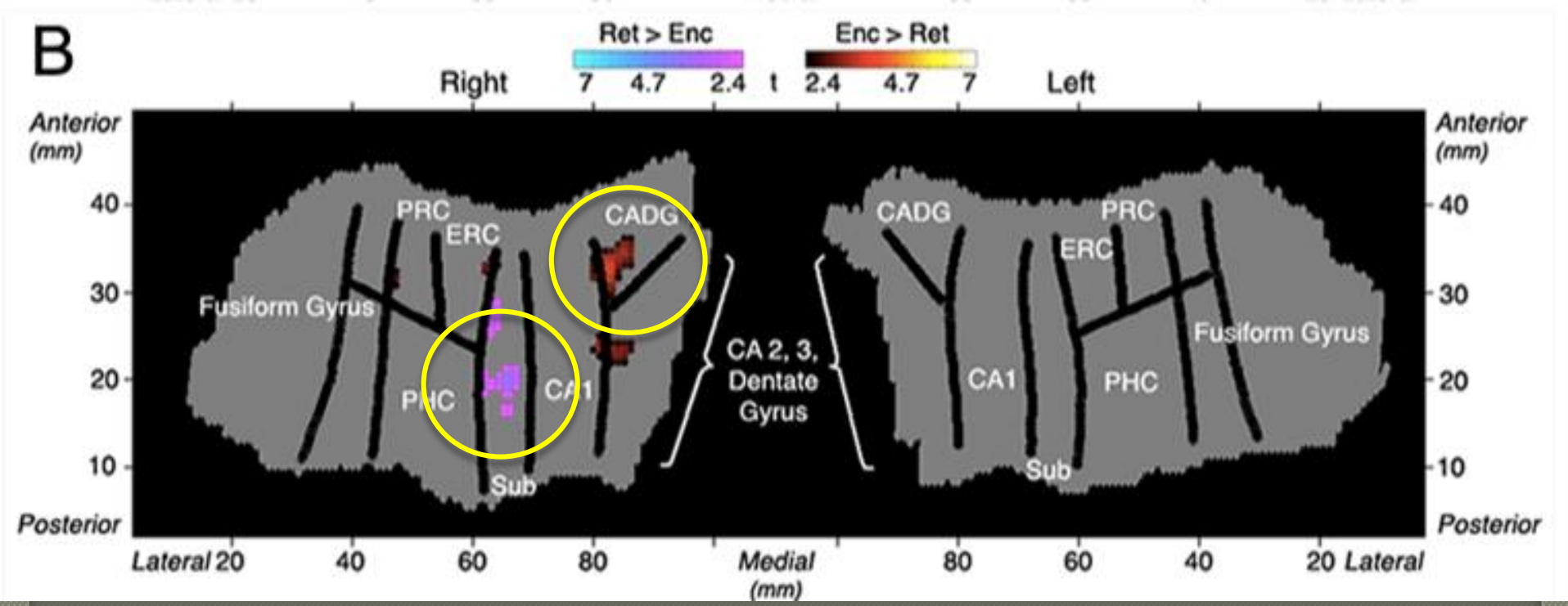
Encoding vs. retrieval in spatial navigation



- Encoding: subjects viewed navigation to novel stores
- Retrieval: viewing navigation to previously learned (target) or novel (lure) store locations
- Block design, same acquisition

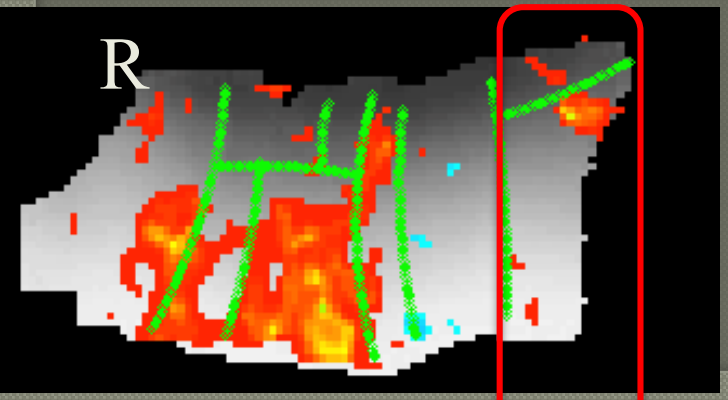
(Suthana et al, Hippocampus, 2011)

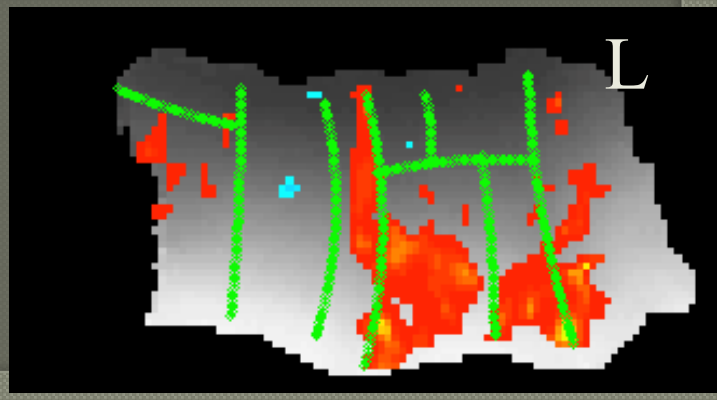
RH differences in encoding vs. retrieval in navigation

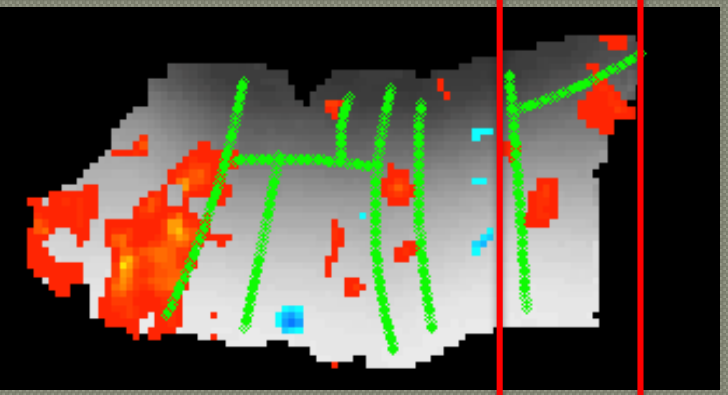


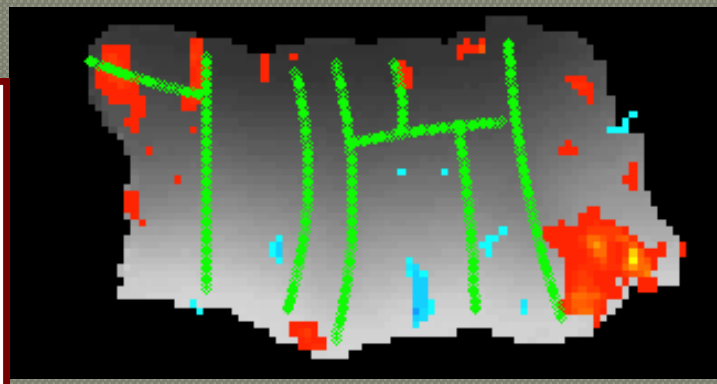
Encoding: Anterior CA3/DG – RH lateralized
Retrieval: Mid-posterior subiculum

