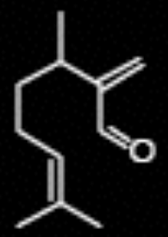
Reading the Mind of a Fly
Neural Coding in the Mushroom Body

What are you thinking...?

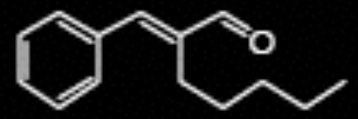
Glenn Turner, Cold Spring Harbor Lab.

KITP Smell15, Jun 11, 2015

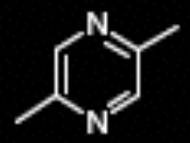
camphor



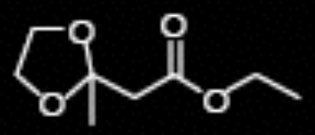
lemon



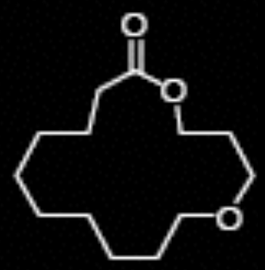
jasmine



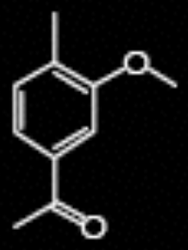
chocolate



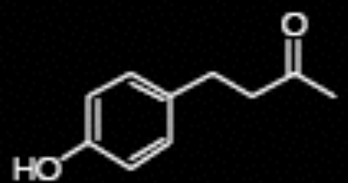
apple



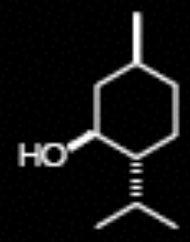
musk



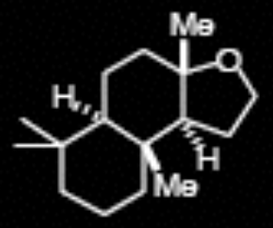
vanilla



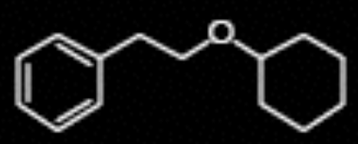
raspberry



peppermint

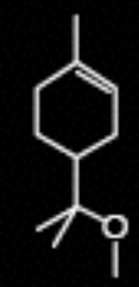


amber

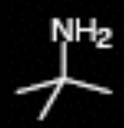


hyacinth

eucalyptus

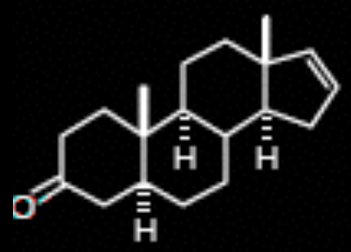


grapefruit



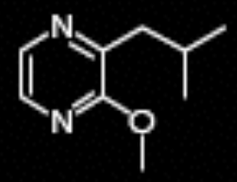
fish

garlic



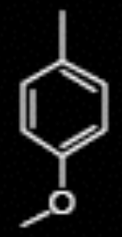
urine

fatty



green pepper

skunk



marigold

woody

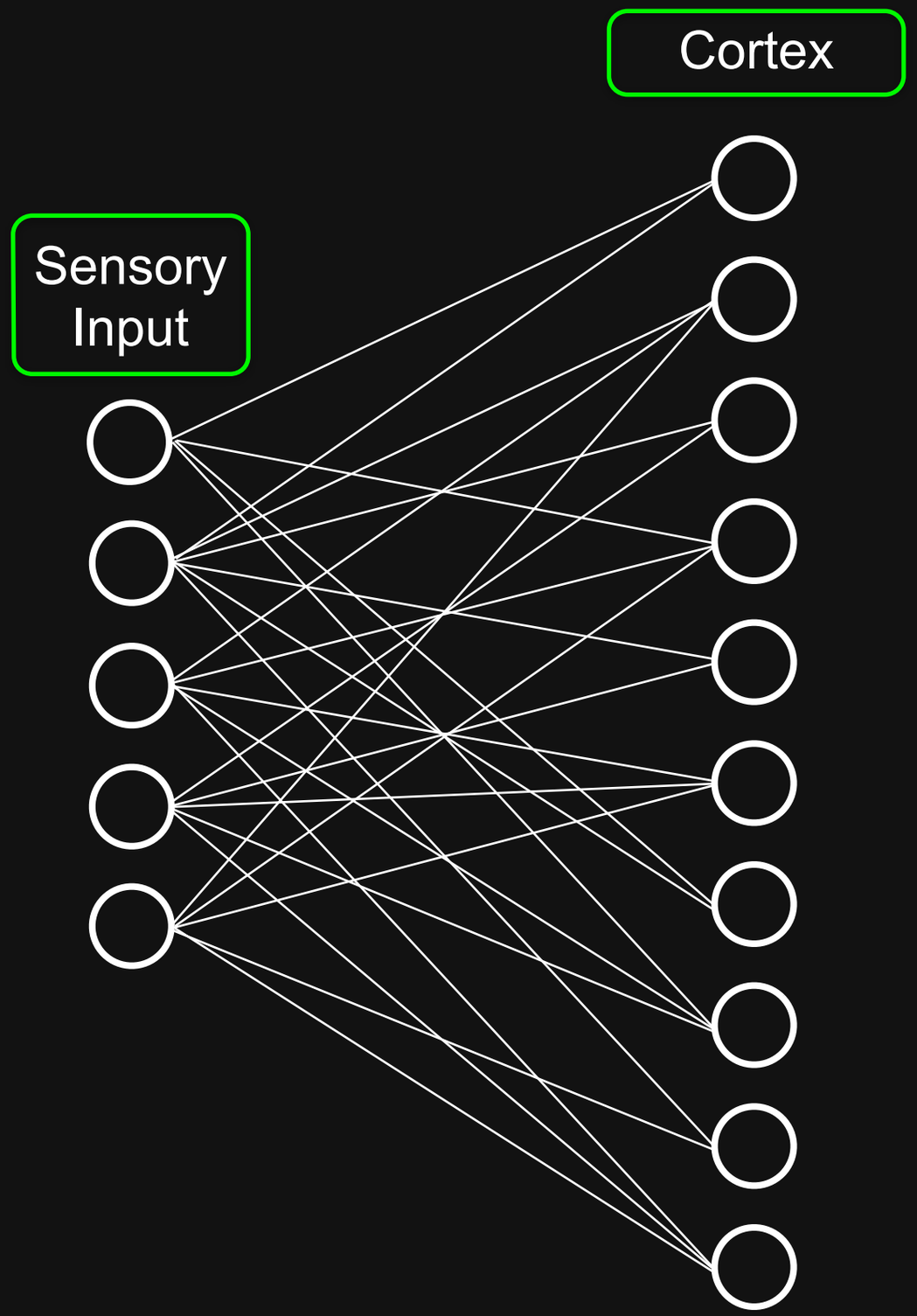
The problem:

How represent so many different stimuli?

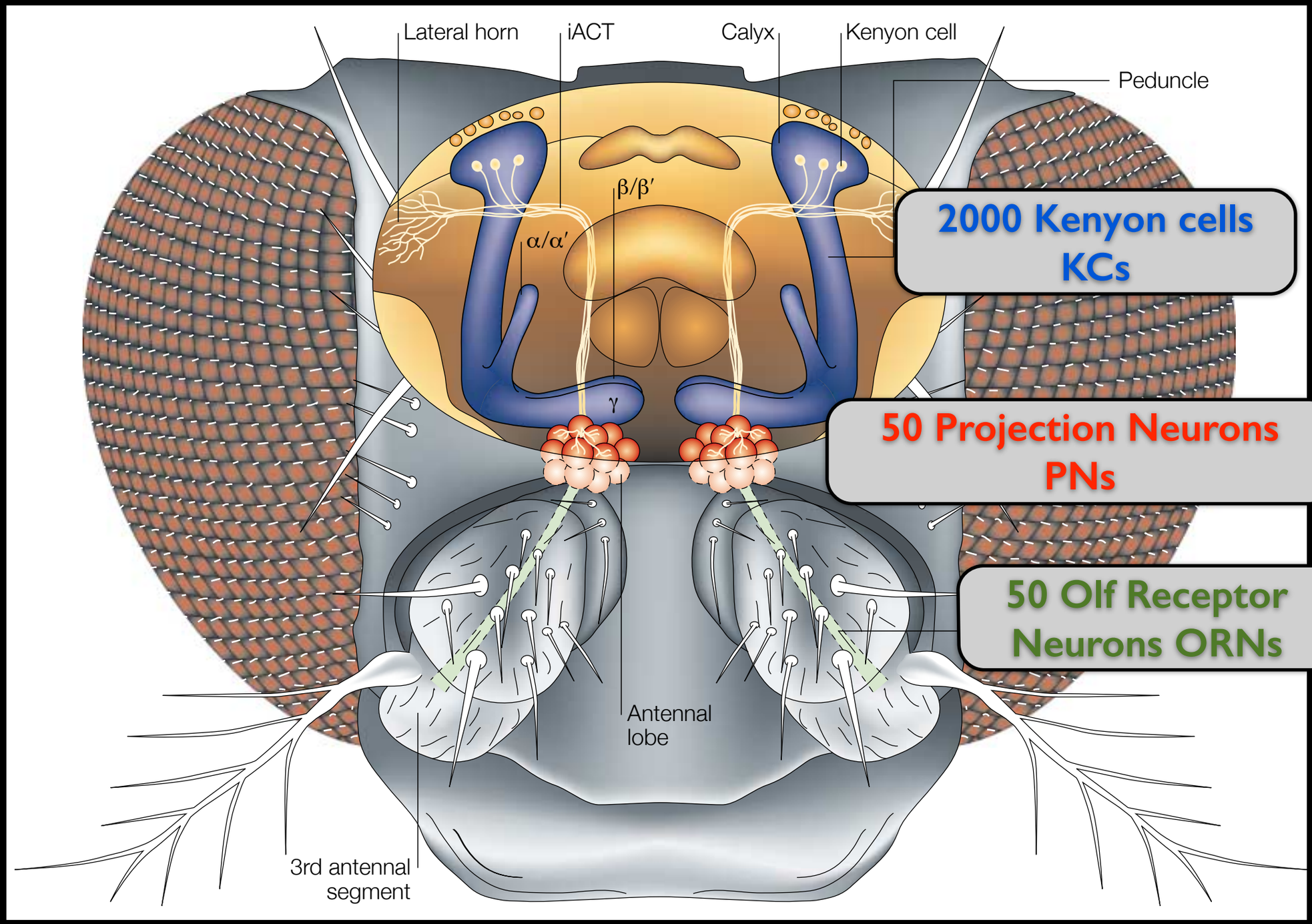
Capacity

Discriminability

Expanding structure of neural circuits

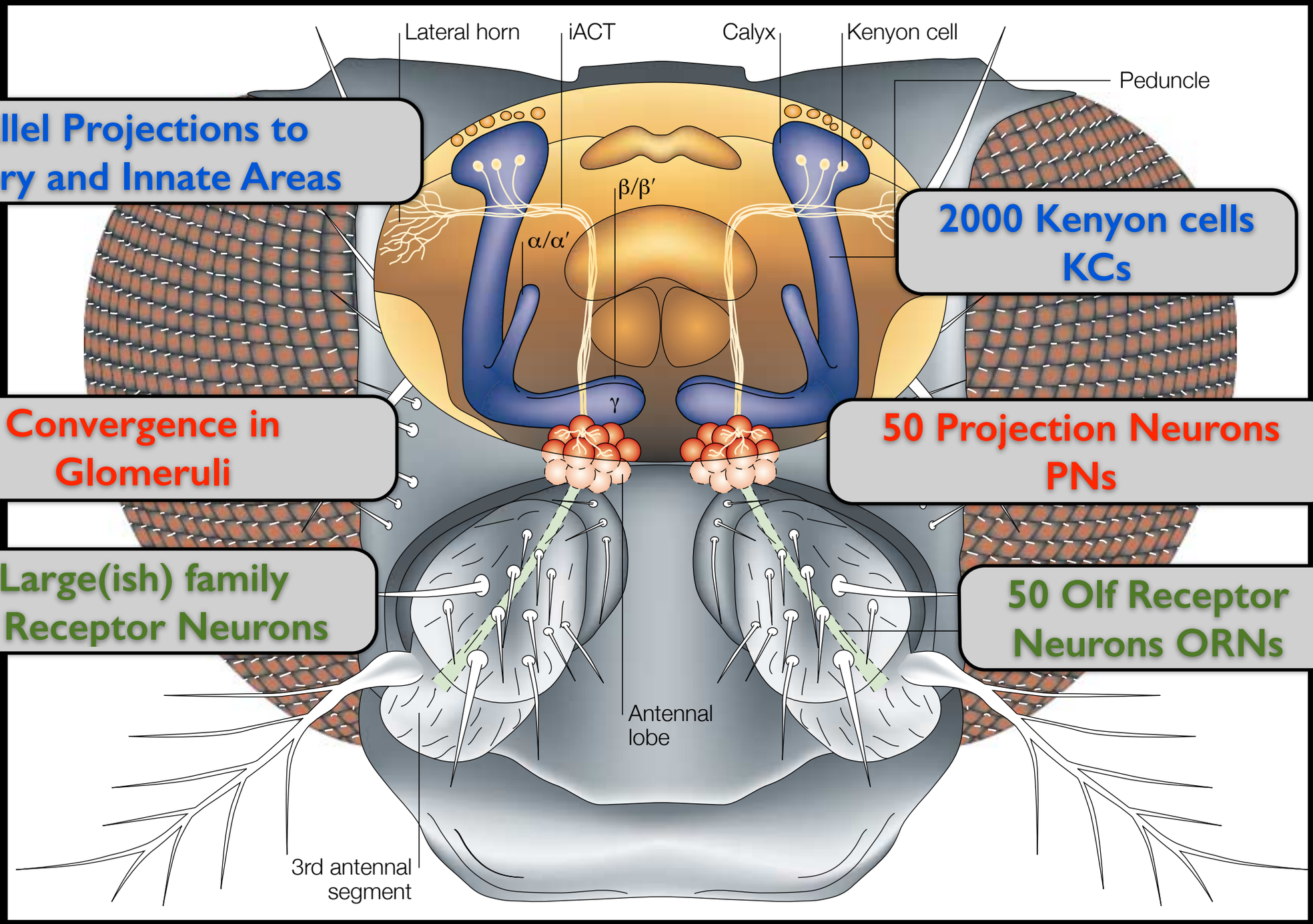


The Olfactory Circuit



Heisenberg Nat Rev Neuro 2003

The Olfactory Circuit



Parallel Projections to Memory and Innate Areas

2000 Kenyon cells KCs

Convergence in Glomeruli

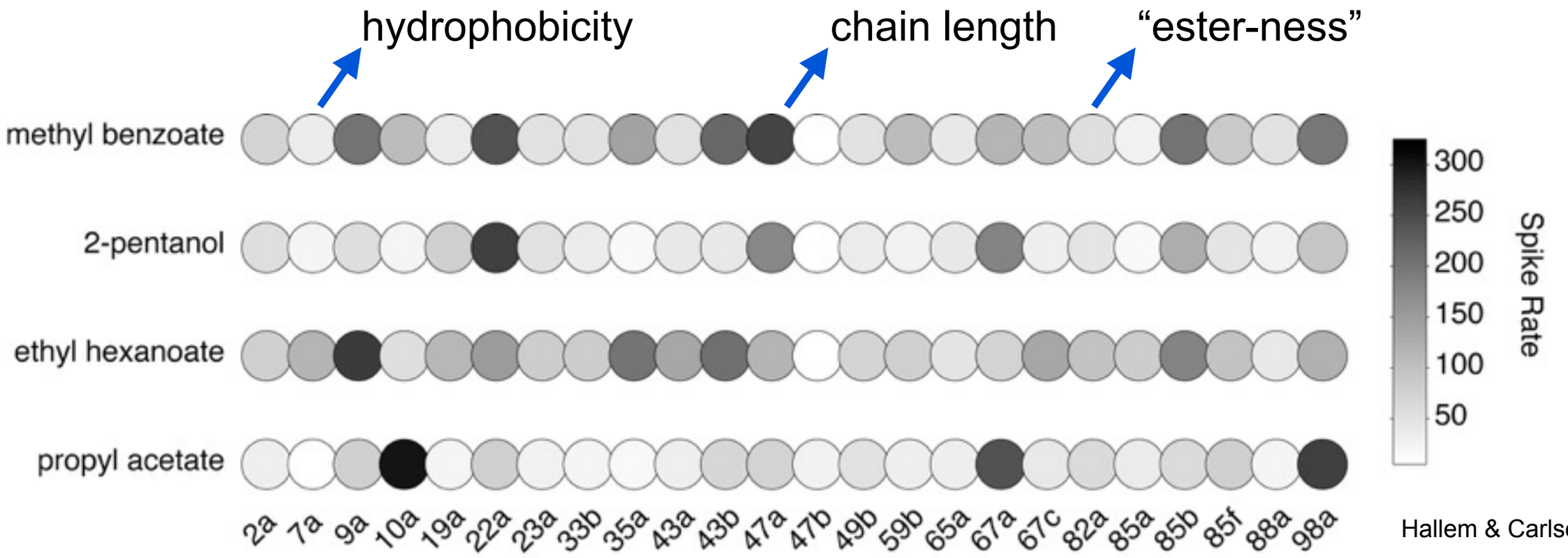
50 Projection Neurons PNs

Large(ish) family of Receptor Neurons

50 Olf Receptor Neurons ORNs

Heisenberg Nat Rev Neuro 2003

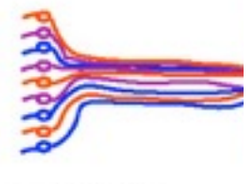
Combinatorial representation of monomolecular odorants