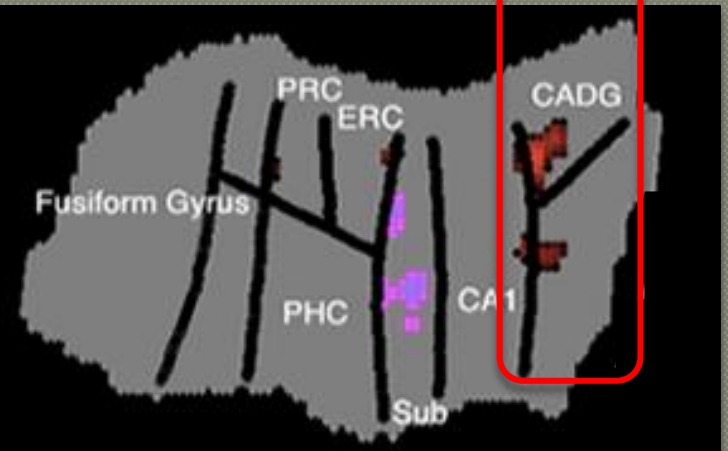
Averaged hippocampal maps

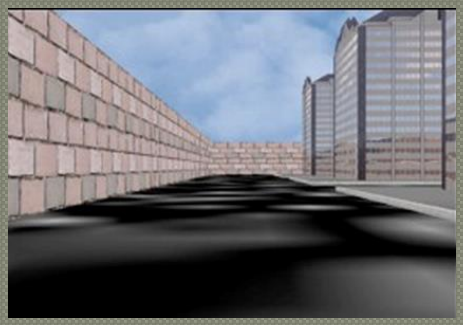


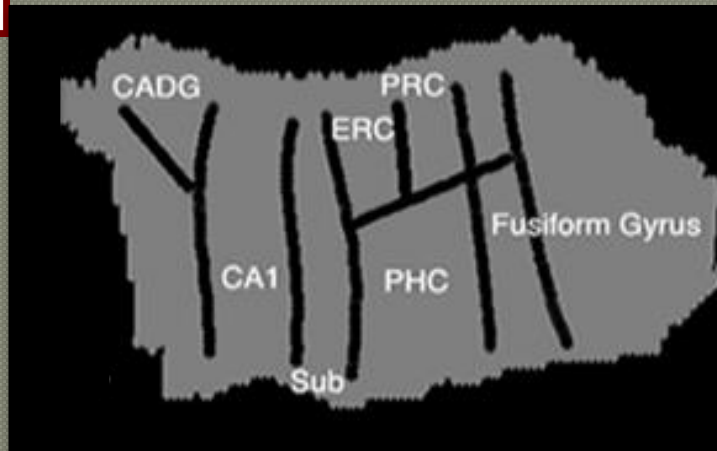




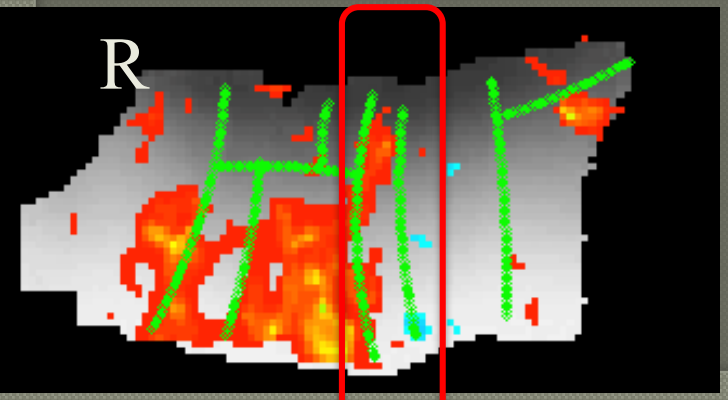


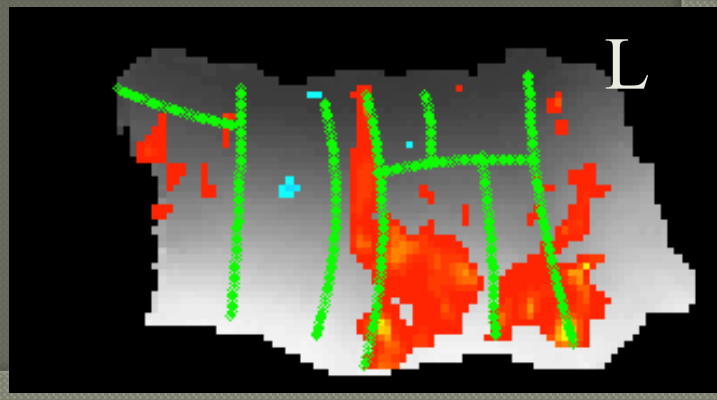


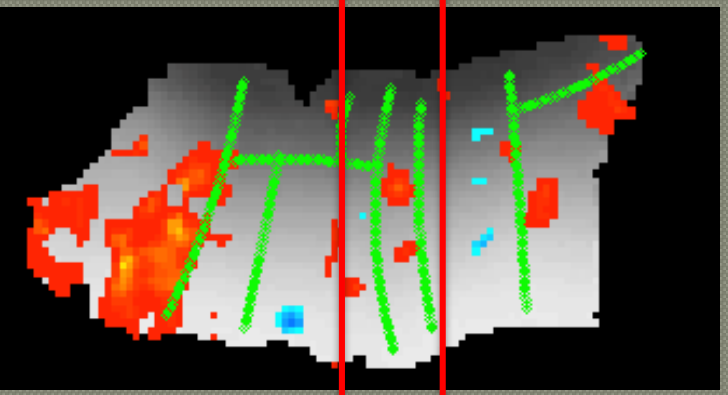


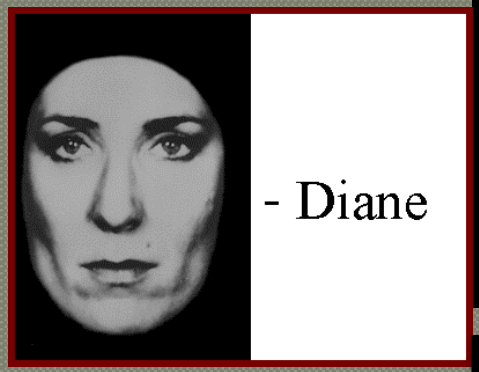


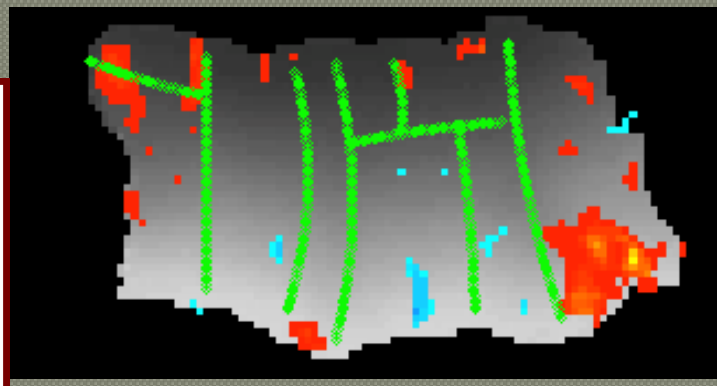
Hippocampal maps across tasks

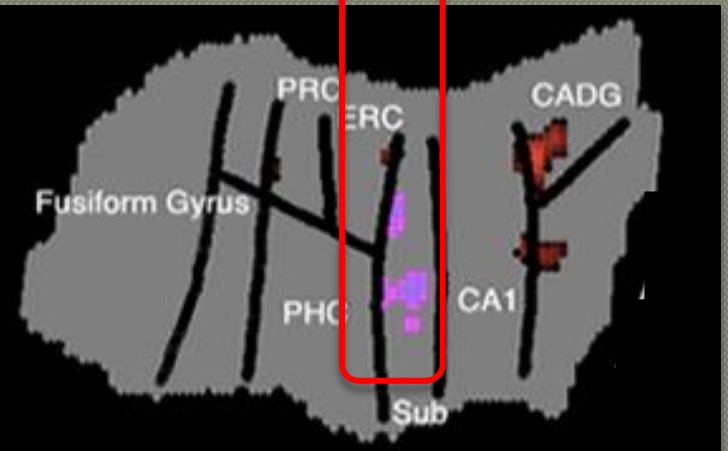


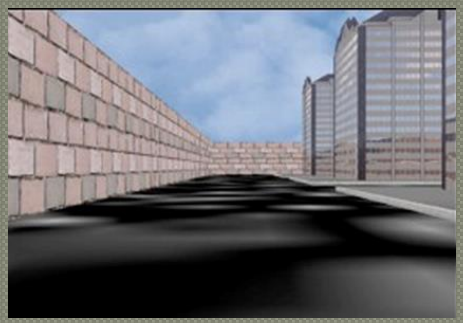


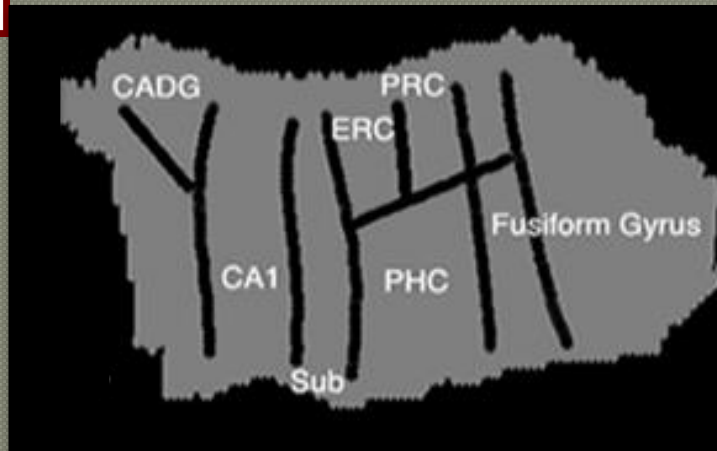












Single unit recording in human hippocampus

1

2

3

4

5

6

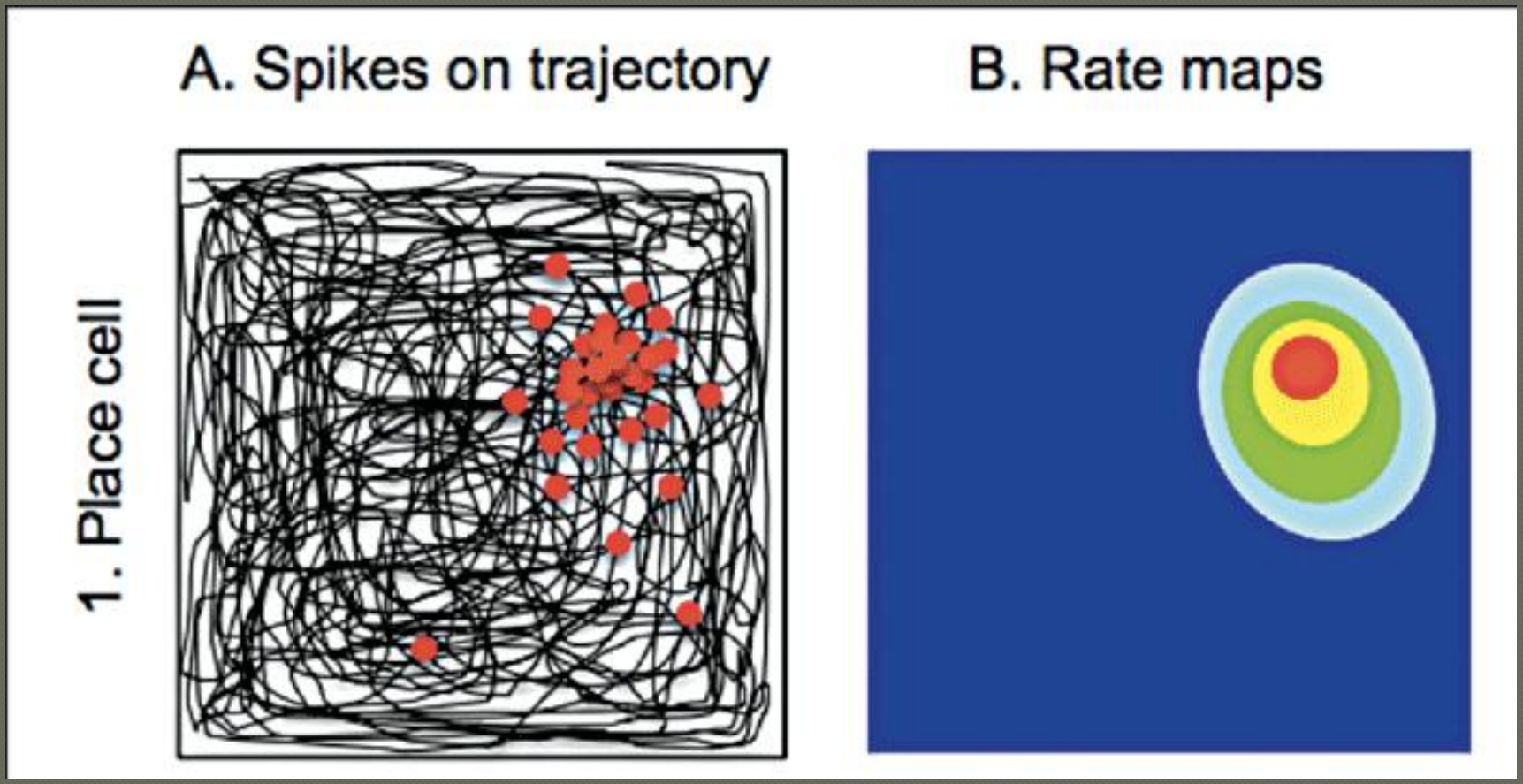
7

8

9

10

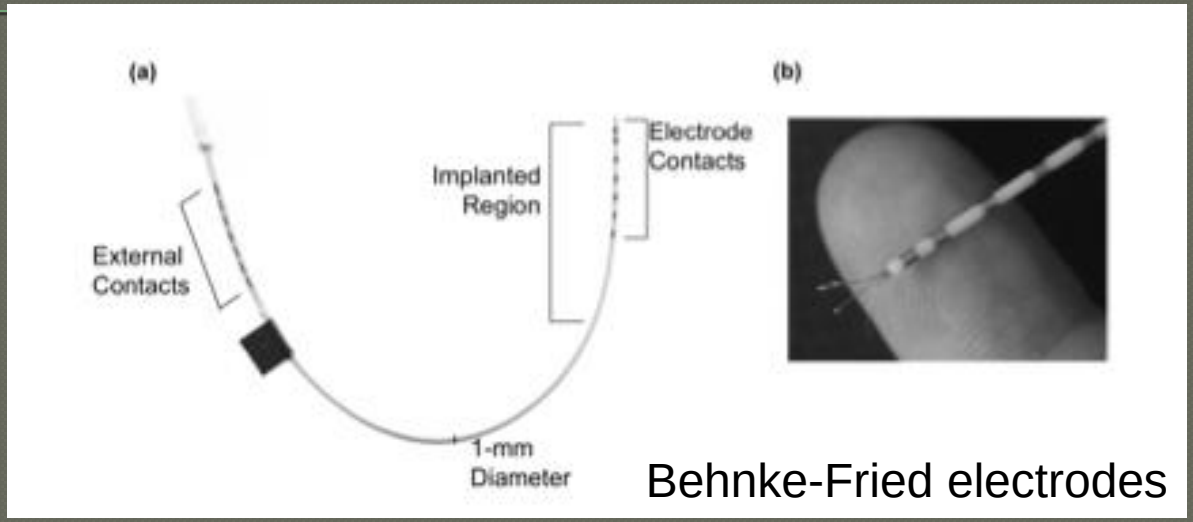
Place cell maps



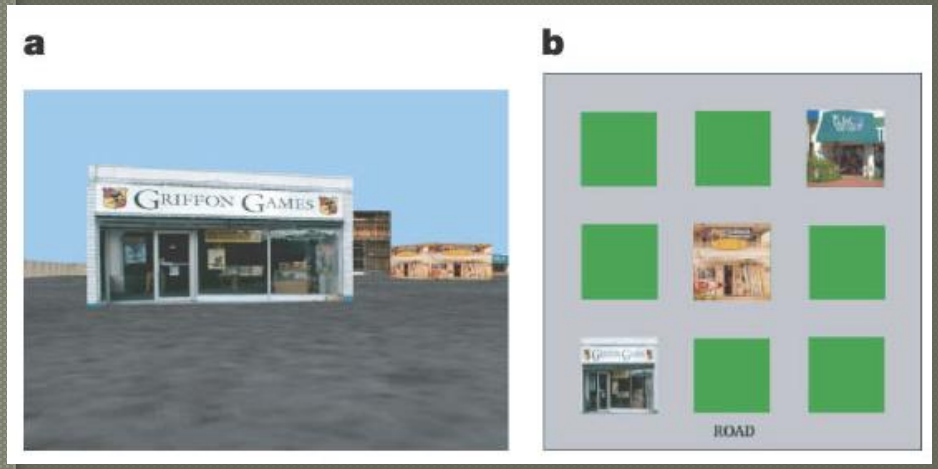
Wood and Chan, review: ACNR, 2015

Place Cells in humans

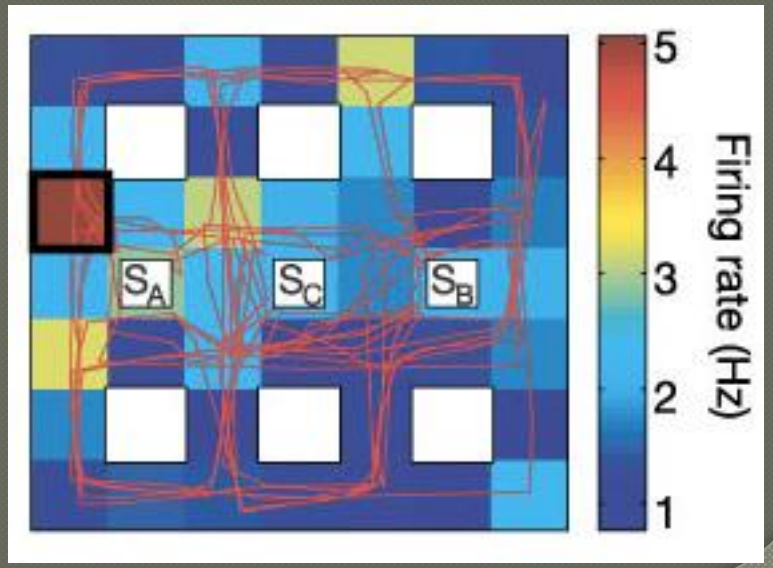
Arne Ekstrom, Ph.D.
Assoc. Prof, UC Davis