Hallem & Carlson 2006

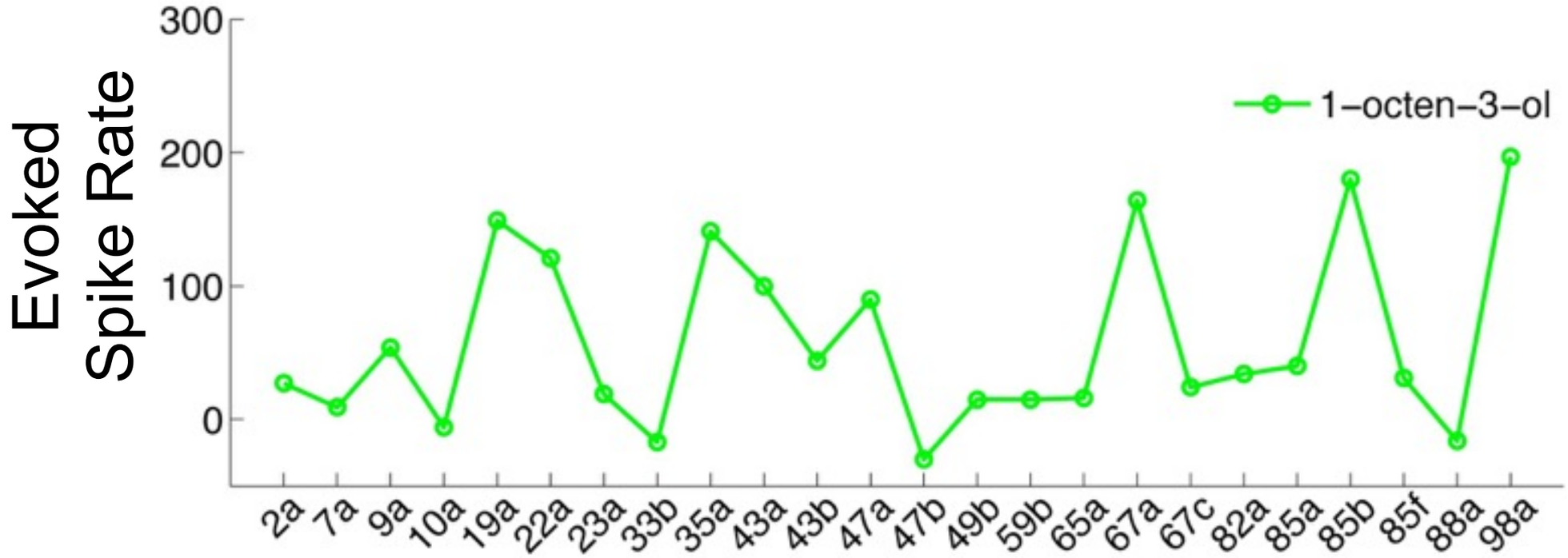
Not 1 odor = 1 neuron

Combination of active ORNs conveys the identity of the odor



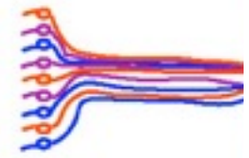
Sensory neuron representations

ORN population response (24 of 51 ORN types) to a single odor



Dense combinatorial representations for high capacity but...

Hallem and Carlson *Cell* 2005



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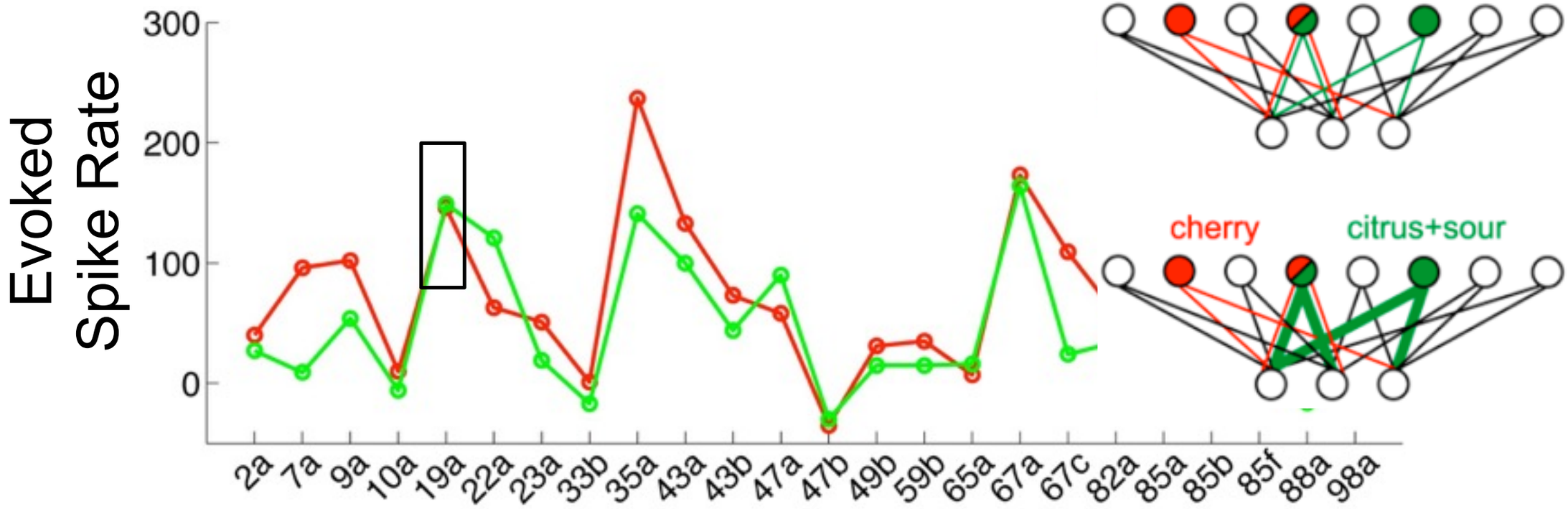


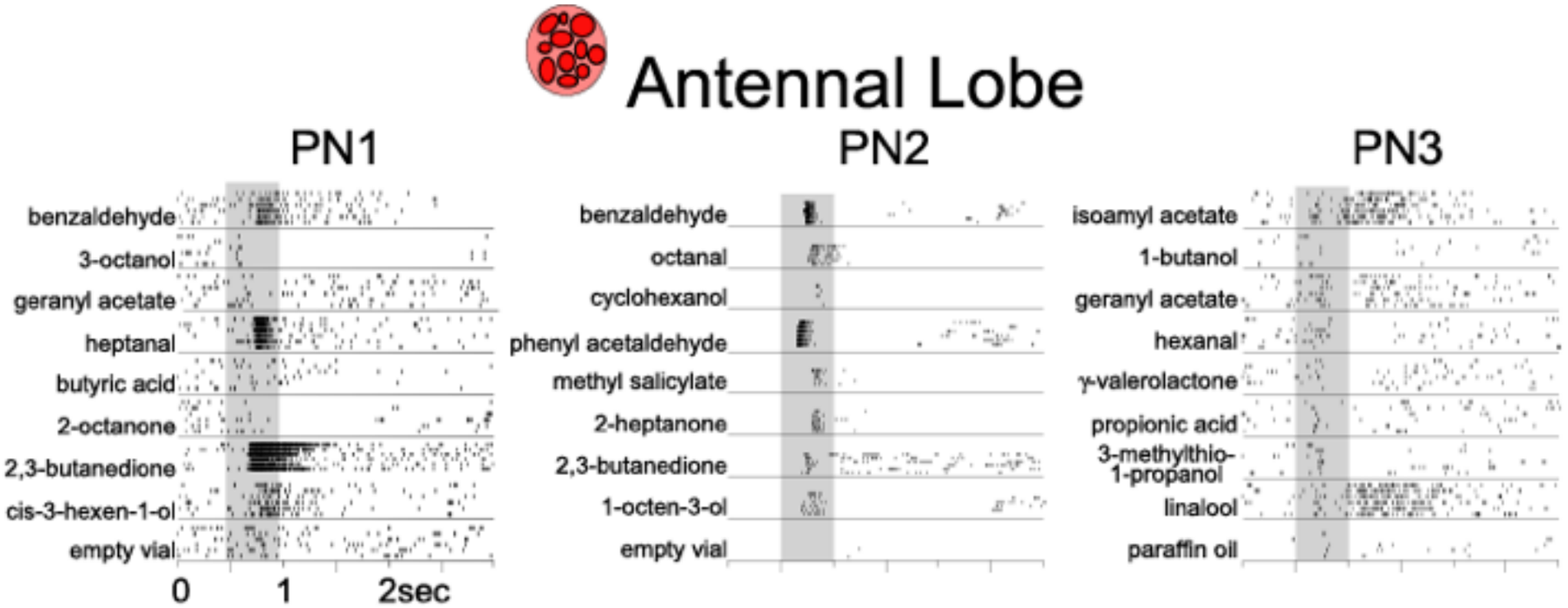
synaptic interference

Dense combinatorial representations for high capacity but...

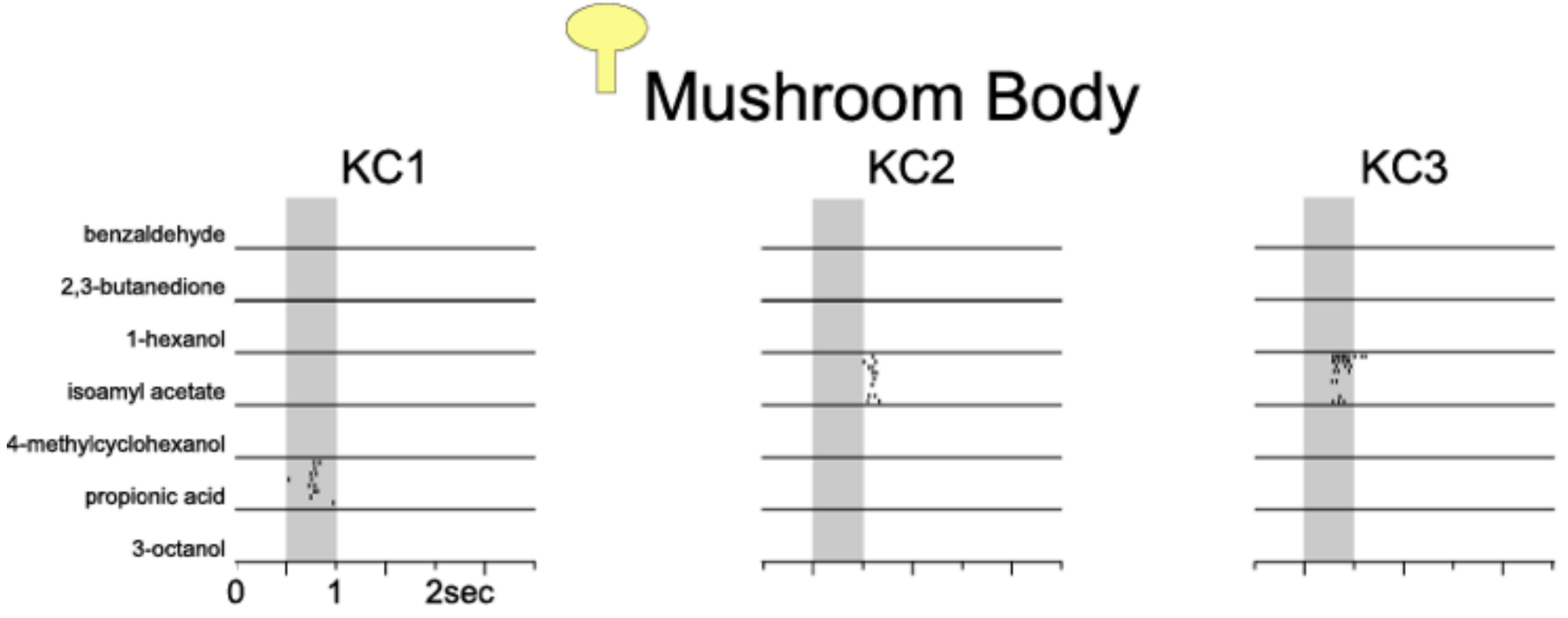
Overlapping odor representations make accurate learning difficult

Hallem and Carlson *Cell* 2005

Sparse and odor-selective activity in the MB



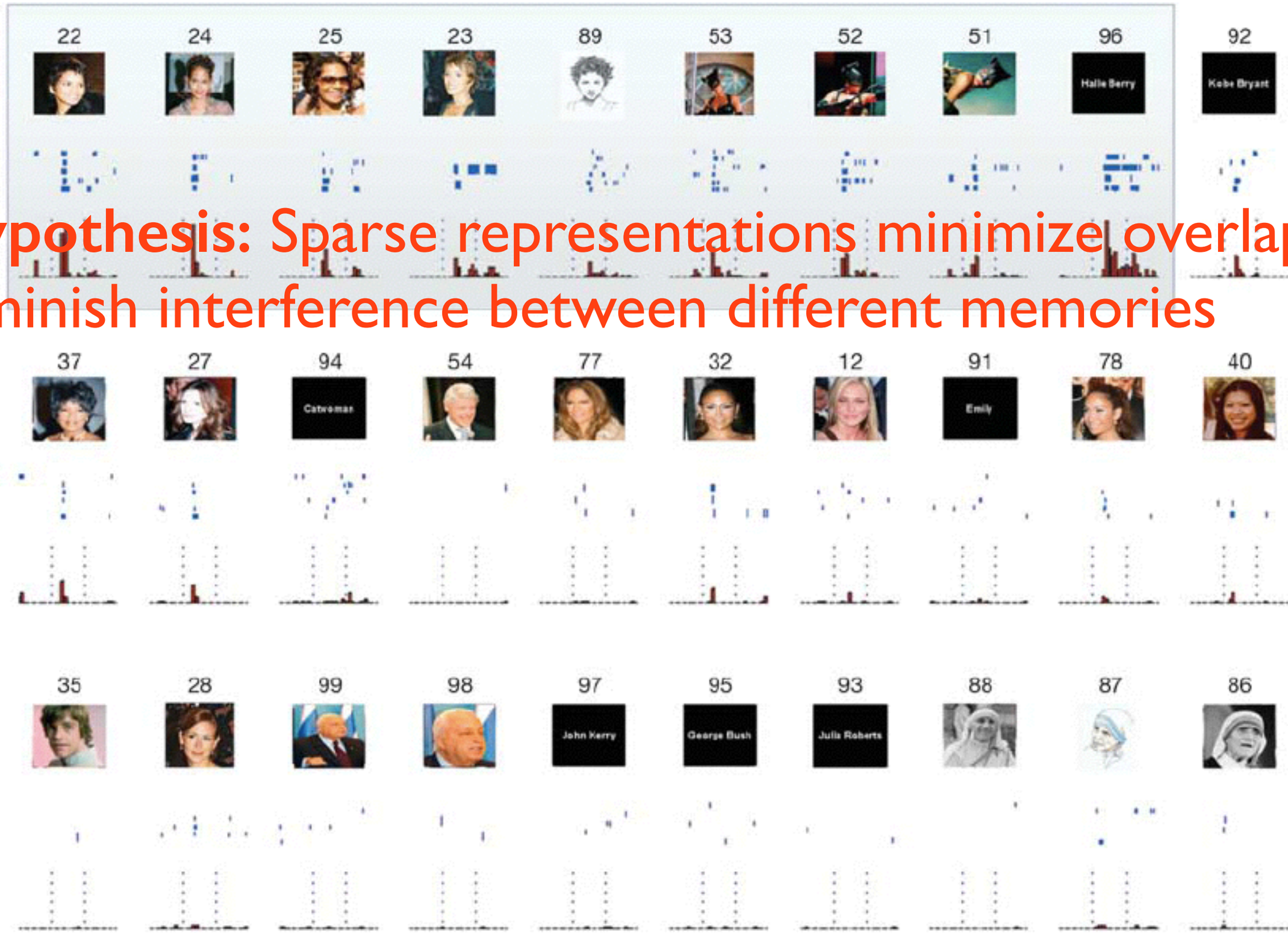
Respond to 50% of odors



Respond to 5% of odors

MB neurons exhibit highly odor-specific responses

Sparse representations in human peri-hippocampal brain areas



Hypothesis: Sparse representations minimize overlap and diminish interference between different memories

Quiroga et al Nature 2005

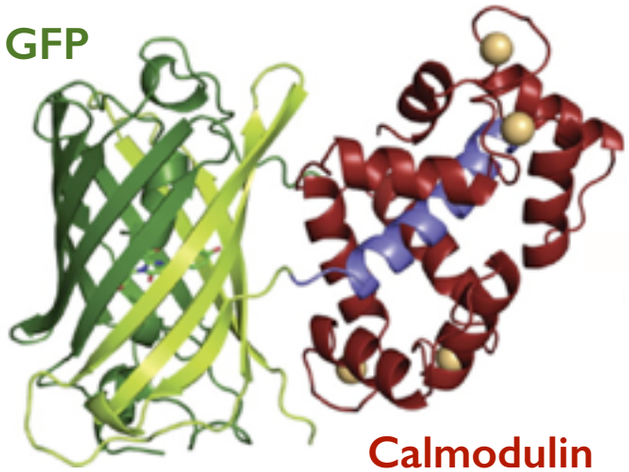
Hypothesis: Sparse representations minimize overlap and diminish interference between different memories

But:

- *Maybe it's just harder to find responding neurons in the MB?*
  - *Odo-topic mapping of responses?*
- *Maybe MB neurons respond differently to natural odors?*
  - *Behaviorally relevant stimuli?*

Tracking activity of neural populations using genetically encoded calcium indicators