Behnke-Fried electrodes



Ekstrom, Kahana, Caplan, Fields, Isham, Newman, Fried I. Nature, 2003



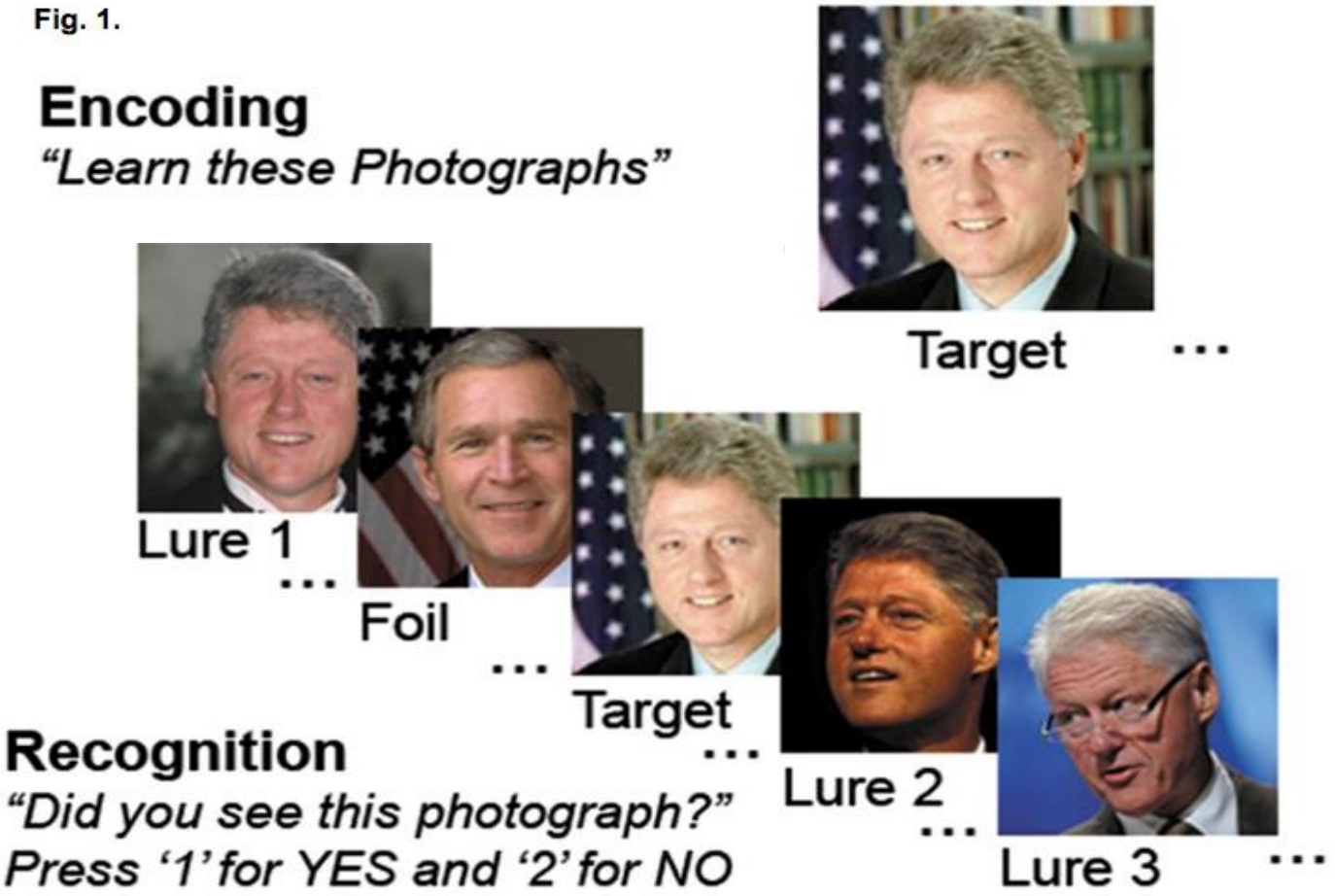
PNAS

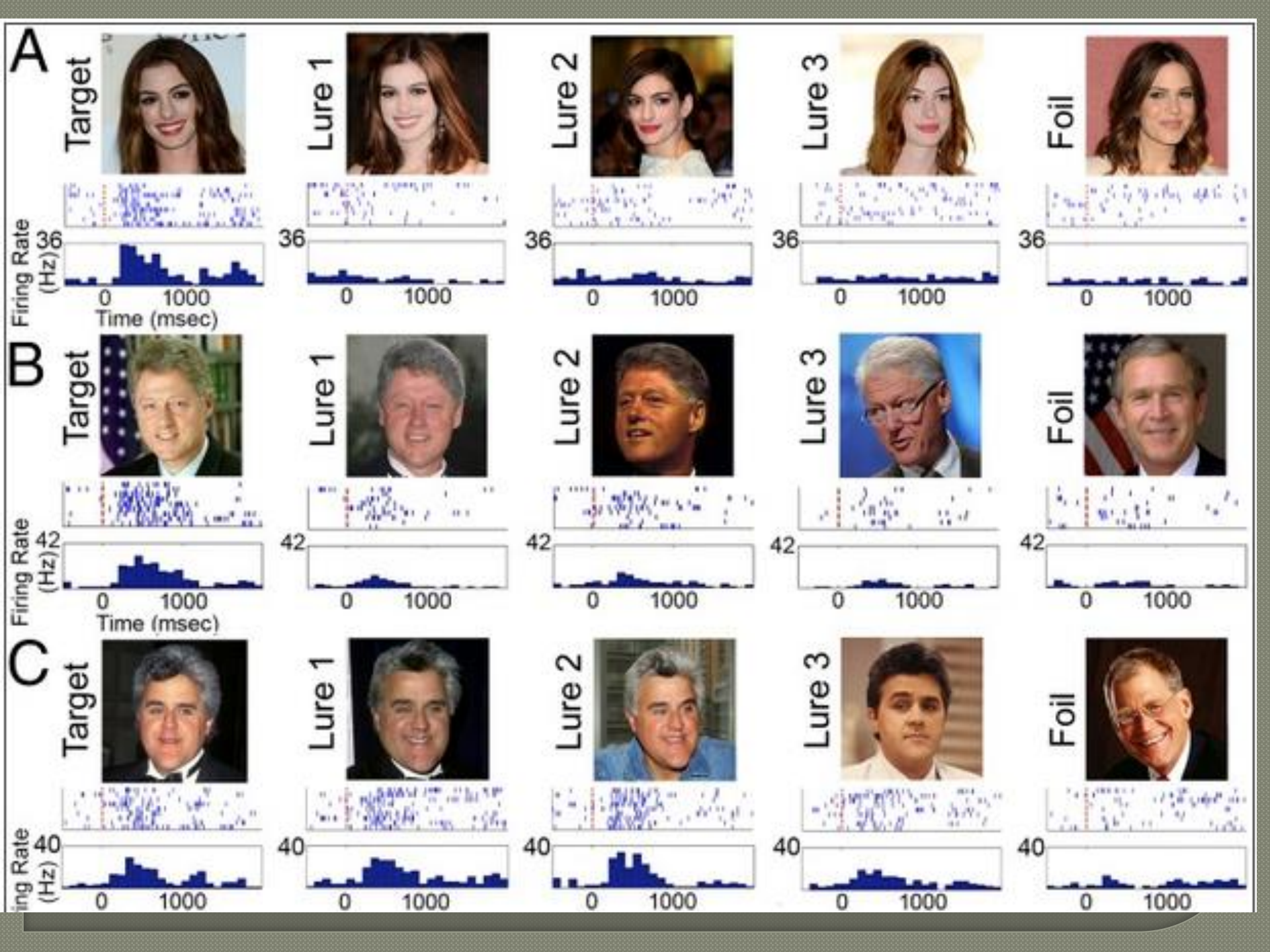
Specific responses of human hippocampal neurons are associated with better memory

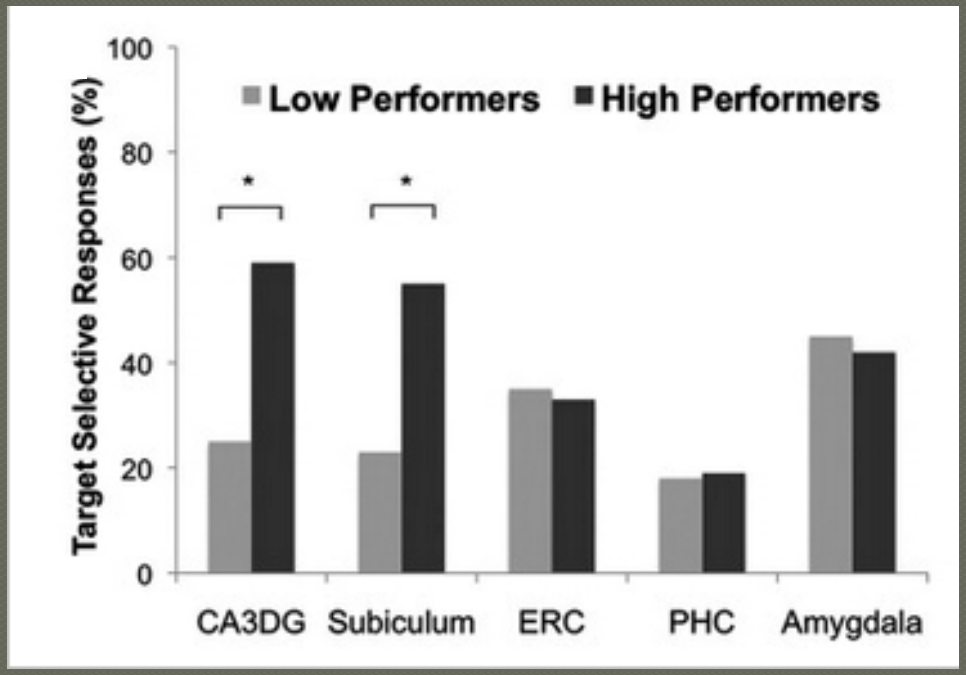
Nanthia A. Suthana[a,b,1], Neelroop N. Parikshak[a], Arne D. Ekstrom[c], Matias J. Ison[d], Barbara J. Knowlton[e], Susan Y. Bookheimer[b,e], and Itzhak Fried[a,f,1]

Nanthia Suthana

Fig. 1.




A
Target
Lure 1
Lure 2
Lure 3
Foil
Firing Rate (Hz)
36
0
1000
Time (msec)
B
Target
Lure 1
Lure 2
Lure 3
Foil
Firing Rate (Hz)
42
0
1000
Time (msec)
C
Target
Lure 1
Lure 2
Lure 3
Foil
ing Rate (Hz)
40
0
1000