GCaMP v3.0



posterior

anterior

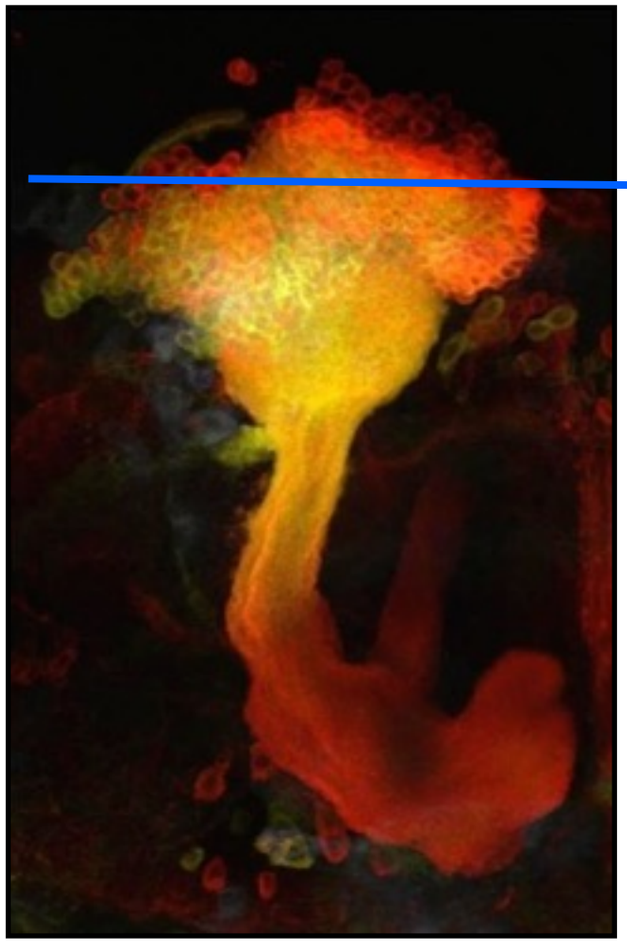
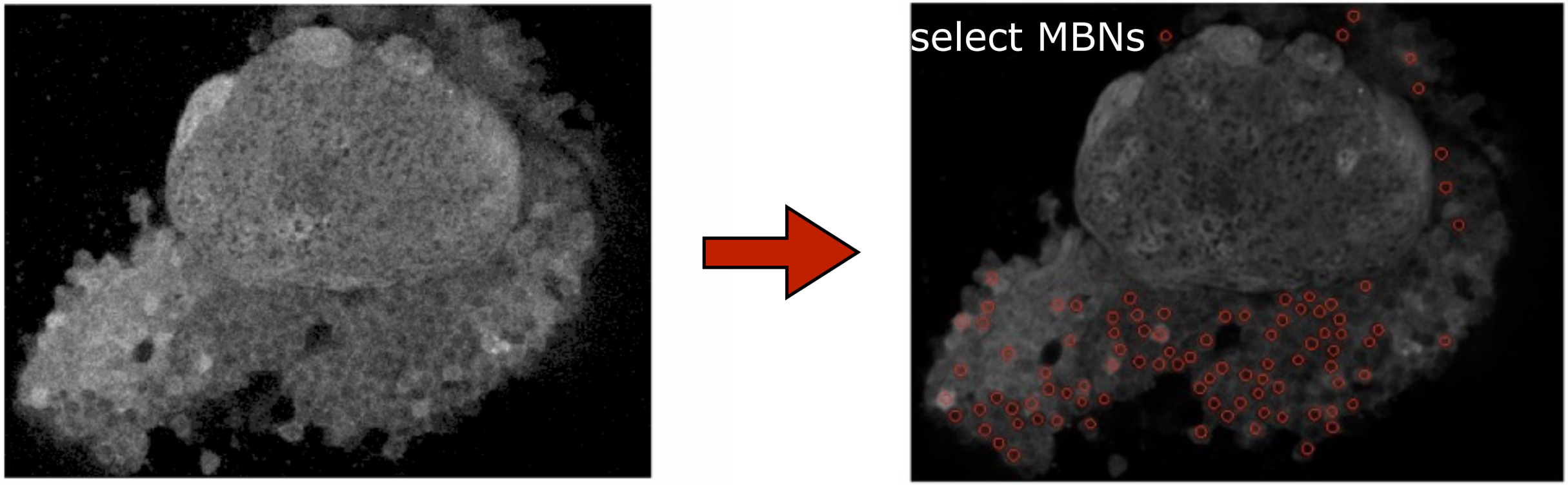


image cell bodies
in this plane
→ track 5-10%
of total population

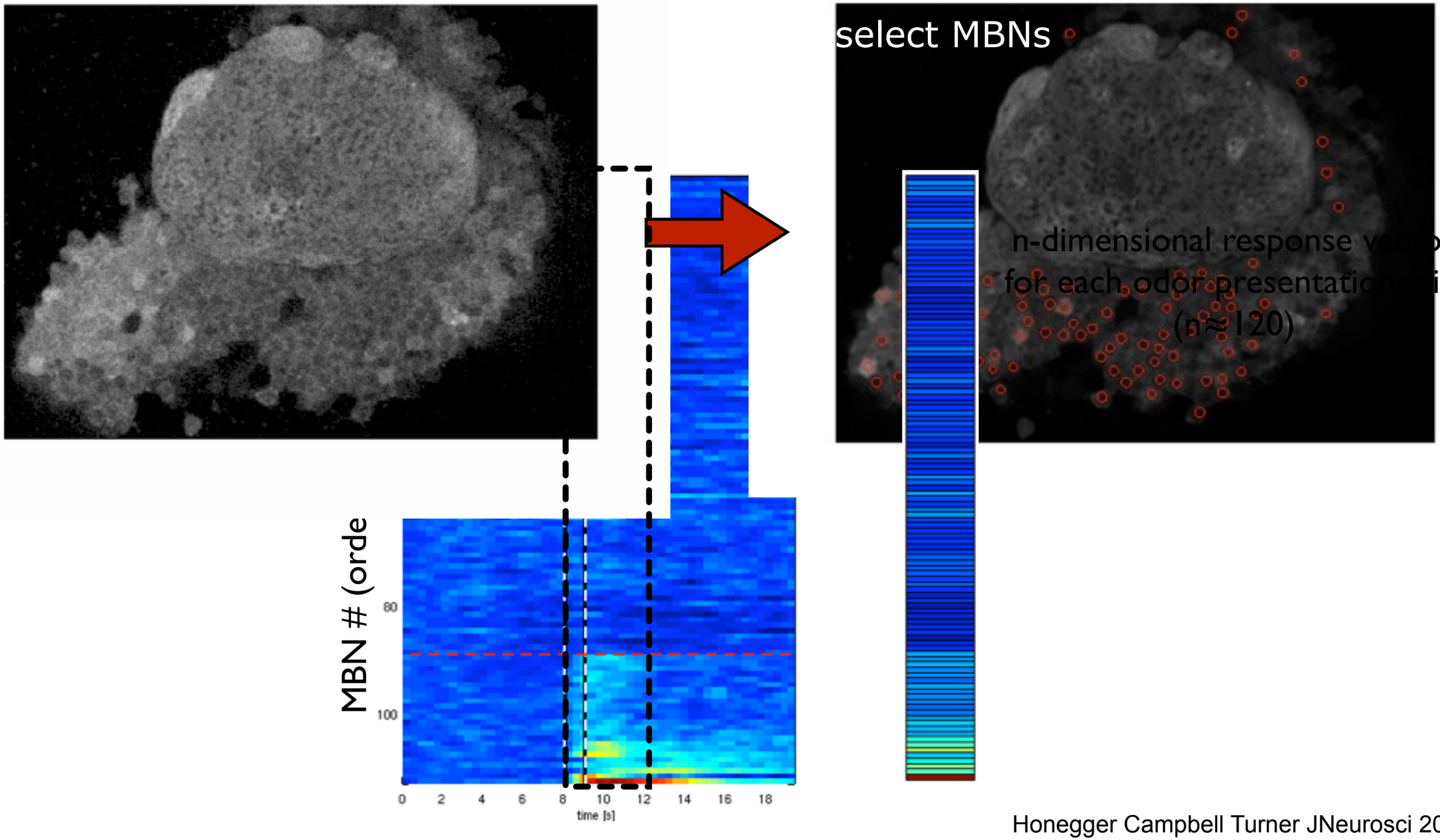
Rob Campbell & Kyle Honegger

Tracking activity of neural populations using genetically encoded calcium indicators

Track ~150 of 2000 MB cells = 5-10% total population

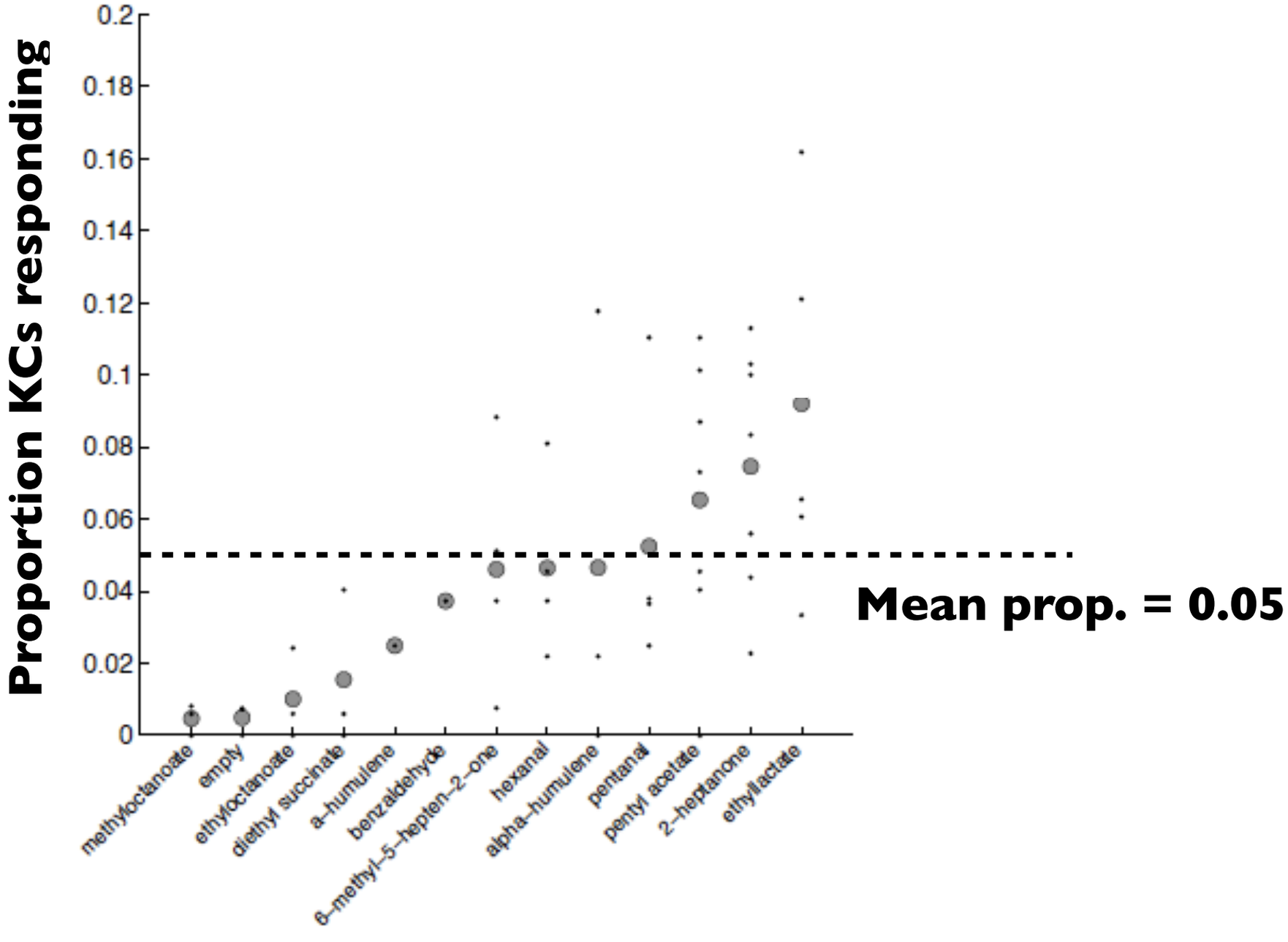


Tracking activity of neural populations using genetically encoded calcium indicators



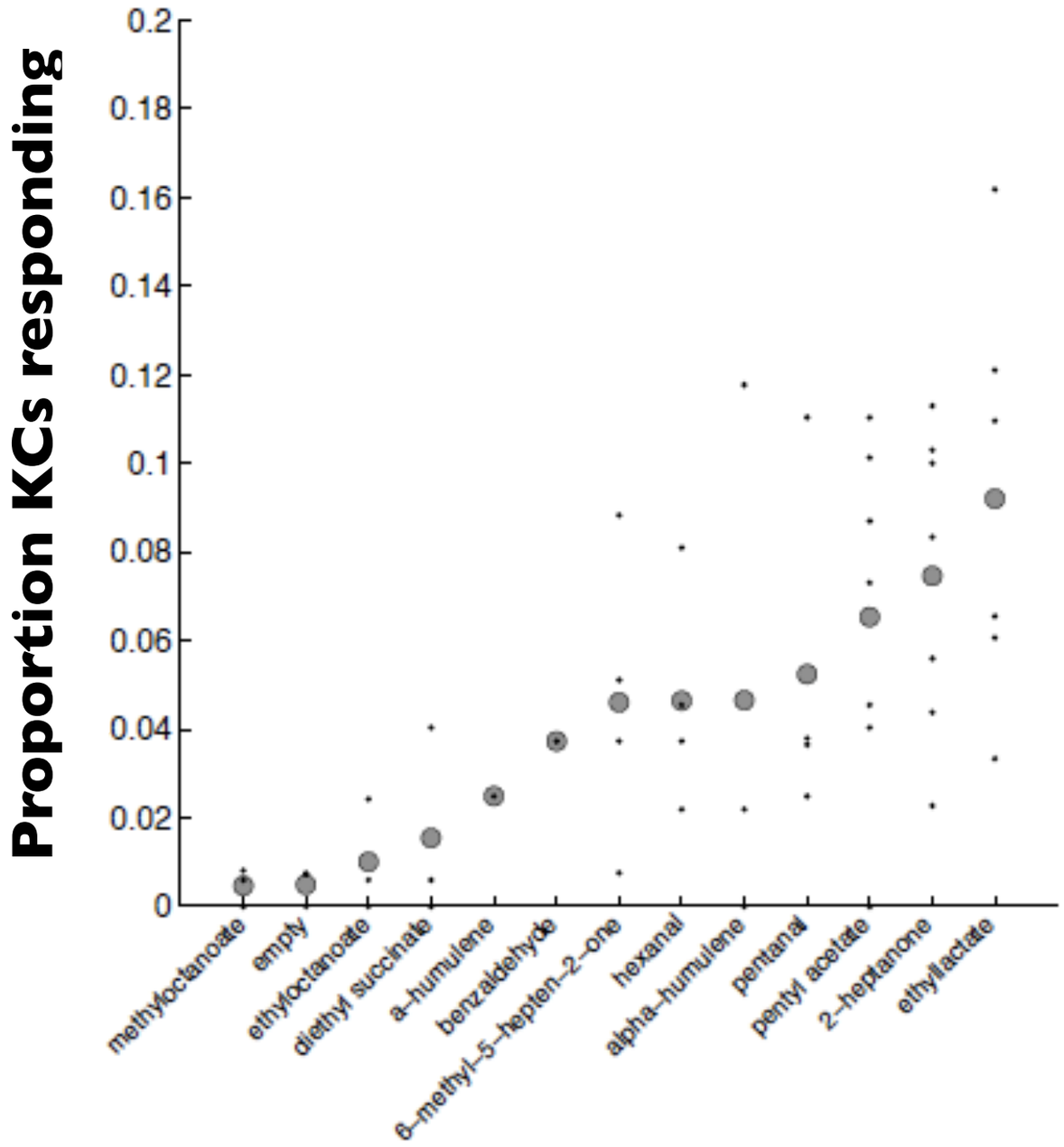
Honegger Campbell Turner JNeurosci 2011

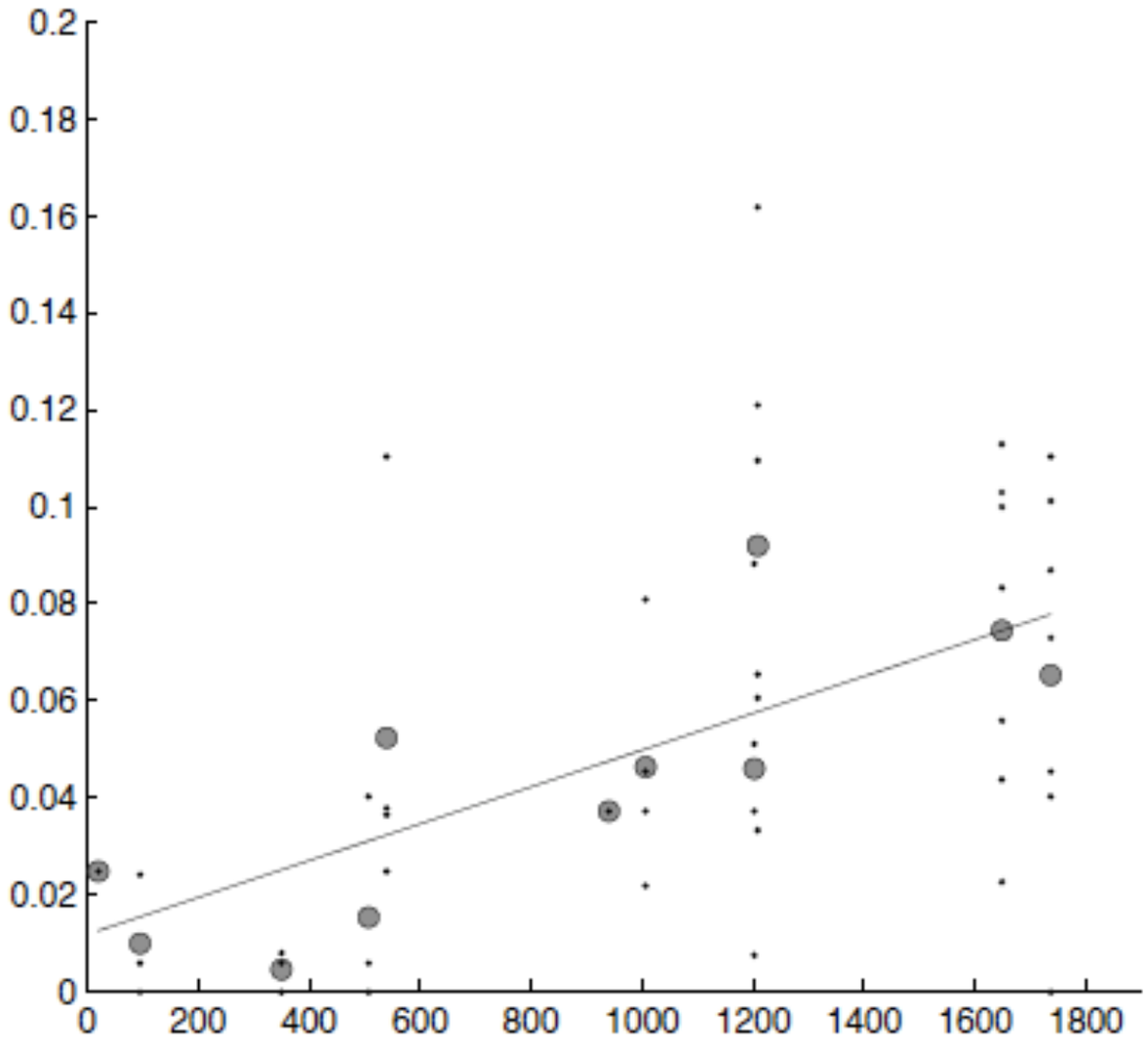
MB Odor Representations are Sparse



n = 8 flies, 933 neurons

MB Odor Representations are Sparse

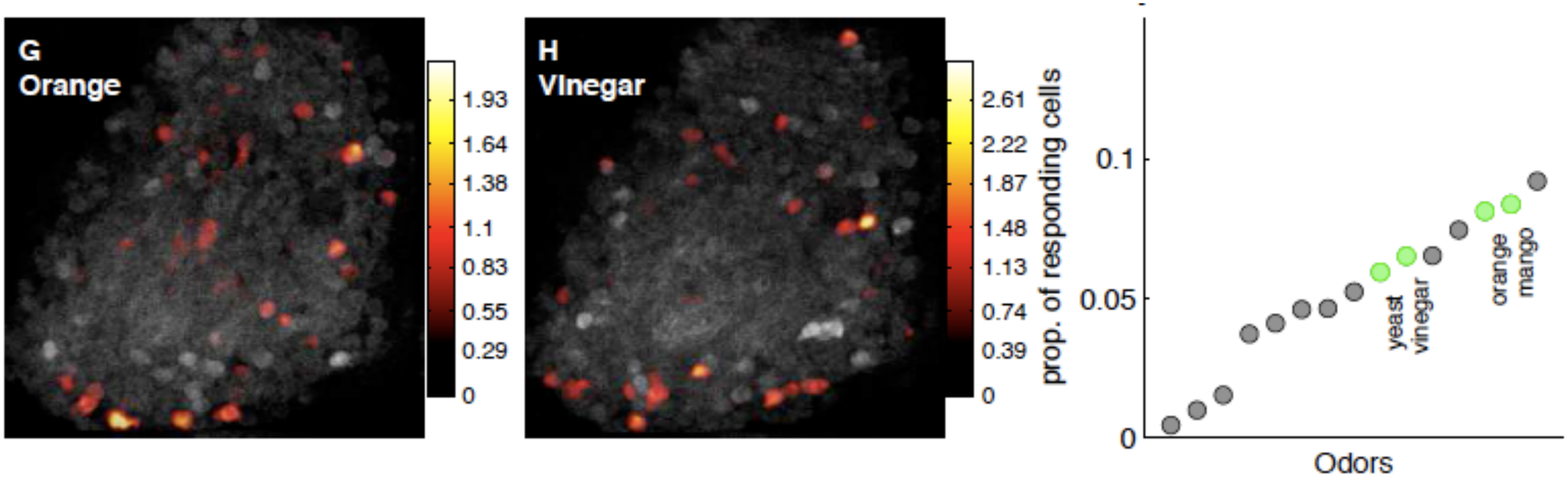




Total OSN activity

(Hallem and Carlson, 2006)

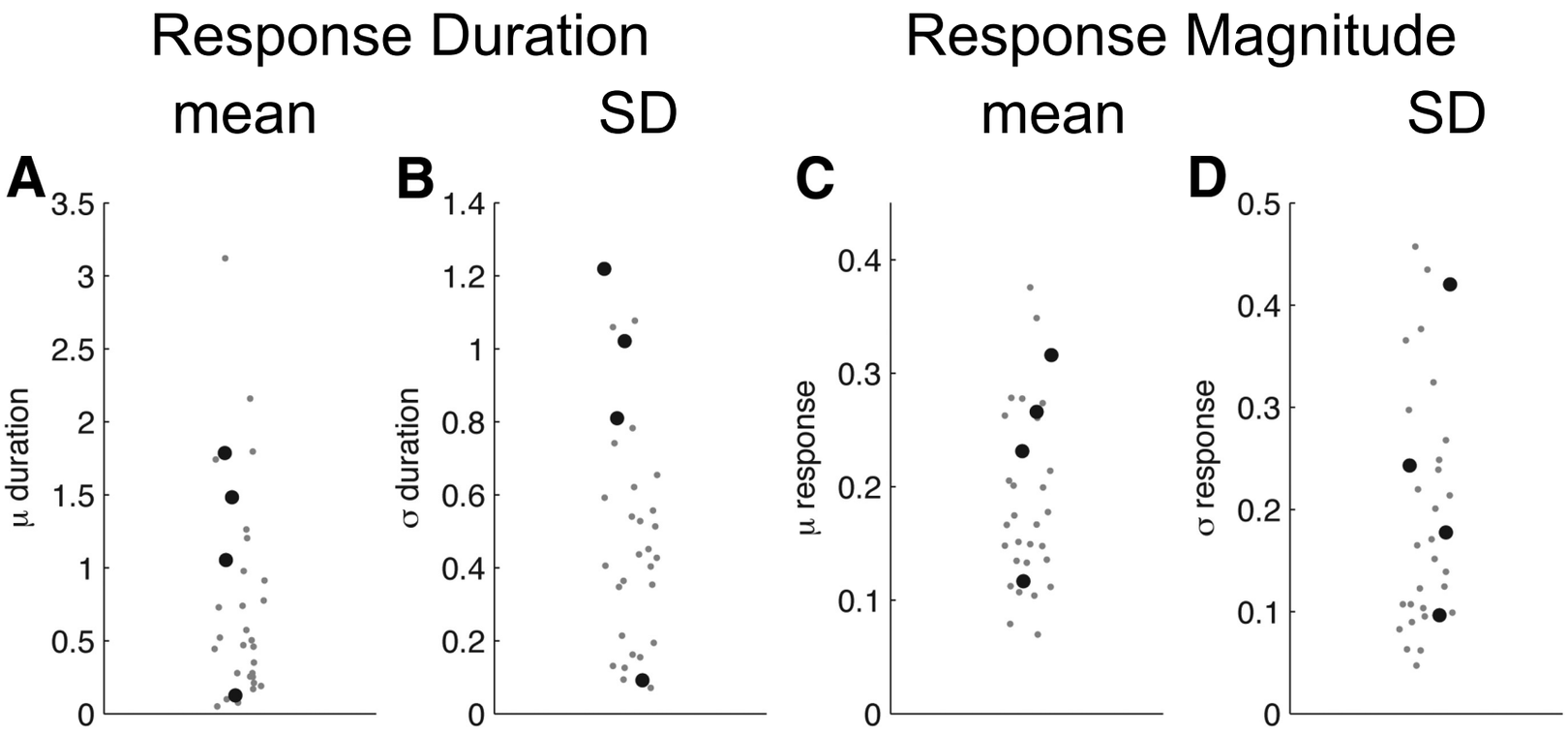
Sparse responses to natural odors



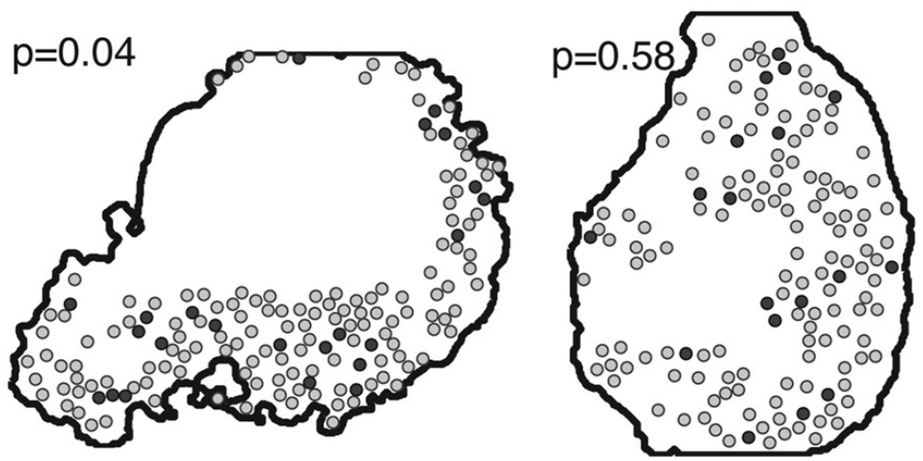
MB not specialized to respond to natural stimuli

Honegger Campbell Turner JNeurosci 2011

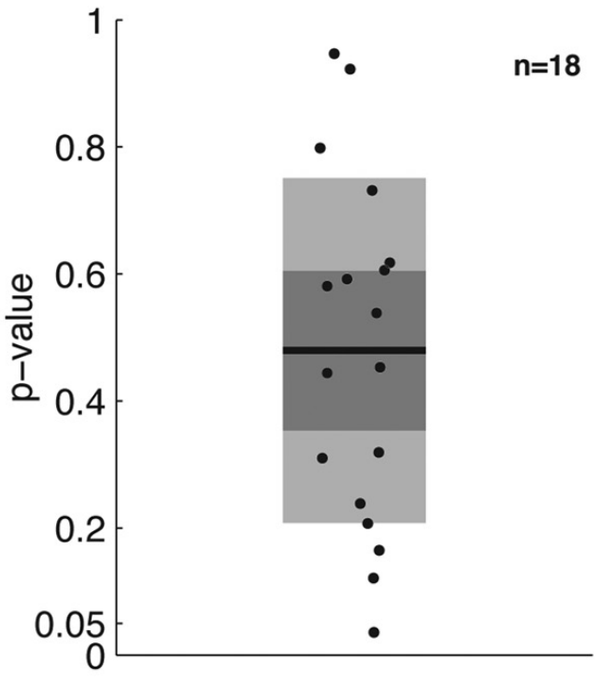
Natural vs Monomolecular Odors



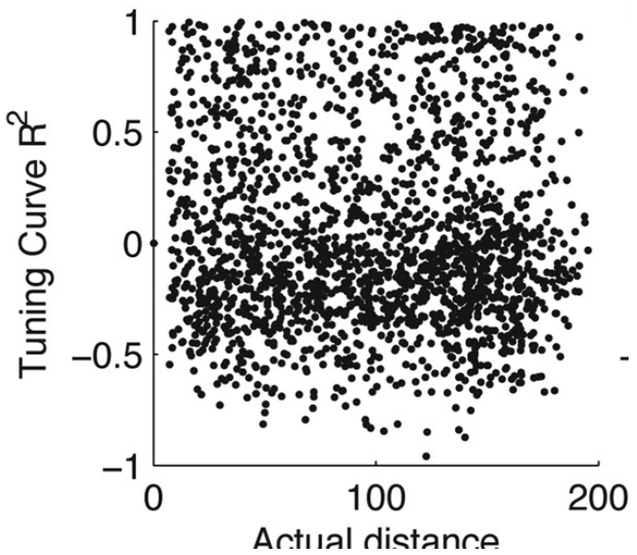
Lack of Spatial Mapping in MB



No clustering of responding cells



No clustering of similar tuning curves



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But:

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  - ✘ *Odo-topic mapping of responses?*
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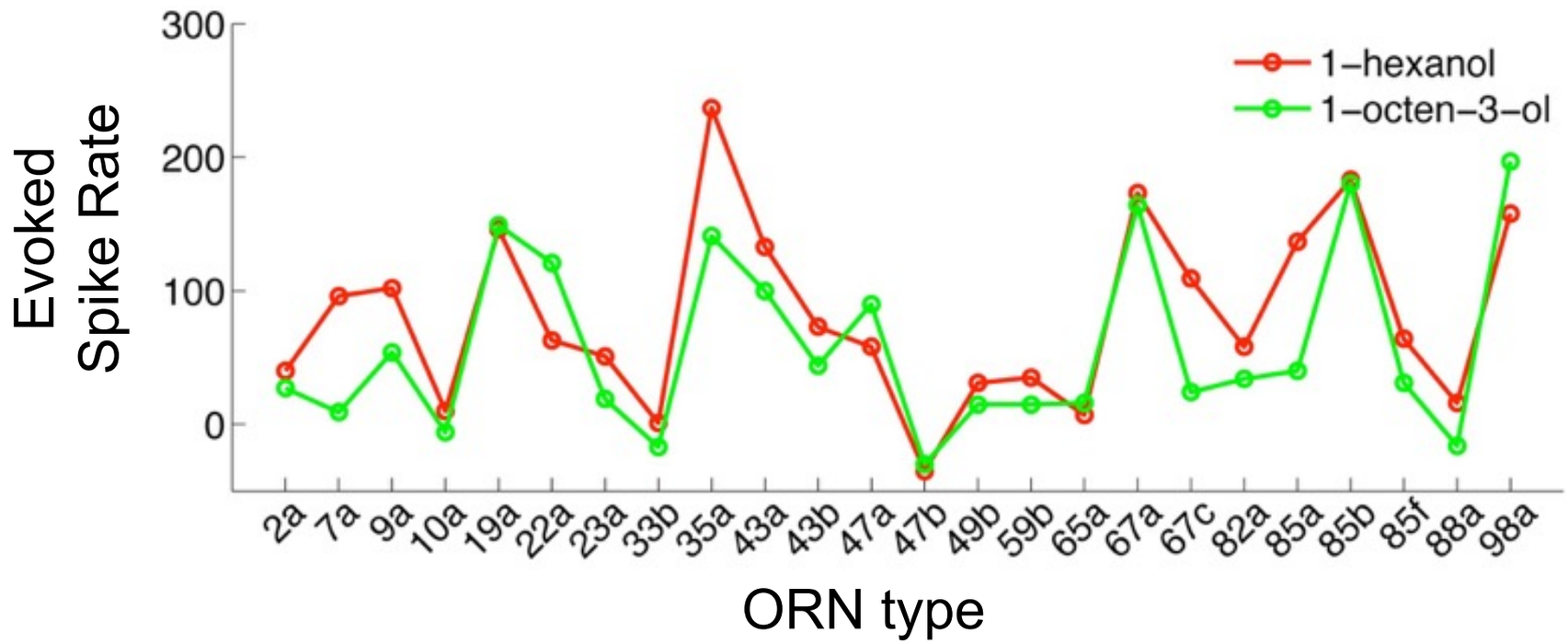
  - ✘ *Behaviorally relevant stimuli?*

Neural coding

What makes two activity patterns perceptibly different?



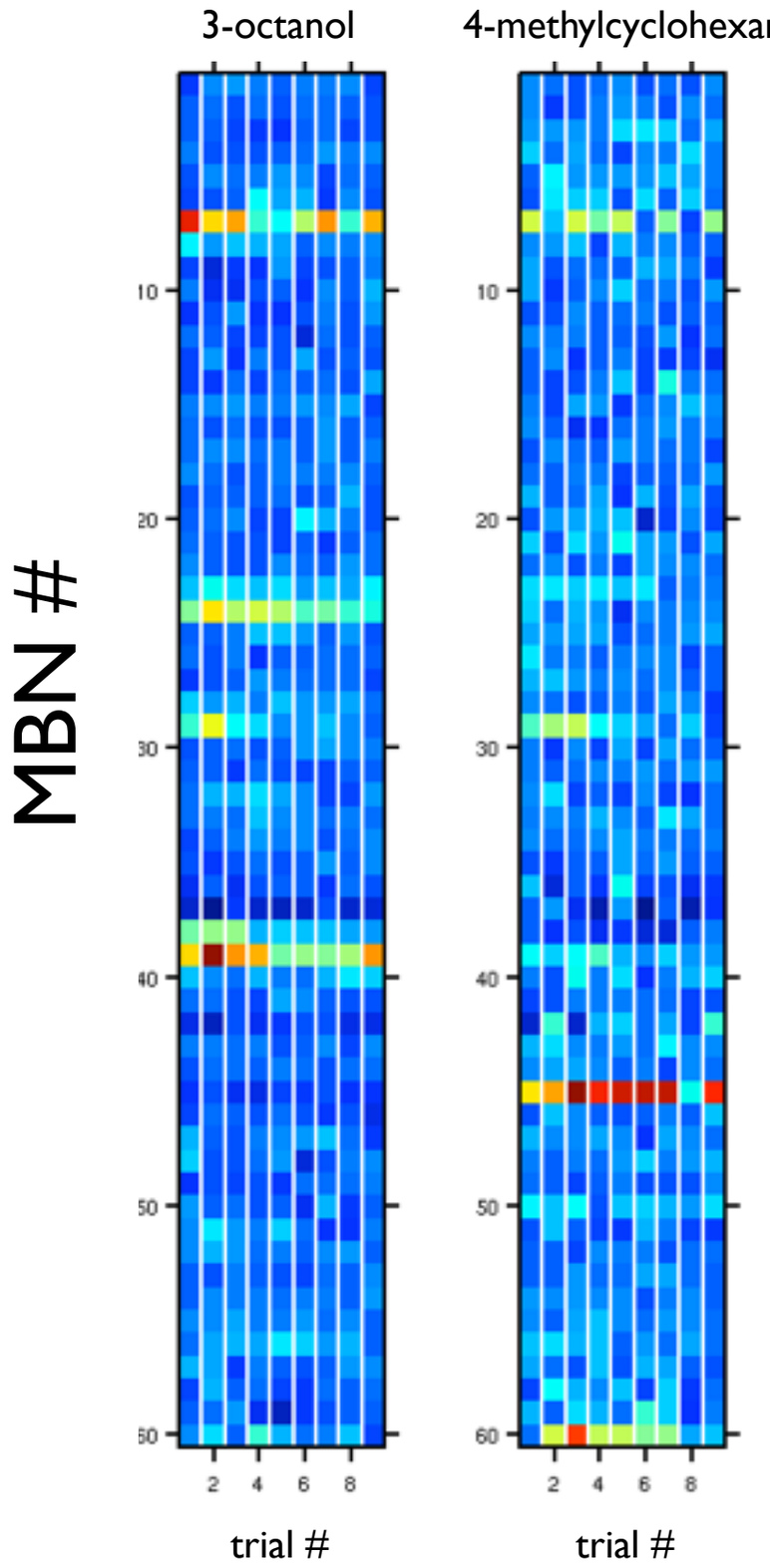
➪ Do flies actually solve this problem?