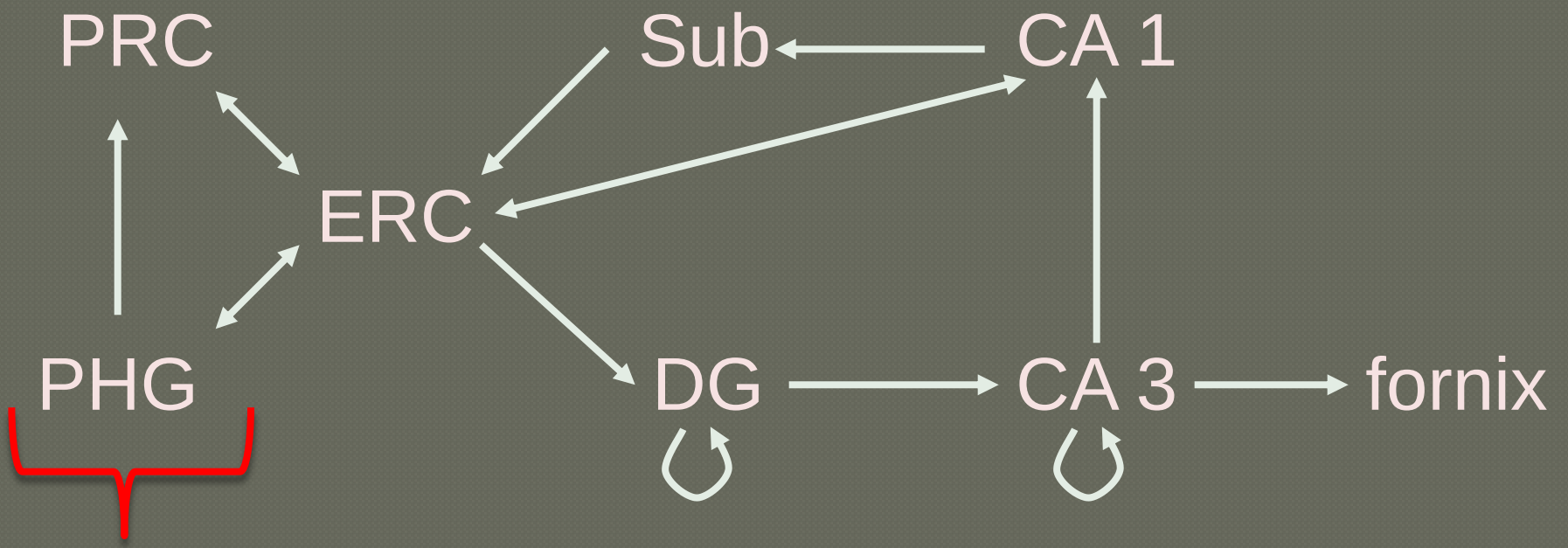


High memory performance is associated with more HC activity

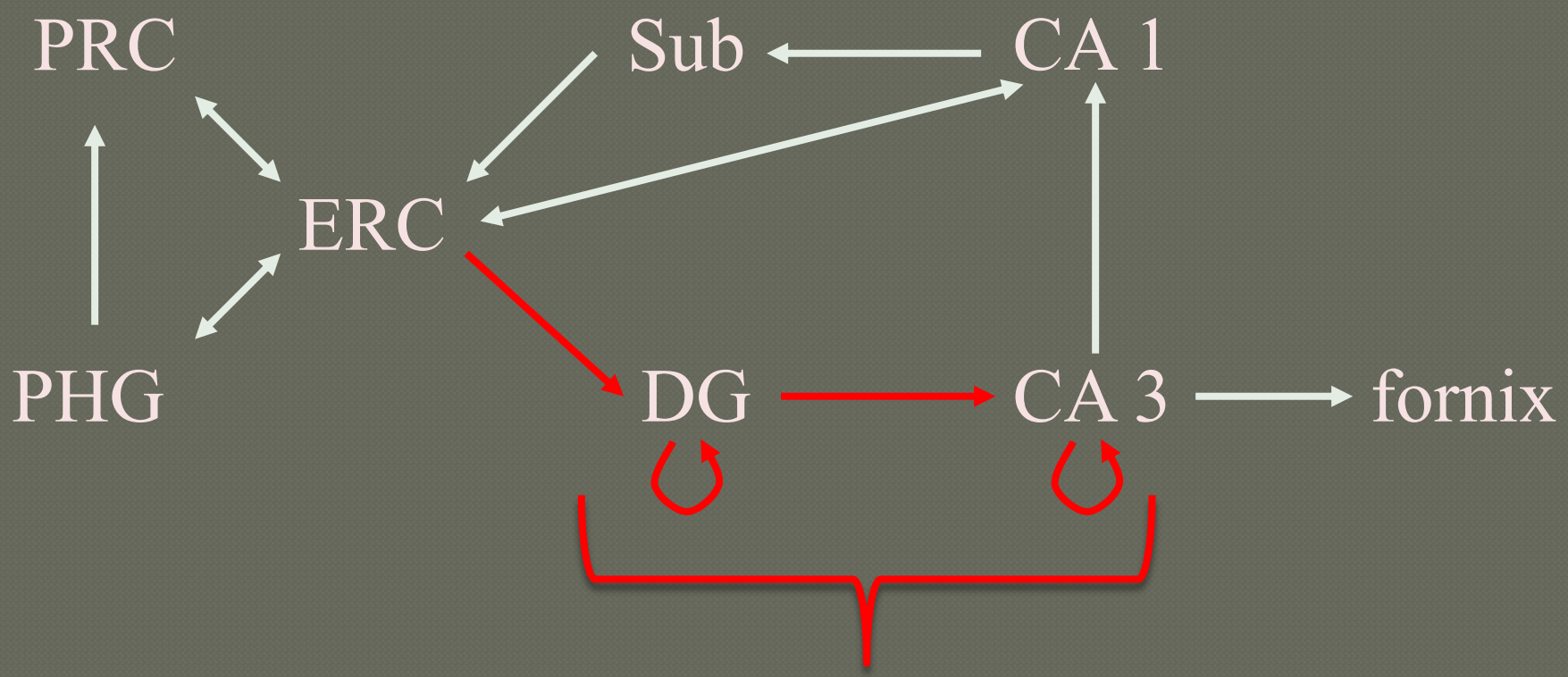
But, do we really have Leno-specific cells?

- Activity has to do with the learning episode in real time- the sensory input of Leno at testing episode
- Consistent with remapping, found in rodent and human place cells
- Suggests that “place cells” also reflect the episode

Within the encoding/retrieval domain, human fMRI data appear to replicate the circuit functions hypothesized in rodents:

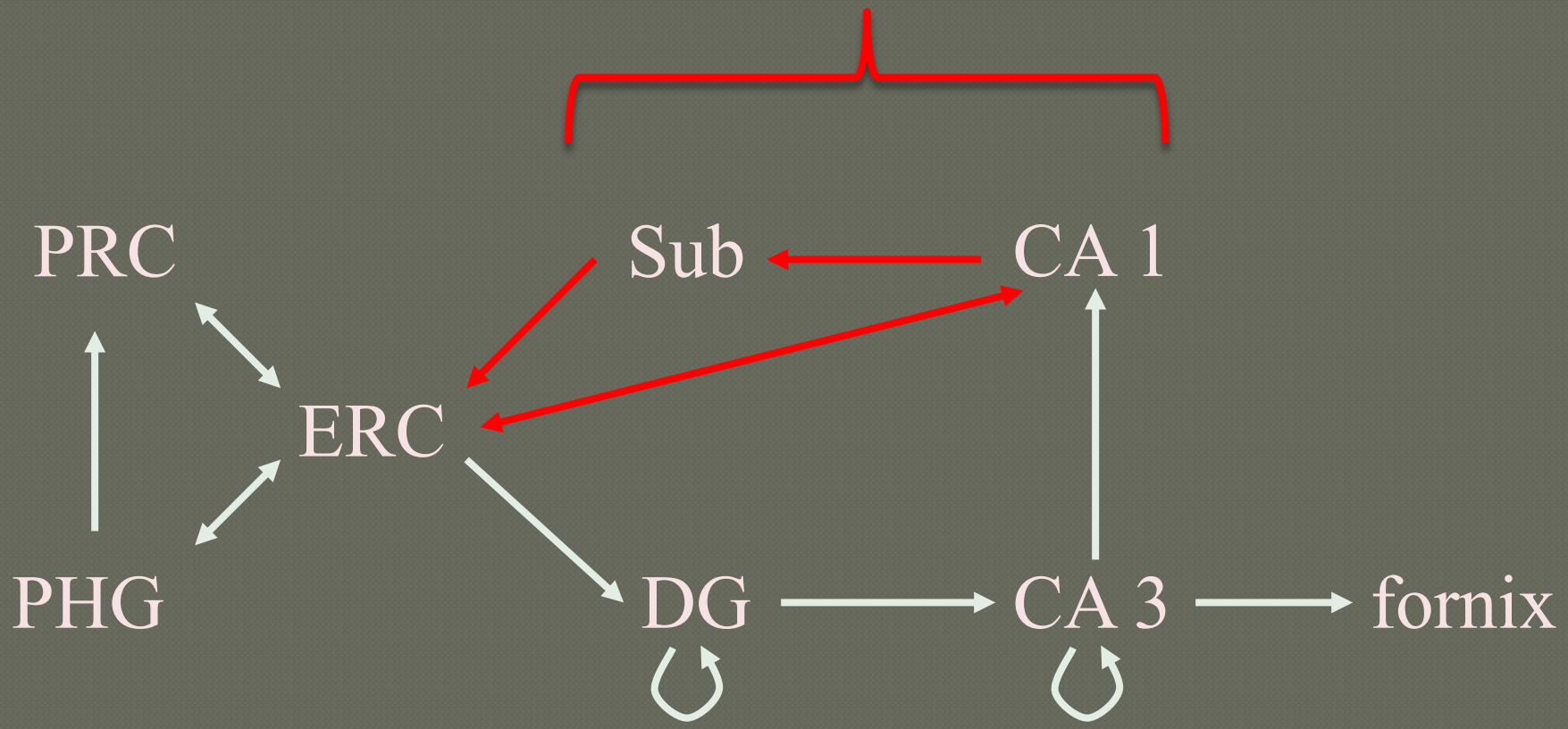


Pre-ERC: content-specific activation



- DG/CA3: Novelty, association formation
- Consistent with general encoding processes
- Recurrent collateral circuits in CA3 and DG appear optimized to encode novel items and associations

Subiculum, CA1: Direct pathway from ERC involved in episodic retrieval processes



The HC processes content indiscriminately

- Other processes in HC circuit
  - Pattern separation/ completion
  - Partial cue reconstruction
  - Remapping
  - Item vs. source memory
  - Gradient along ERC that sends different content into HC along the long axis
- Within the HC, same functional circuitry regardless of task content
- **The difference between animal and human HC is not in how the HC works, but in the unique information entering the HC**

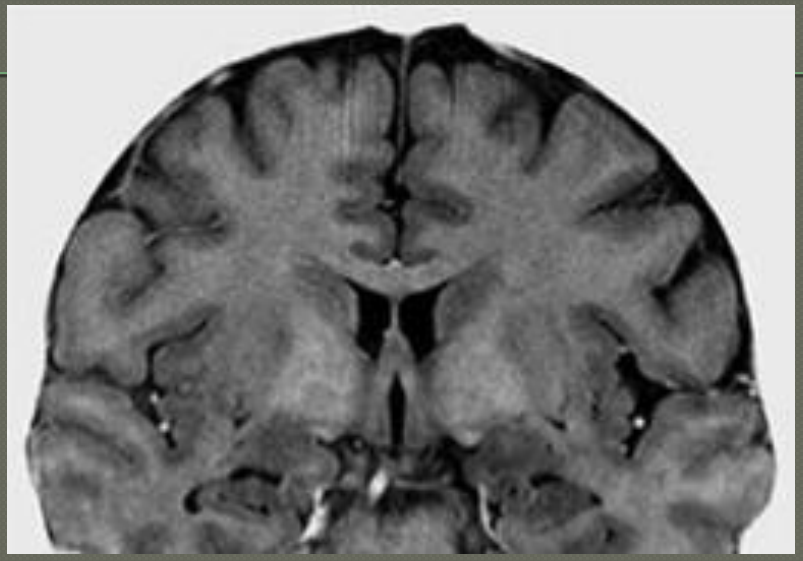
Why is the hippocampus so vulnerable?