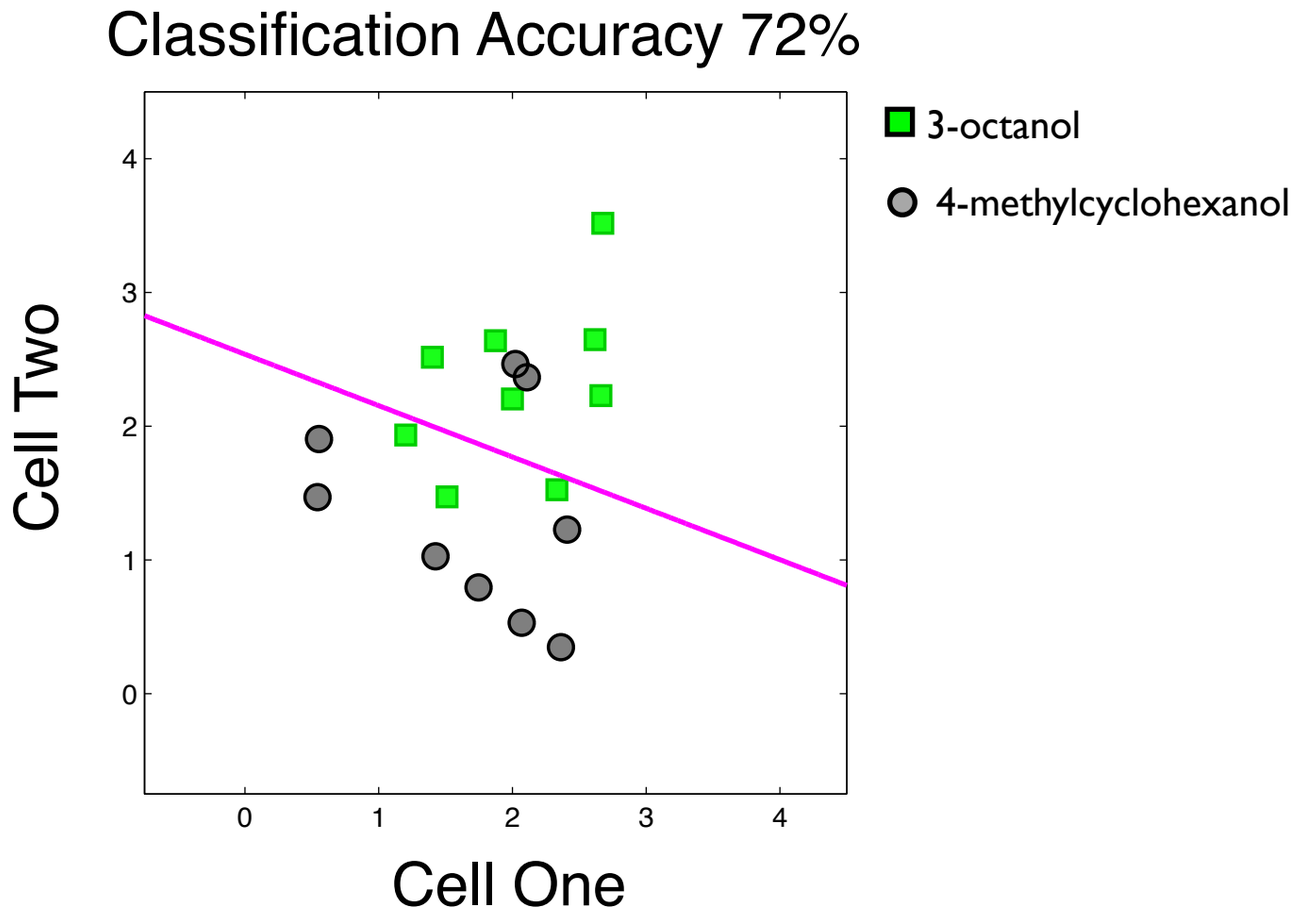
Are these stimuli distinct?

1) Can we see they're evoke distinct responses in the MB?

2) Do the flies learn they're distinct?

Pattern separation in the Mushroom Body
Classifying odors by population activity

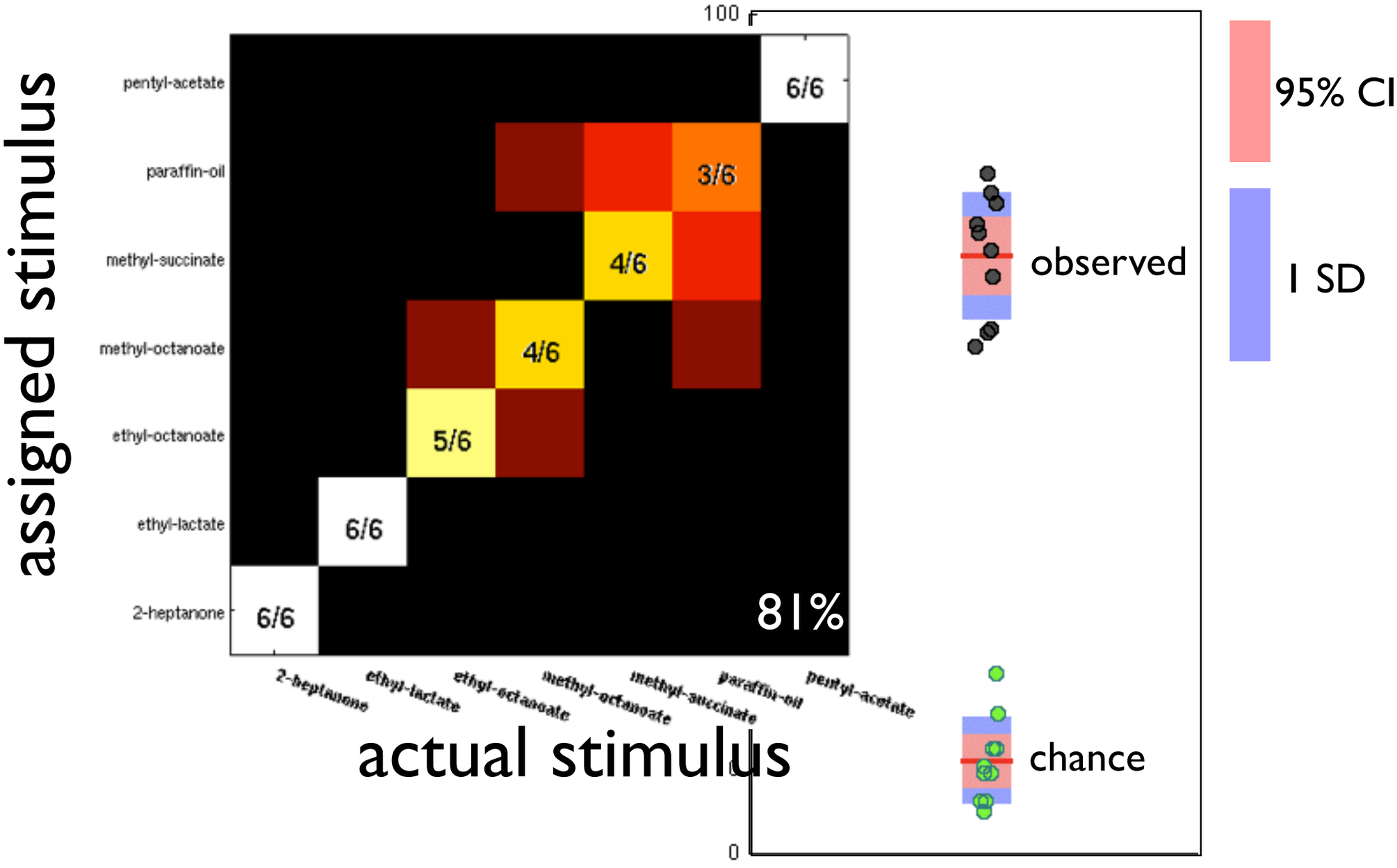




Linear Discriminant Analysis (LDA)
to assign odor identity on
trial-by-trial basis

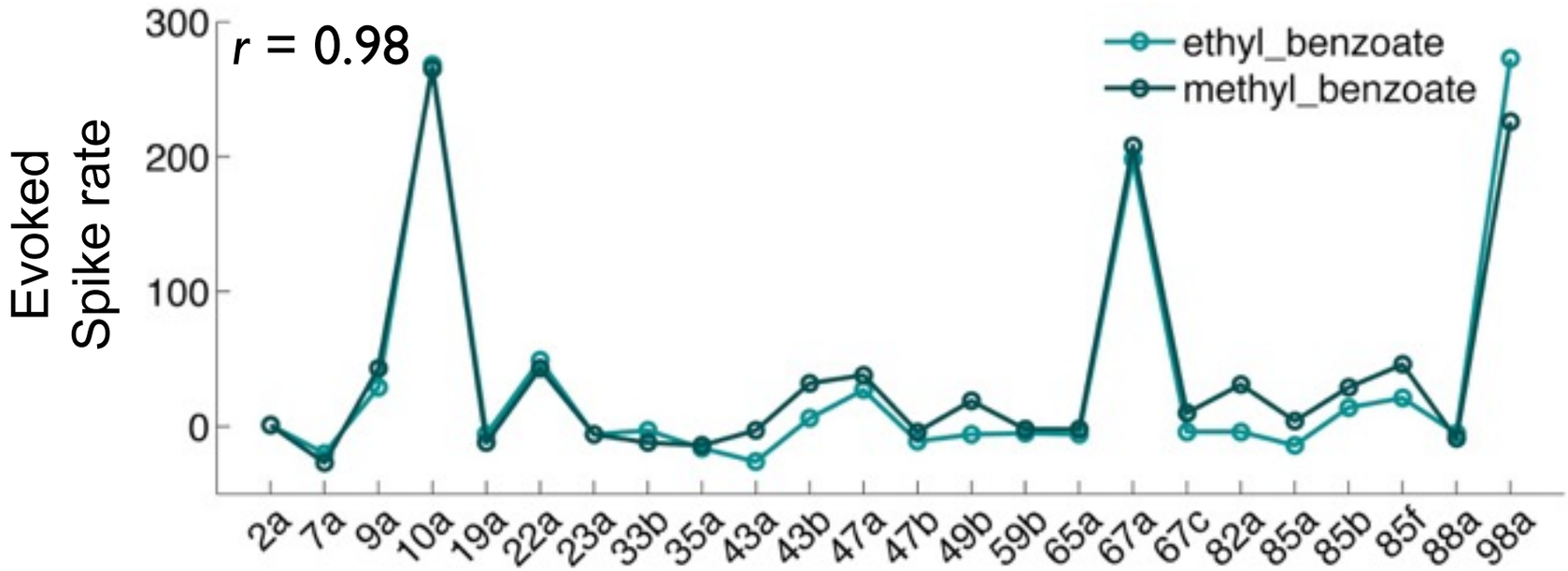
Rob Campbell & Kyle Honegger

Pattern separation in the Mushroom Body
Classifying odors by population activity



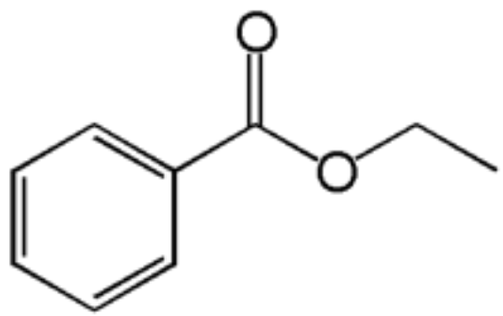
Rob Campbell & Kyle Honegger

Pattern separation in the Mushroom Body
A difficult monomolecular discrimination



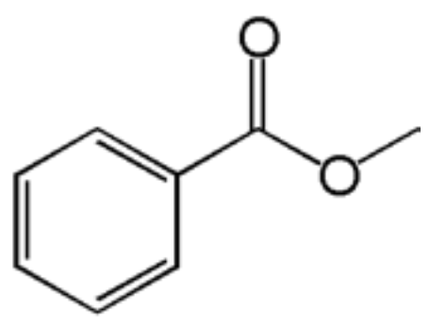
Hallem & Carlson 2006

ethyl benzoate



vapor pressure
1mm Hg @ 44°C

methyl benzoate



vapor pressure
1mm Hg @ 39°C

Are the most similar pair of monomolecular odorants distinguishable:

1) behaviorally

2) in MB activity patterns

Pattern separation in the Mushroom Body
A difficult monomolecular discrimination

Olfactory behavior

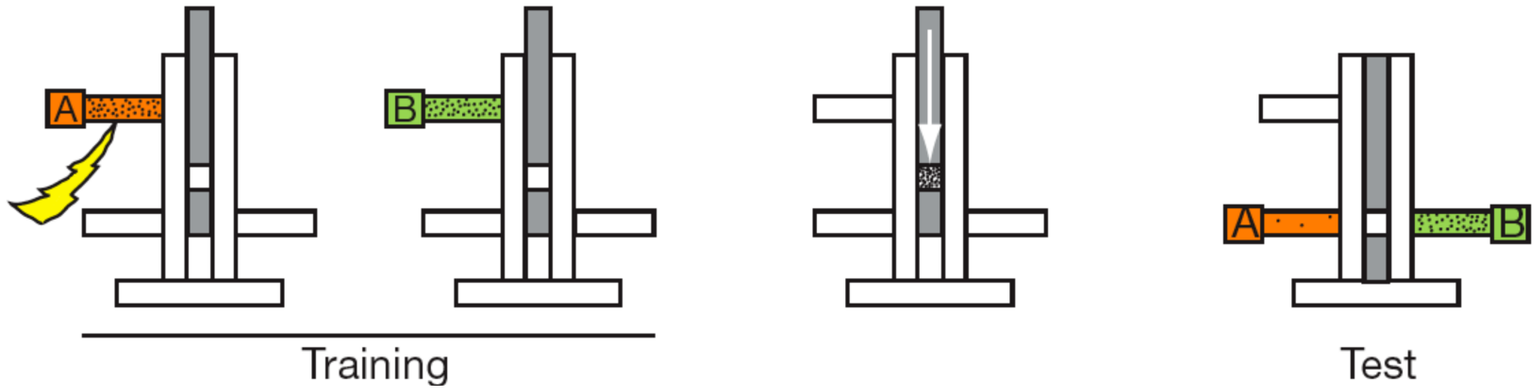
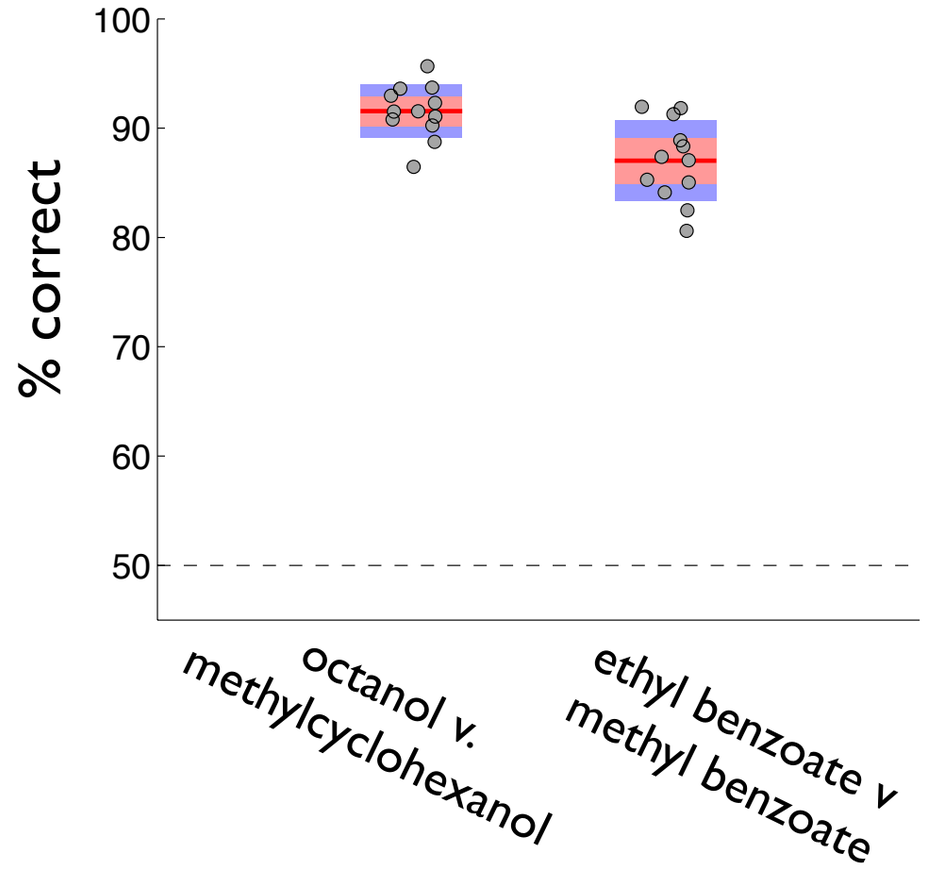
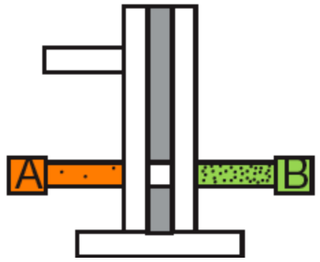
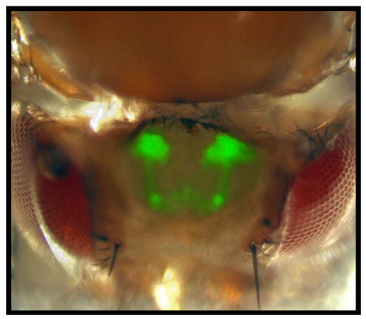


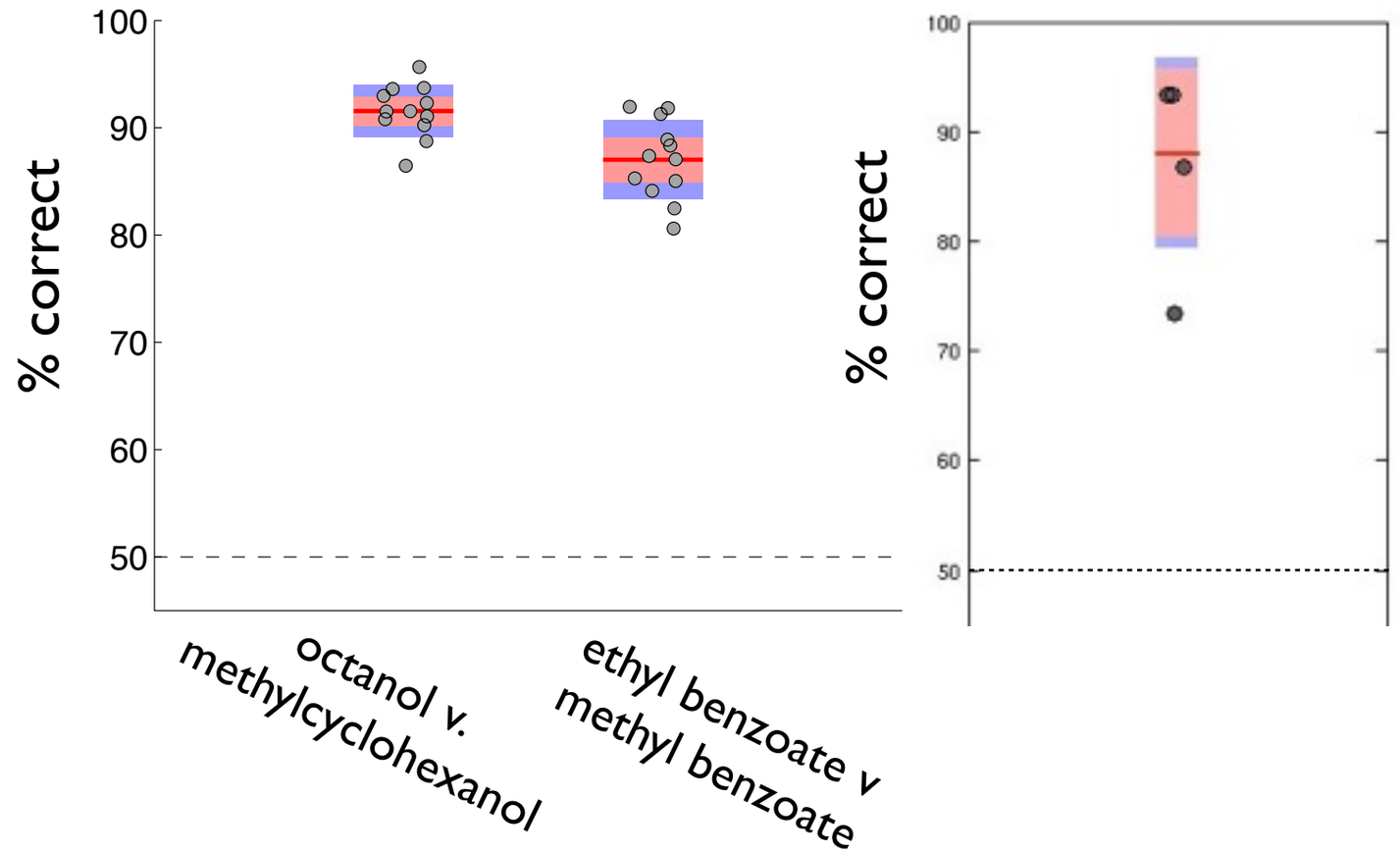
image: Vosshall *Nature* 2007



Pattern separation in the Mushroom Body
A difficult monomolecular discrimination

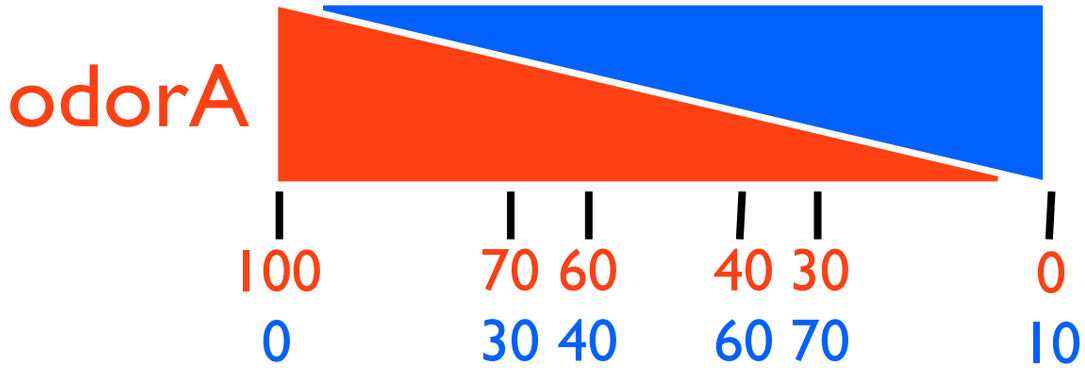


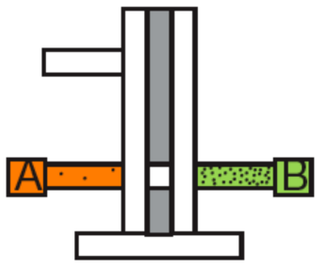


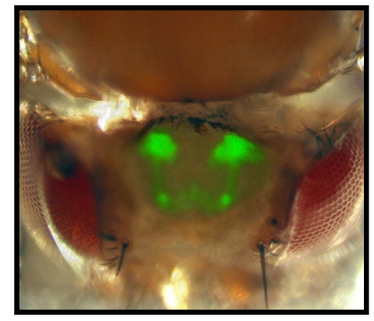


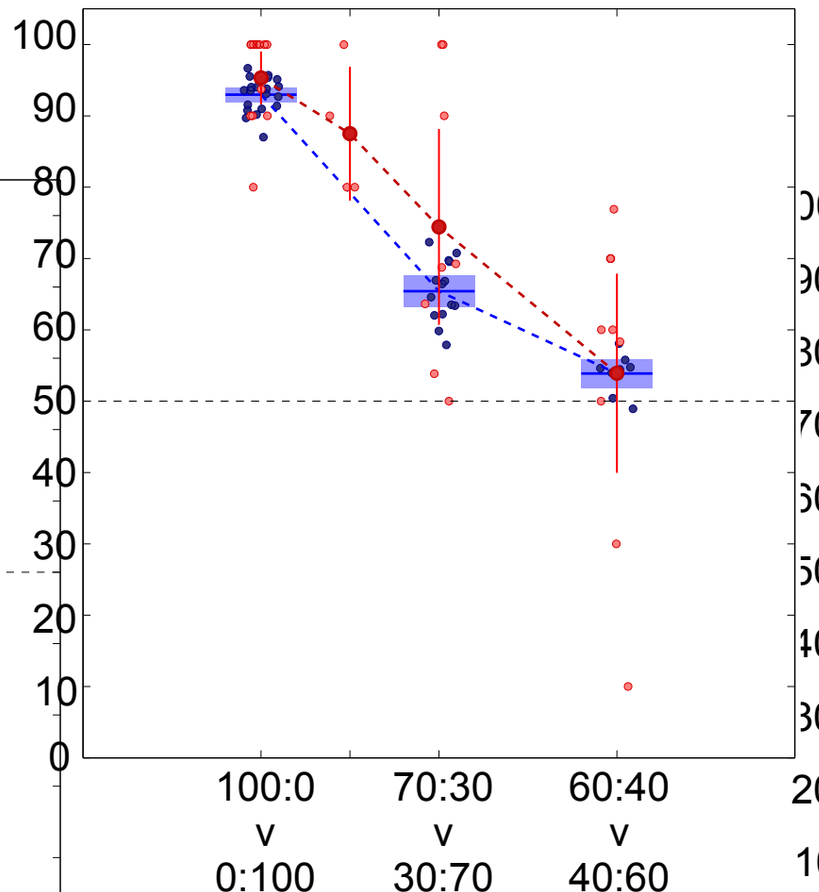
The fly's behavior is coarsely similar to our artificial read-out

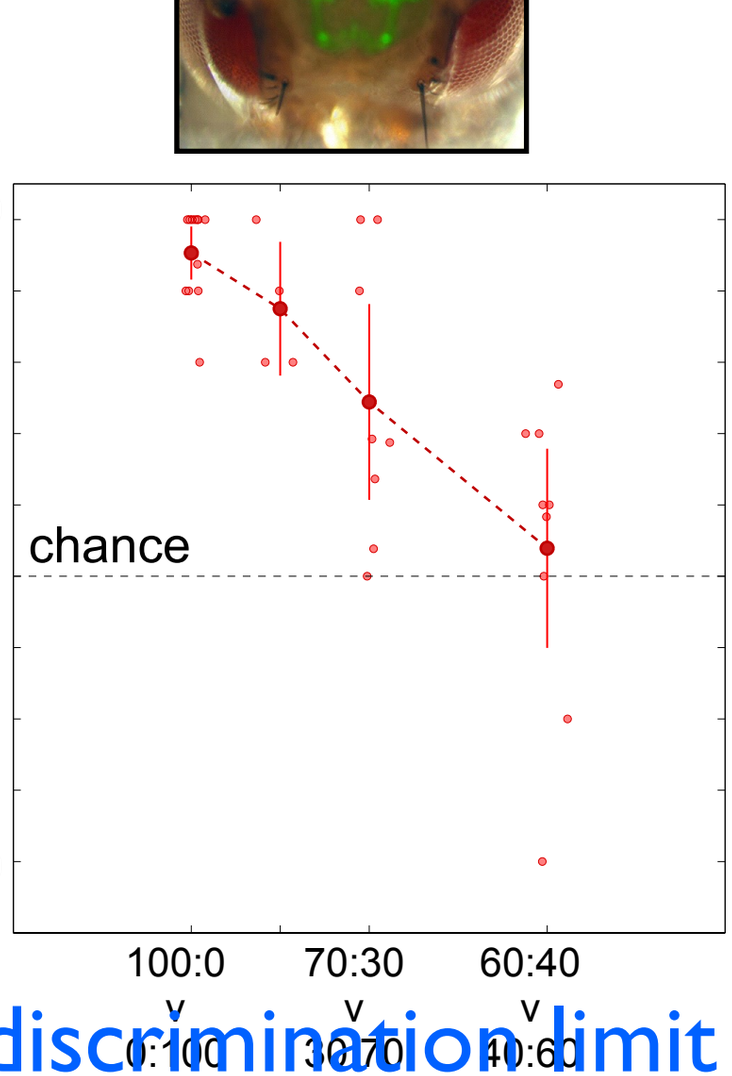
Pattern separation in the Mushroom Body
Connecting psychometric & neurometric measures









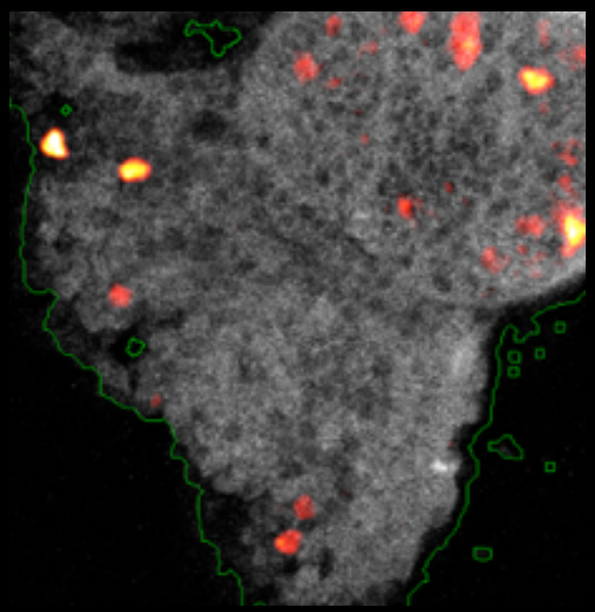


Neural read-out matches behavior near discrimination limit

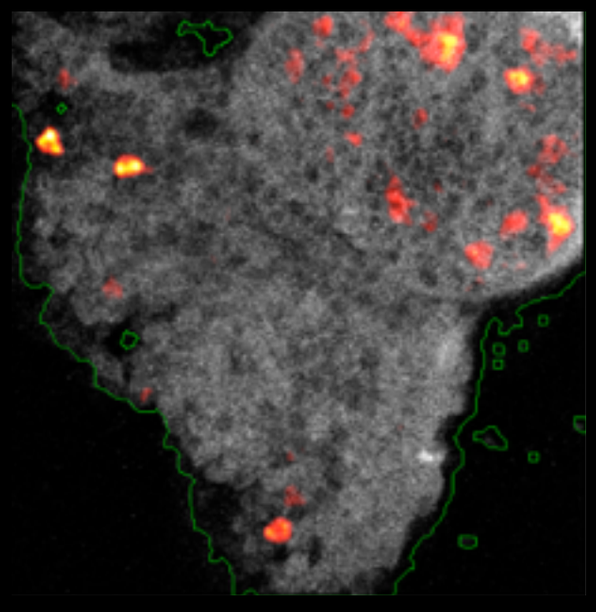
Rob Campbell & Kyle Honegger

Odor generalization

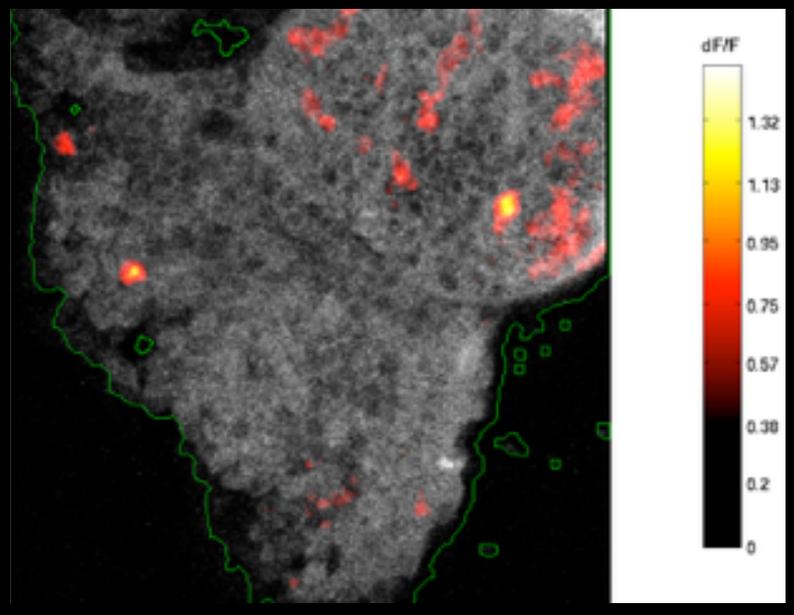
Pentyl acetate

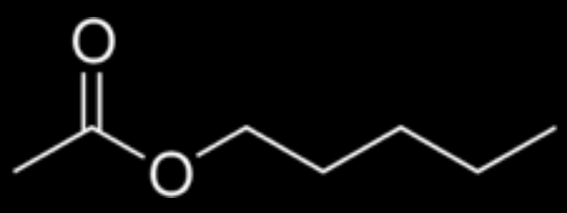


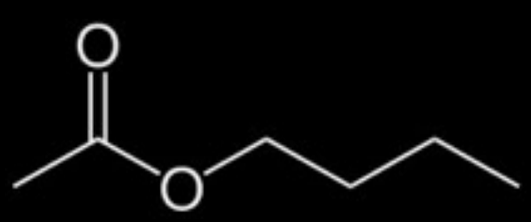
Butyl acetate

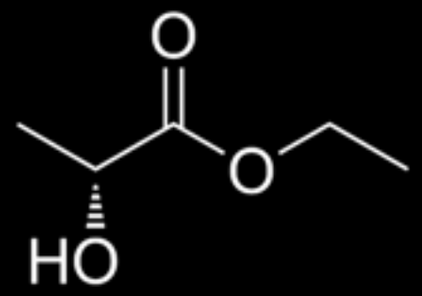


Ethyl lactate





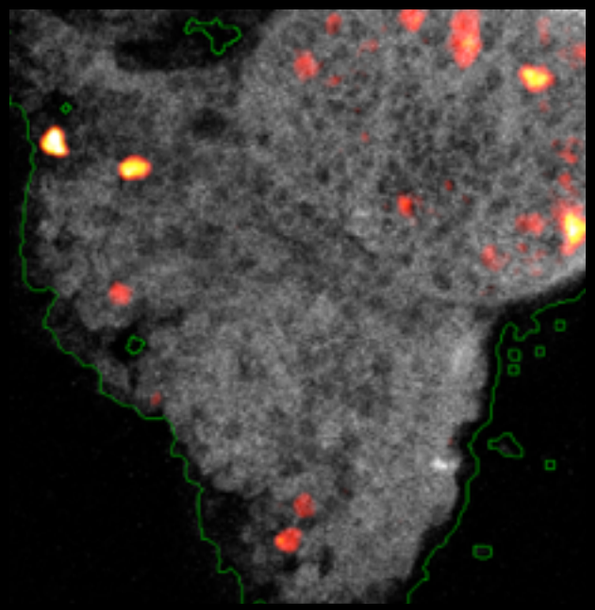




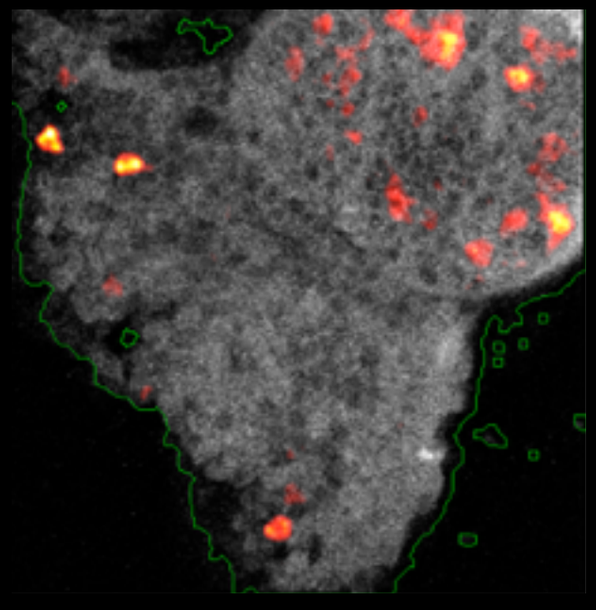
PA and BA evoke similar KC patterns
Do associations with PA generalize to BA?