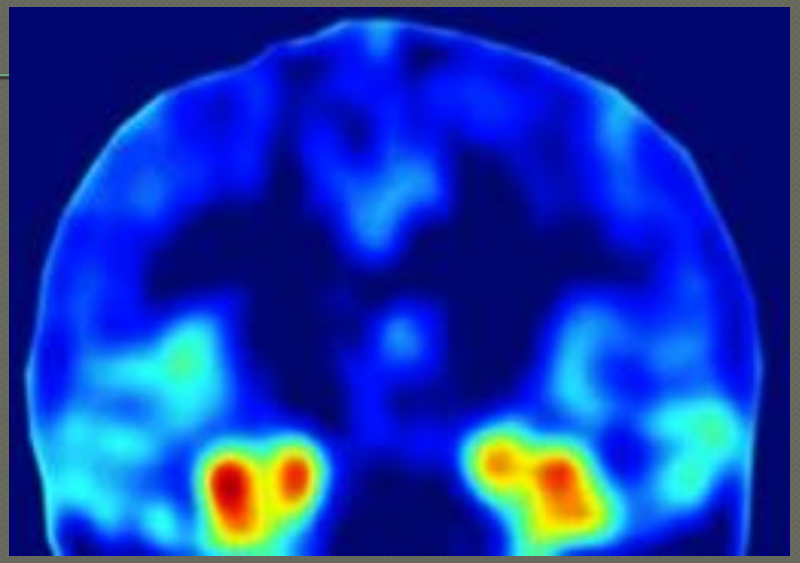
- Viral encephalitis (herpes) and fever
- Anoxia
- Epilepsy- predominant in MTL
- Stress
- Aging/AD

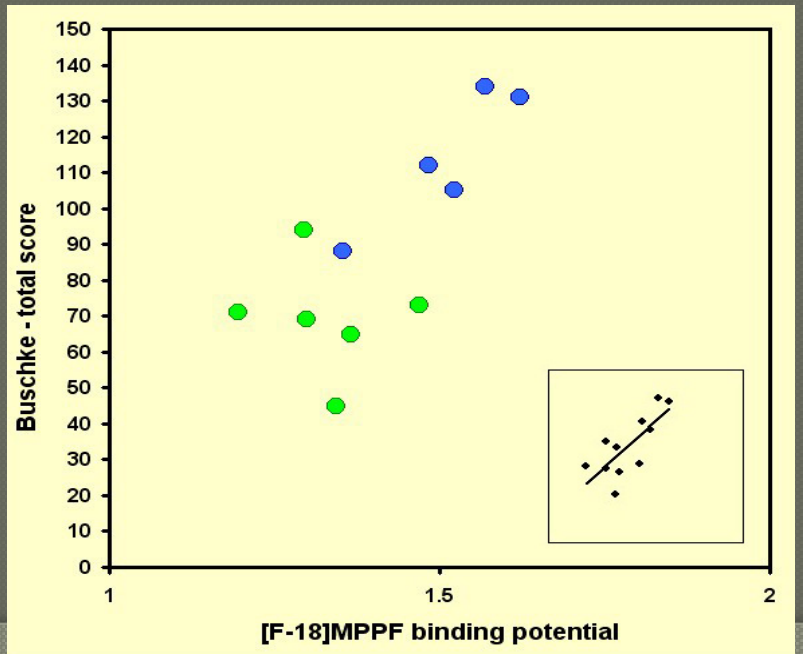
Hippocampal vulnerability- Stress

- Stress
  - Stress impacts HC structure and function
    - Plus: Learned fear responses are essential for survival
  - Serotonin receptors in HC respond to stress throughout lifespan
    - Plus: Associated with superior memory

^{18}F-MPPF PET (5HT1a receptors)





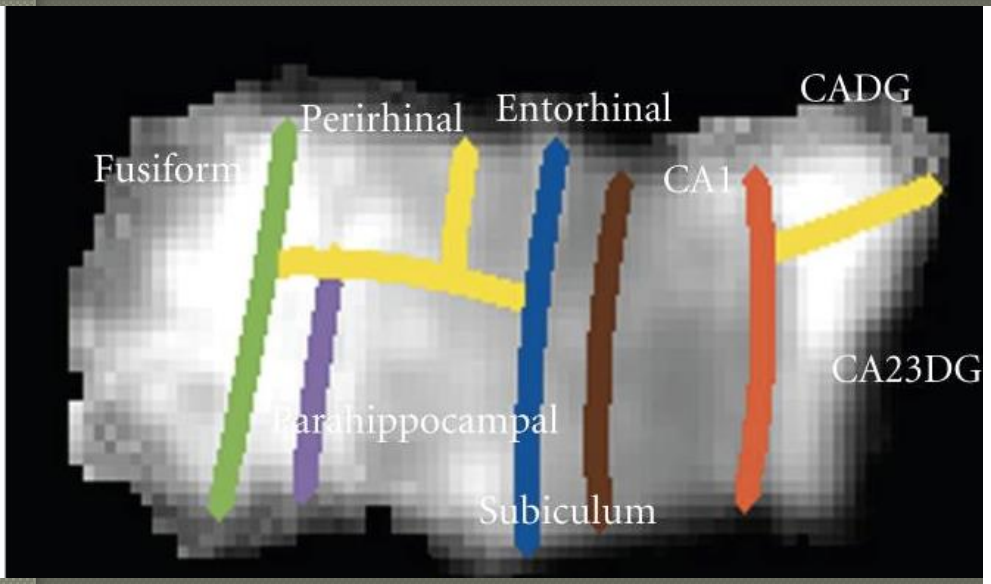


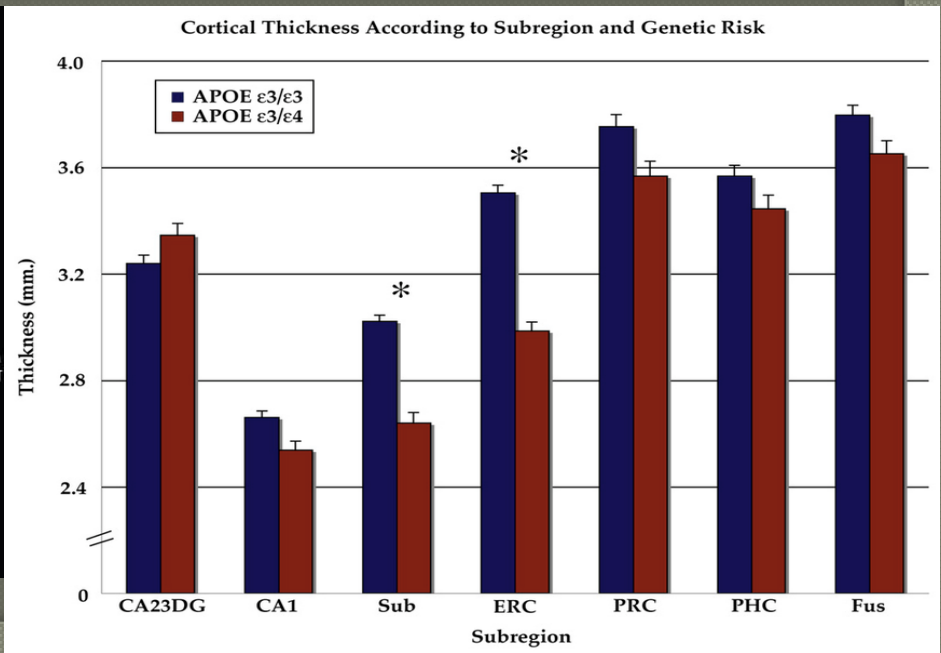
MPPF binding is highly correlated with memory (r >.9) (Kepe et al)

Hippocampal vulnerability - Aging, AD-risk

- Cognitively normal, older APOE-4 carriers have reduced thickness in ERC and subiculum

Alison Burggren, Ph.D.

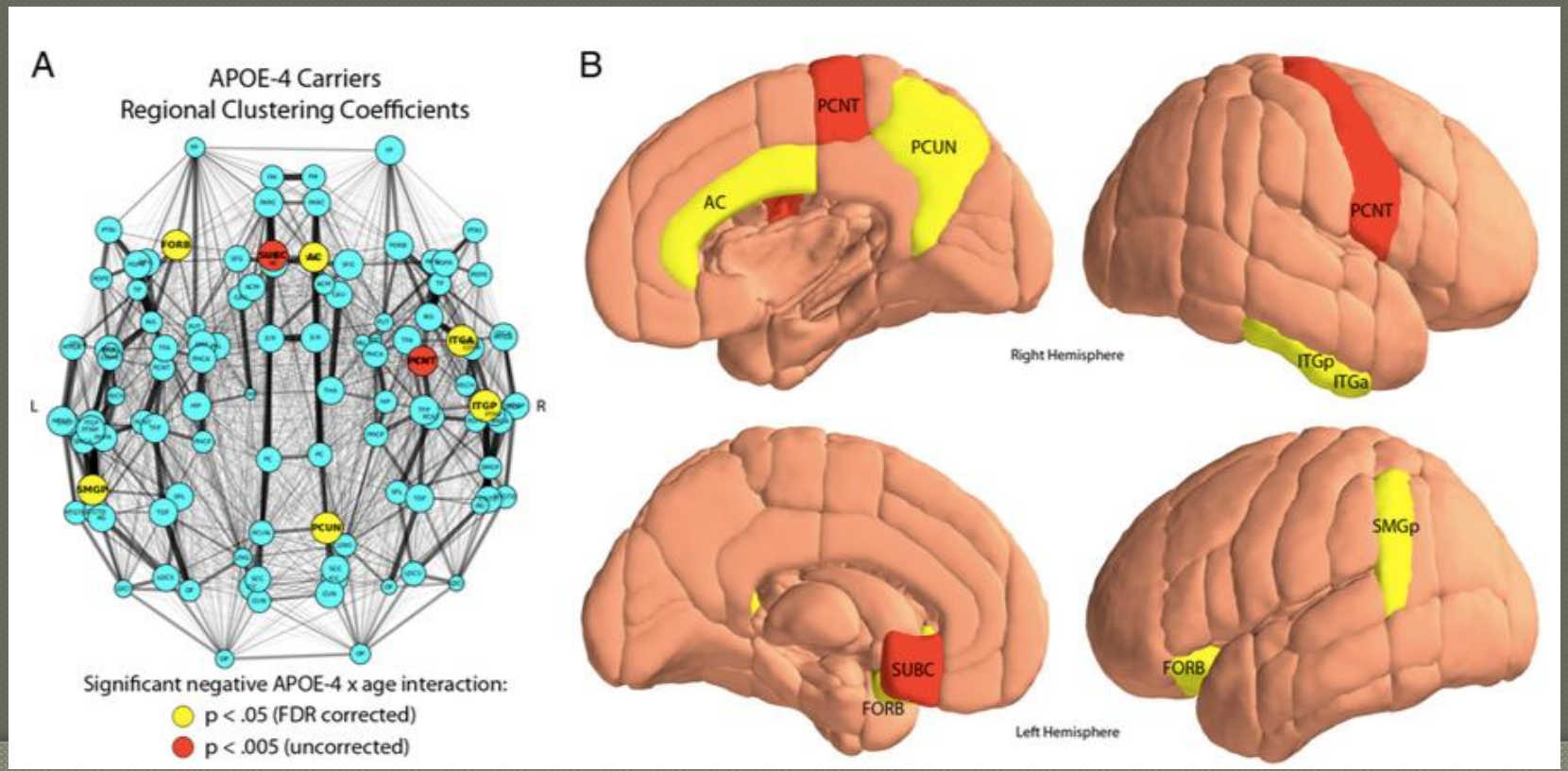




Network structure in healthy older APOE-4 carriers with DTI

- HC is part of the DMN, affected in AD
- DMN clustering coefficient decreases more rapidly with age in APOE-4 carriers