Odor generalization

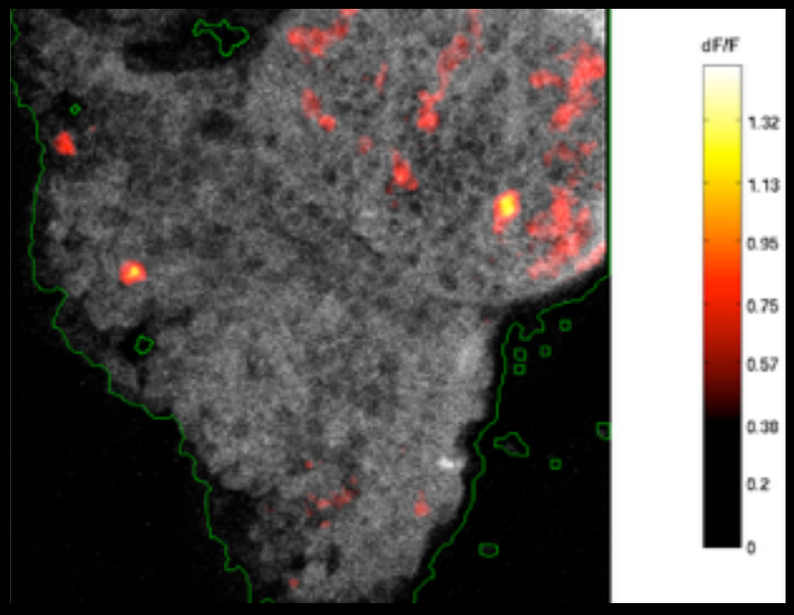
Pentyl acetate



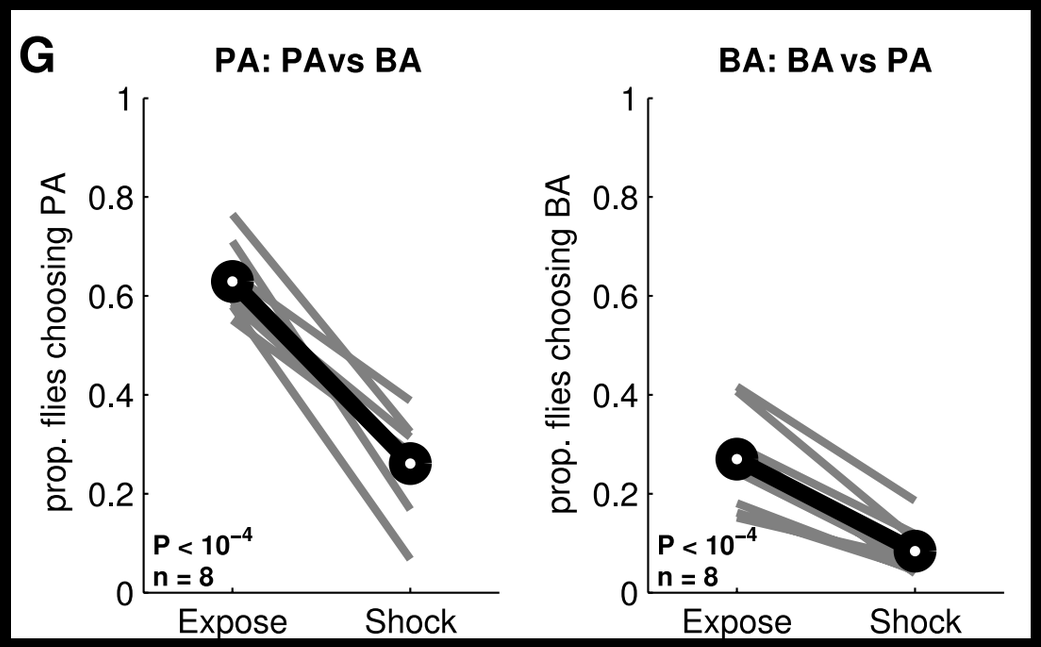
Butyl acetate



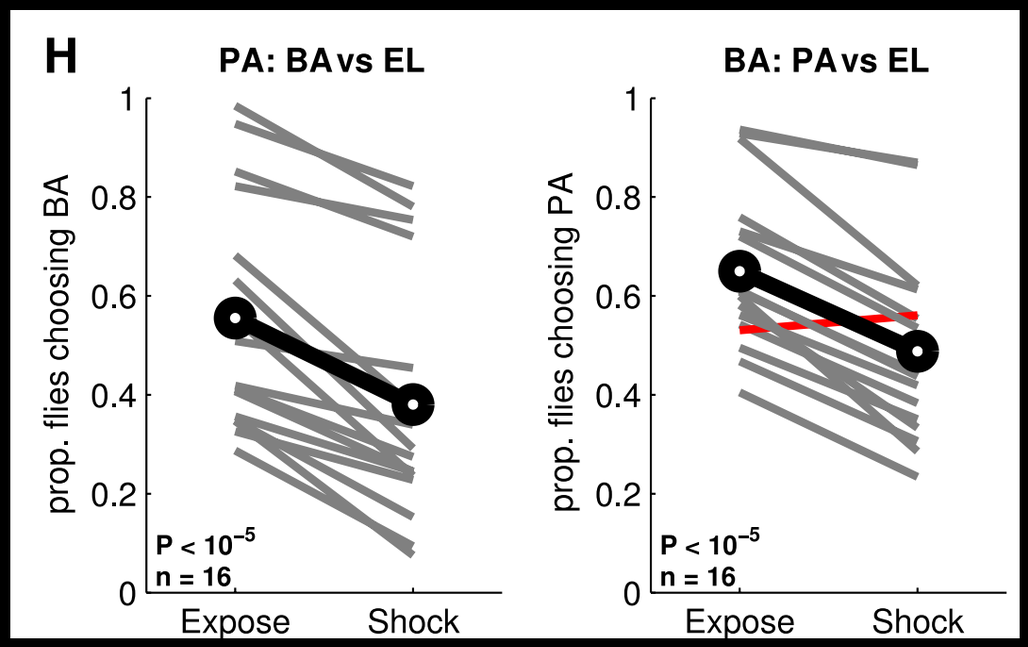
Ethyl lactate



Discriminate



Generalize



MB activity patterns reflect

i) Discrimination of similar odors approaching psychophysical limit

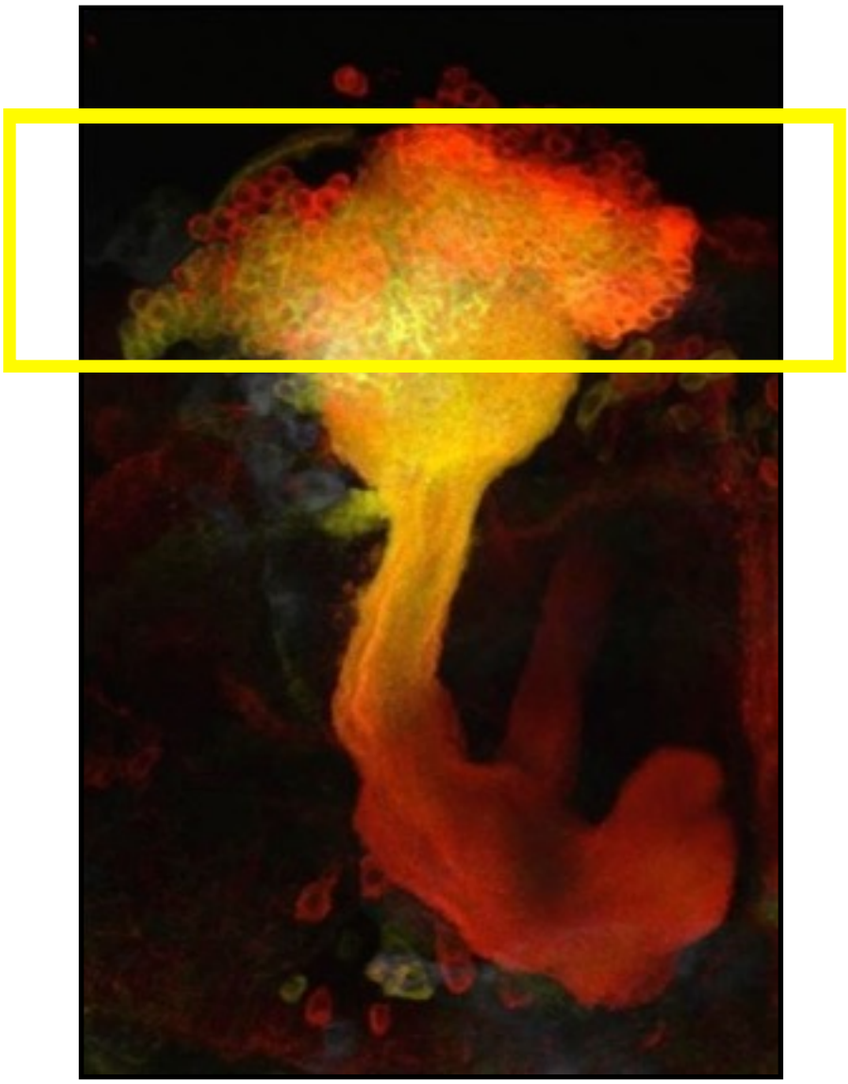
ii) Generalization of associations from one odor to another

Behavior sets biological bounds on interpreting neural activity

What features of the neural activity are responsible?

Neural activity patterns for Just Noticeably Different stimuli

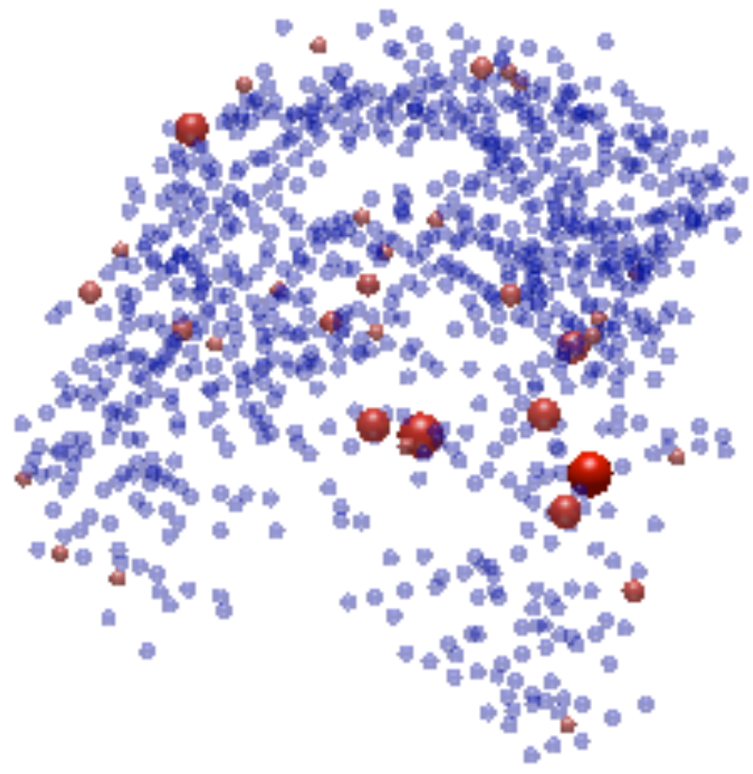
Imaging MB volumes



responses of ~1500 cells
50-80% of the population

Neural activity patterns for Just Noticeably Different stimuli

Imaging MB volumes

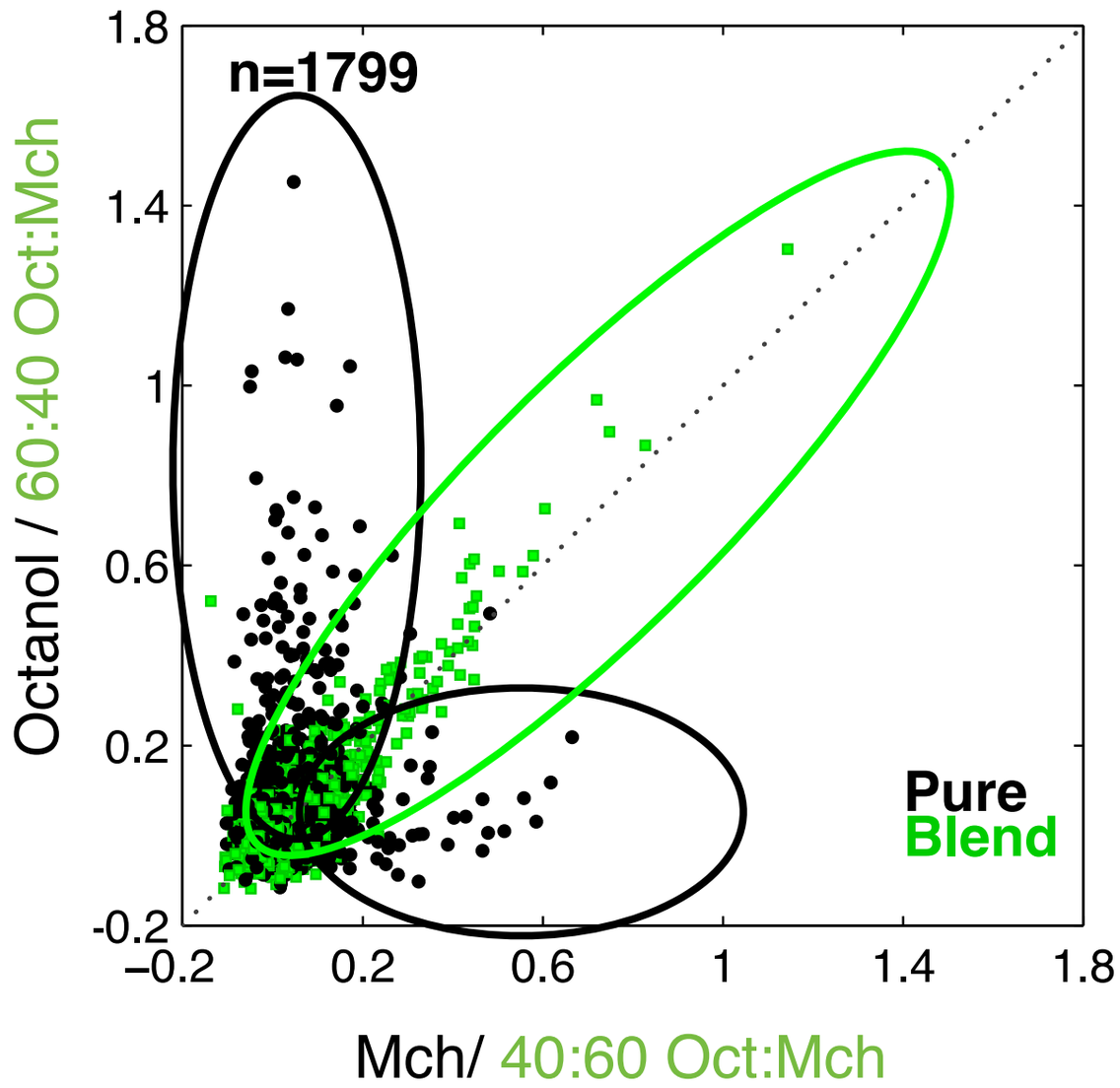


respond differentially
60:40 vs. 40:60

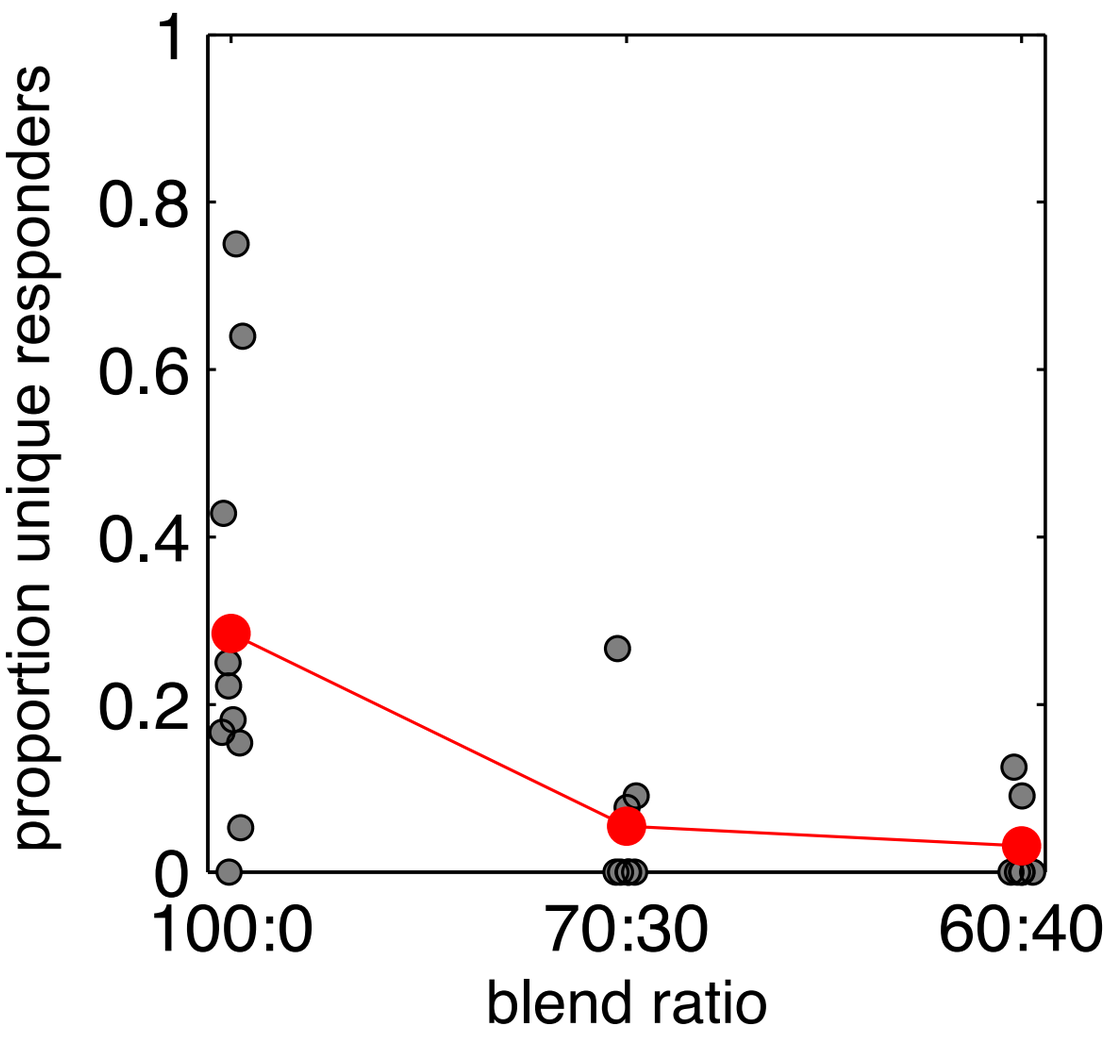
Neural activity patterns for Just Noticeably Different stimuli