Jesse Brown, Ph.D.



Unique network connectivity in young APOE-4 carriers

Tessa Harrison

Dissertation orals

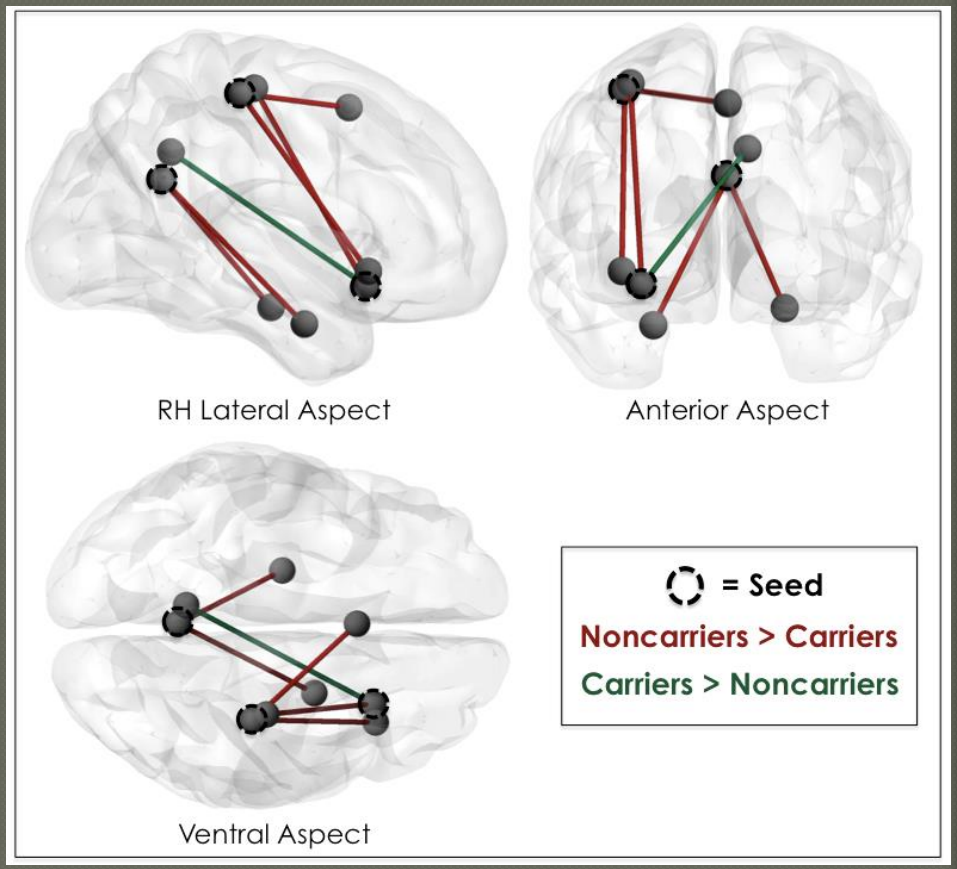
OHBM, Hamburg

OHBM, Honolulu

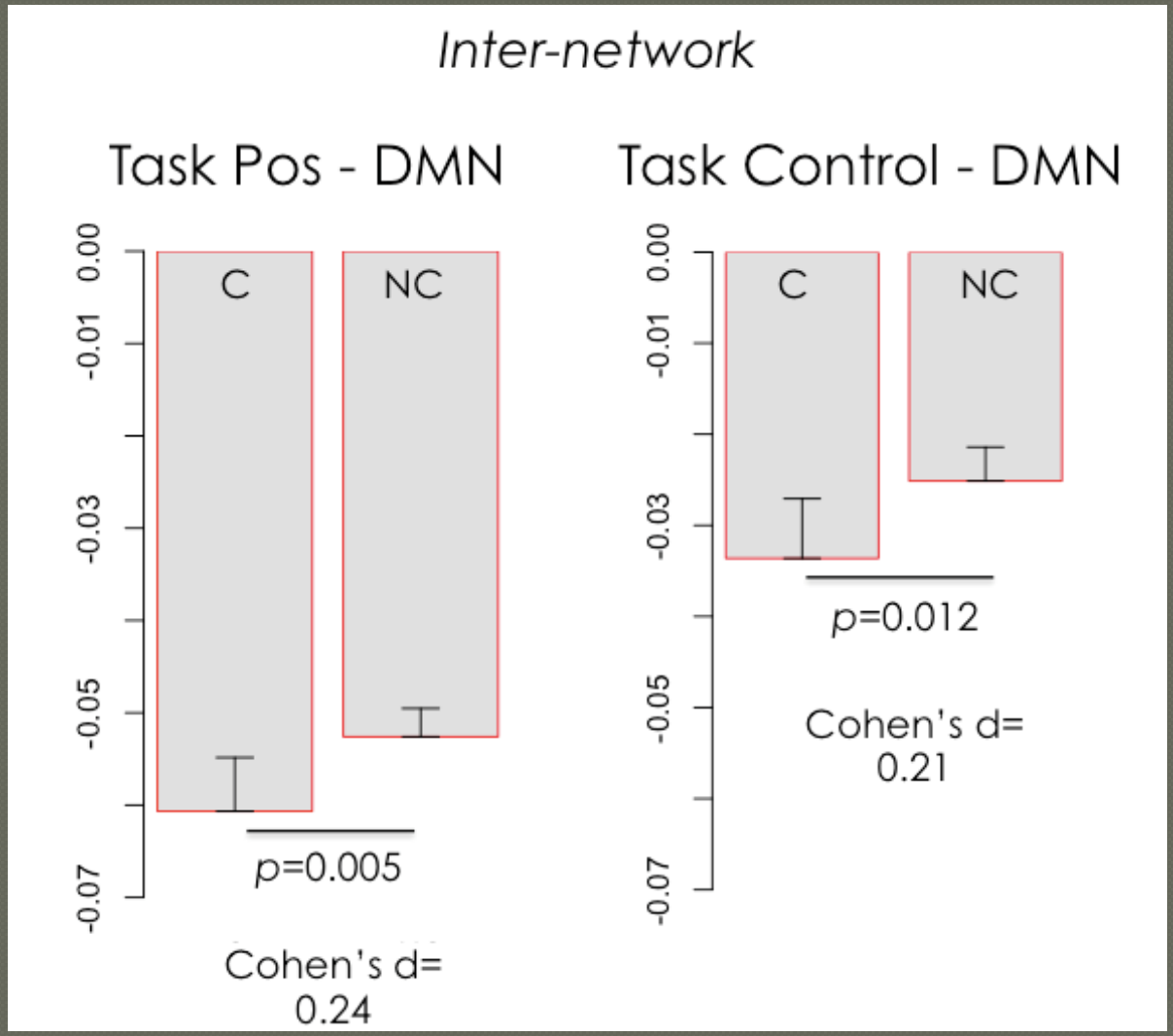
LA Science Center

Unique network connectivity in young APOE-4 carriers

- Resting state fMRI in 570 subjects from the Duke Genetics Study ages 18-22
- Seed-Based Analysis of DMN, sensory motor networks



APOEε4 carriers have relatively greater segregation between networks



NeuroImage

Volume 65, 15 January 2013, Pages 364–373

APOE e4 polymorphism in young adults is associated with improved attention and indexed by distinct neural signatures

J.M. Rusted[a], S.L. Evans[a], S.L. King[a], N. Dowell[b], N. Tabet[c], P.S. Tofts[b]

RESEARCH ARTICLE | NEUROSCIENCE

Differential splicing and glycosylation of Apoer2 alters synaptic plasticity and fear learning

Catherine R. Wasser[1,2,*,†], Irene Masiulis[2,†], Murat S. Durakoglugil[1,2], Courtney Lane-Donovan[1,2], Xunde Xian[1,2], Uwe Beffert[2], Anandita Agarwala[2], Robert E. Hammer[3], and Joachim Herz[1,2,4,5,*]

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† These authors contributed equally to this work.

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Benefits of a vulnerable hippocampus?

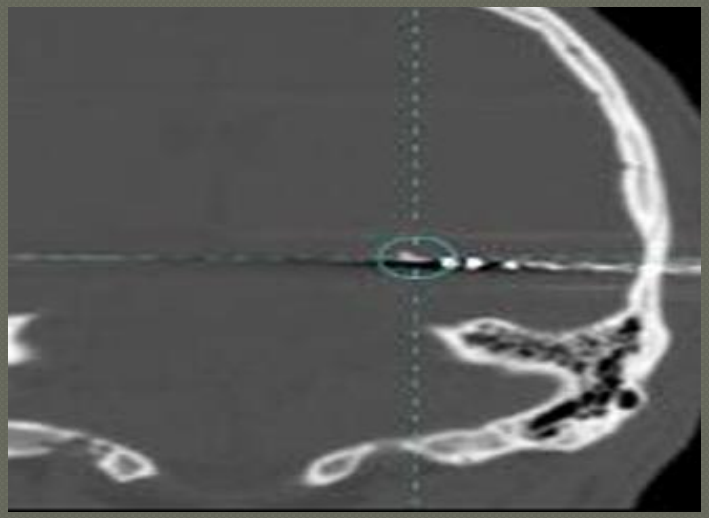
- Vulnerable to anoxia
  - High oxygen utilization → higher baseline activity
  - Pre-exposure to mild hypoxia is protective of later hypoxia (Gidday et al 1994)
- Epilepsy- HC remembers new firing patterns
  - Kindling model is a primary means to study LTP
- Sensitive to stress
  - Facilitates memory for emotionally salient events that may increase survivability
- Aging and genetic risk for memory loss
  - APOE-4 may confer unique (unknown) advantages in information processing; may enhance LTP (antagonistic pleiotropy)

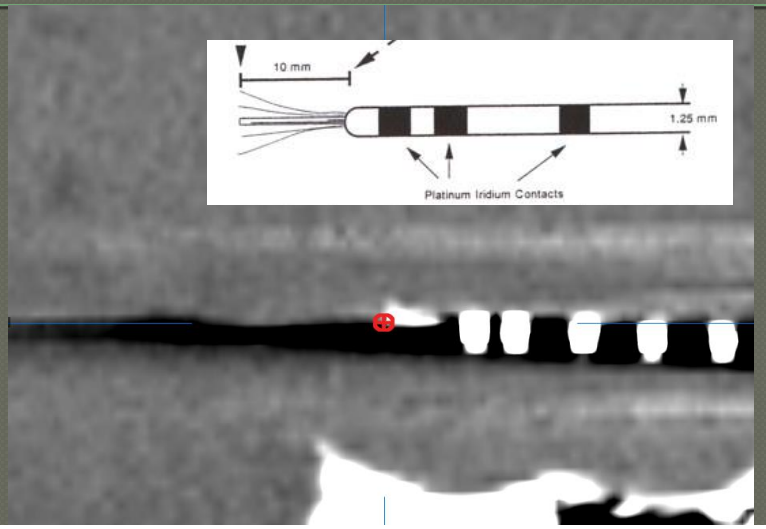
Conclusions

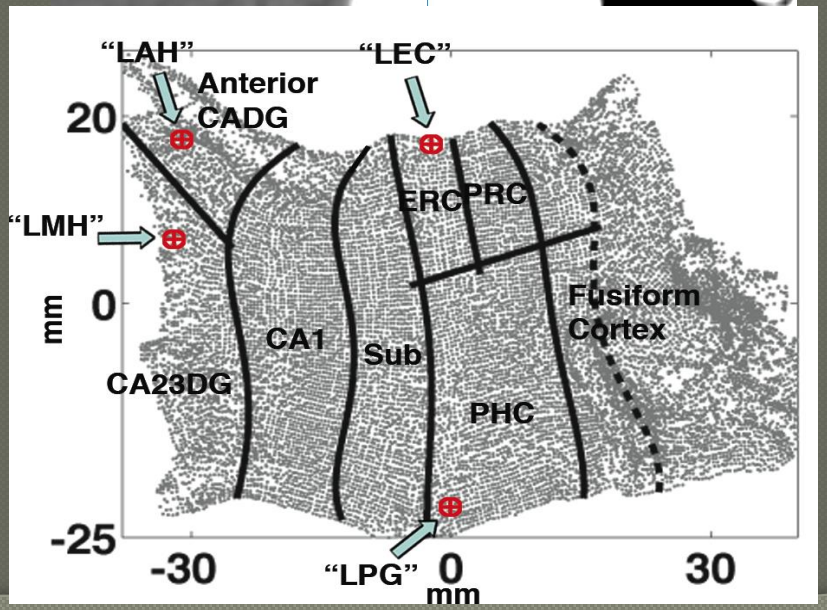
- Using HR fMRI with similar tasks/methods, we see heterogeneity in HC sub-regions just as in rodent
- Across content areas, same processes (encoding and retrieval) have same sub-regional anatomy
- HC anatomy is process-determined, but content-promiscuous
  - Permits tremendous plasticity and response flexibility
- What is unique about the human HC is not how it functions, but the content it receives
- The same feature of input flexibility creates an inevitable vulnerability in the HC


Thank you!

Correlating fMRI, Neural firing and local field potentials Ekstrom et al,. 2007





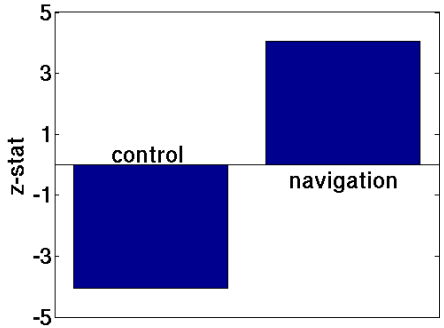


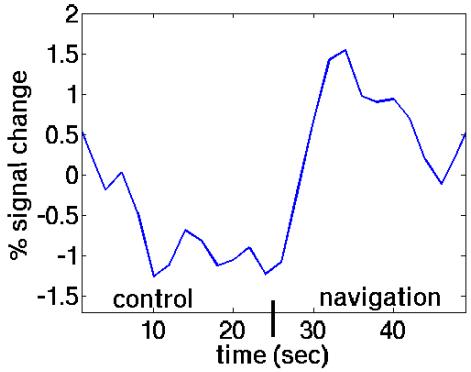
Correlating fMRI, Neural firing and local field potentials

Ekstrom et al, Hippocampus. 2007

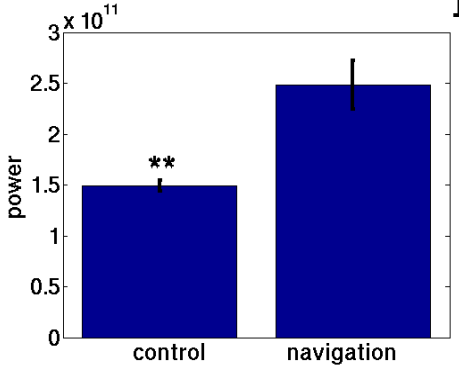
“Yellow Cab” Freely navigated city to find passengers, deliver to stores

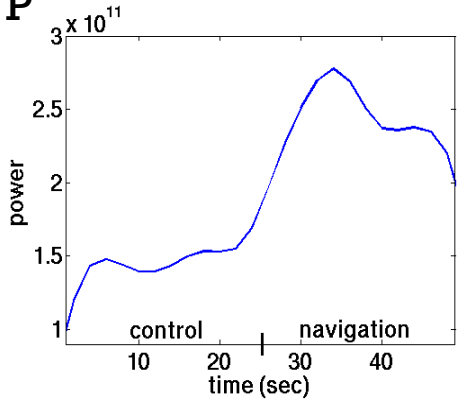
BOLD



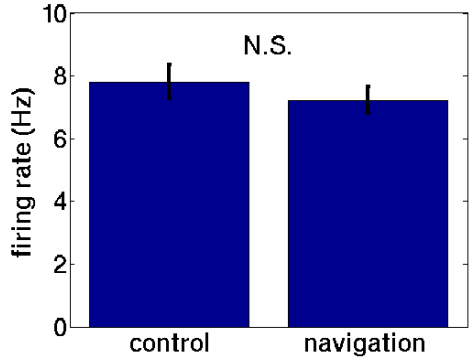


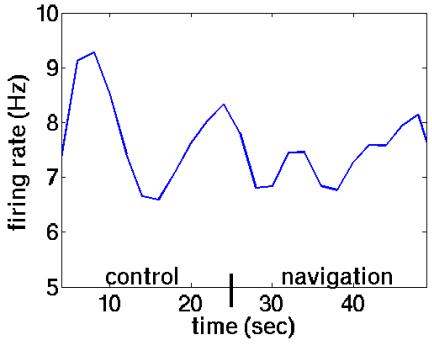
LFP

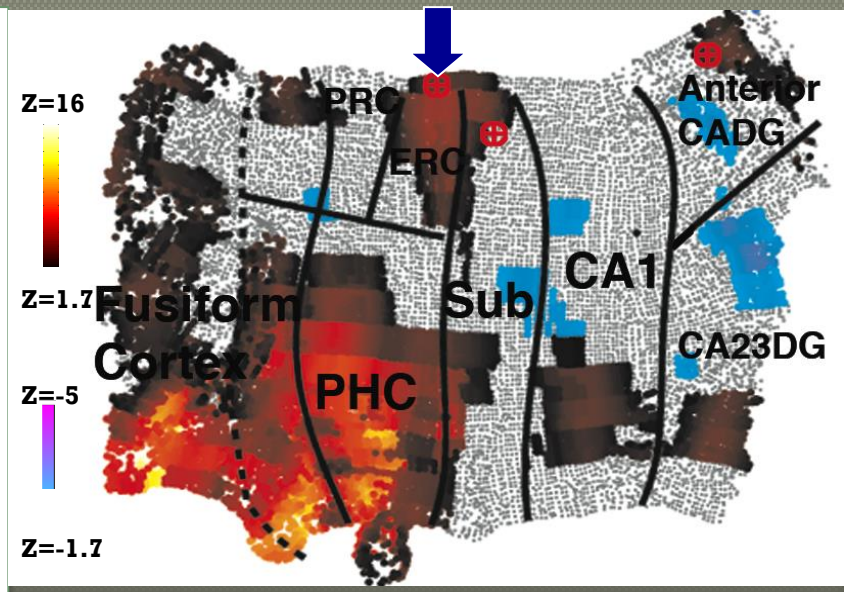




Neurons







BOLD correlates with LFP in theta band