Pure odors: 100% classification accuracy

60:40 Blends: 58% classification accuracy

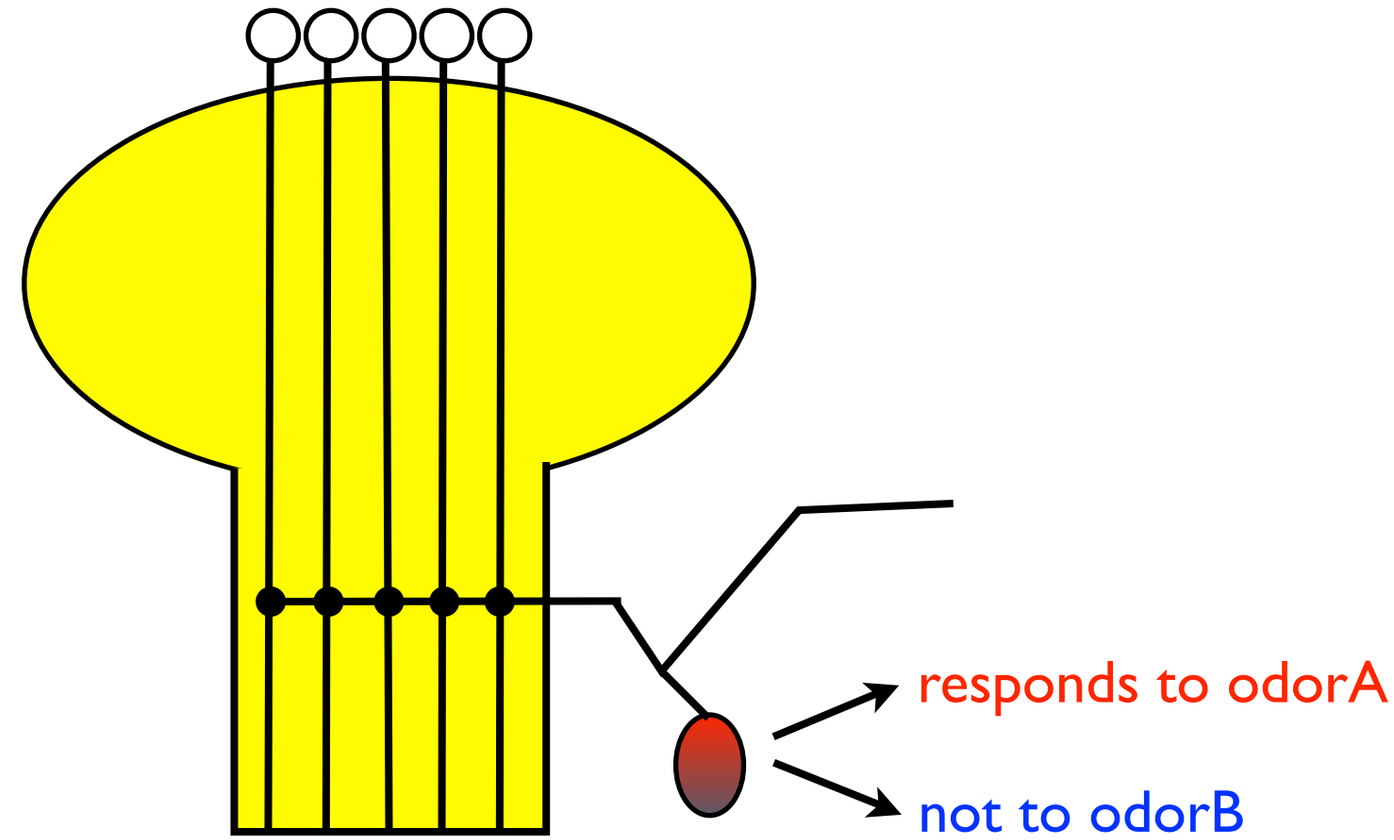


Differentially responding neurons

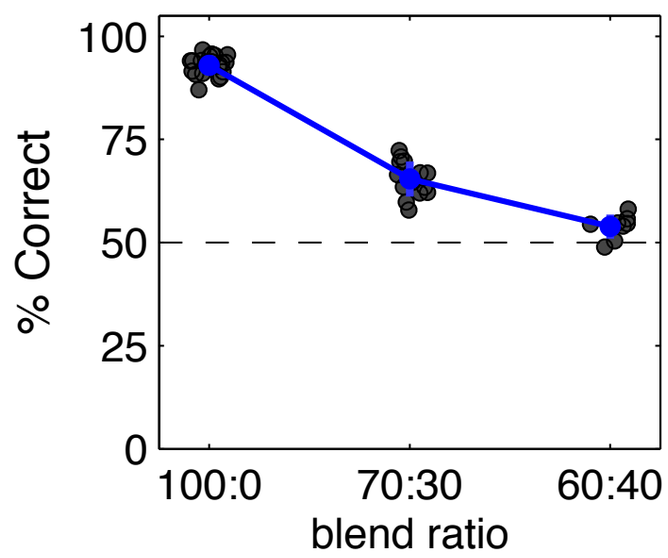


Number of non-overlapping neurons roughly tracks the difficulty of the discrimination

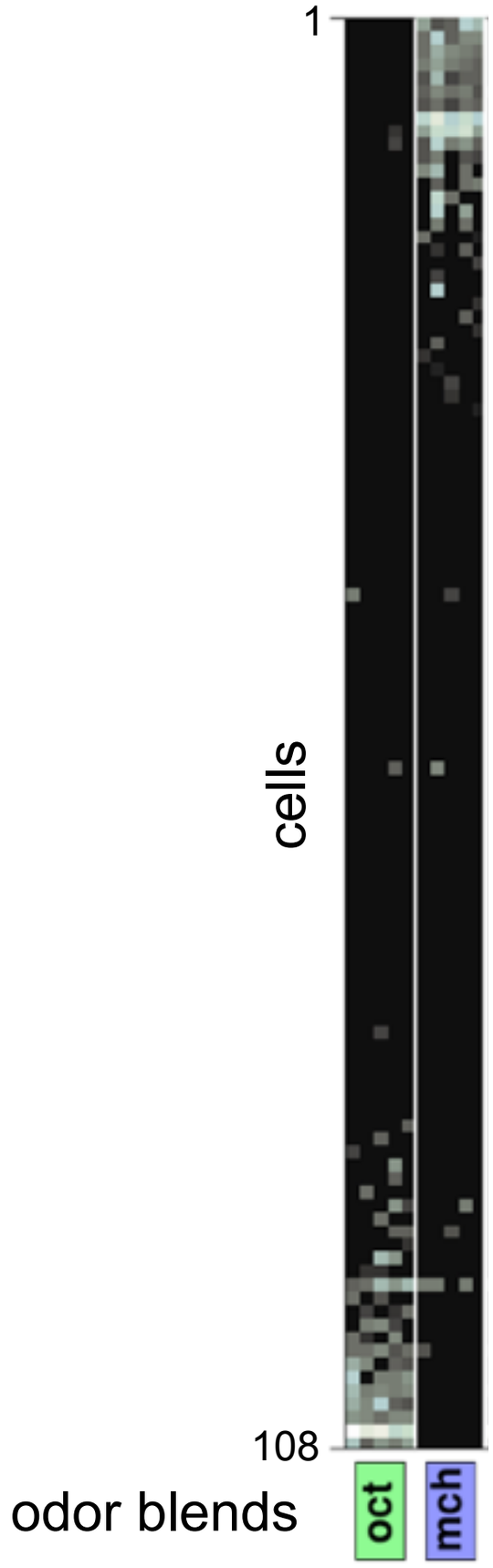
Modeling odor-specificity of learning



Behavior

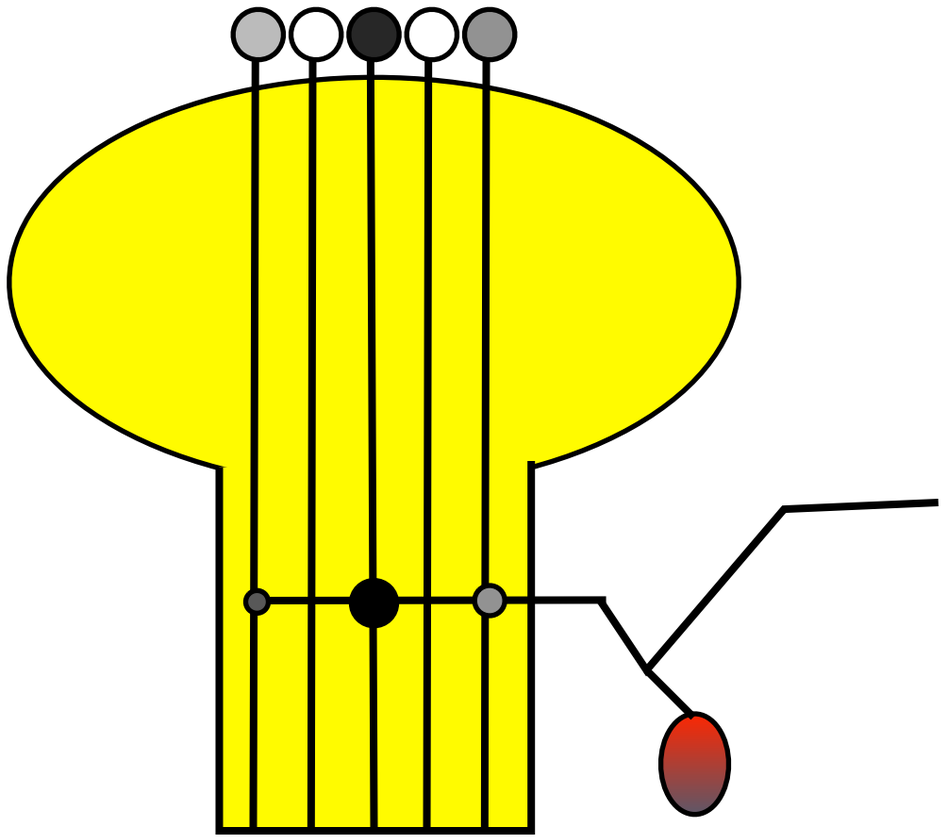


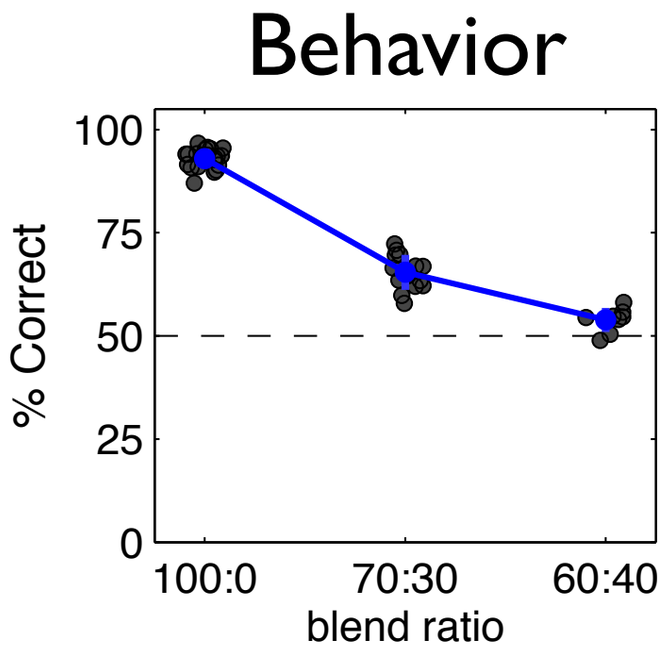
MB odor response patterns

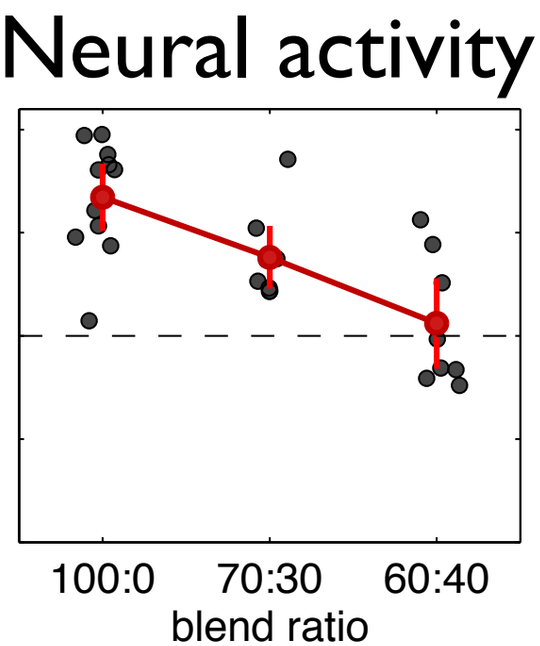


Modeling odor-specificity of learning

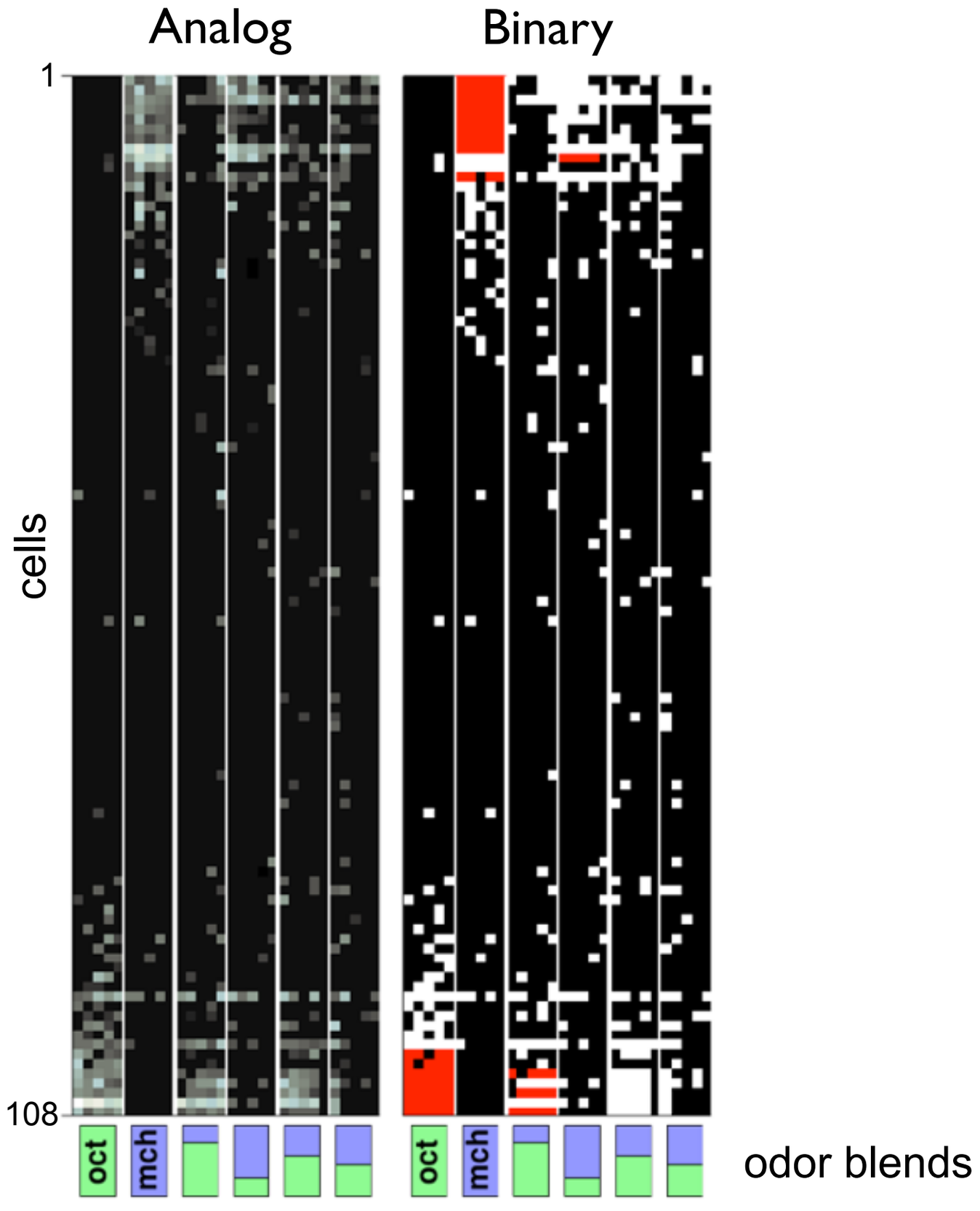
Synaptic plasticity based on spike rate code





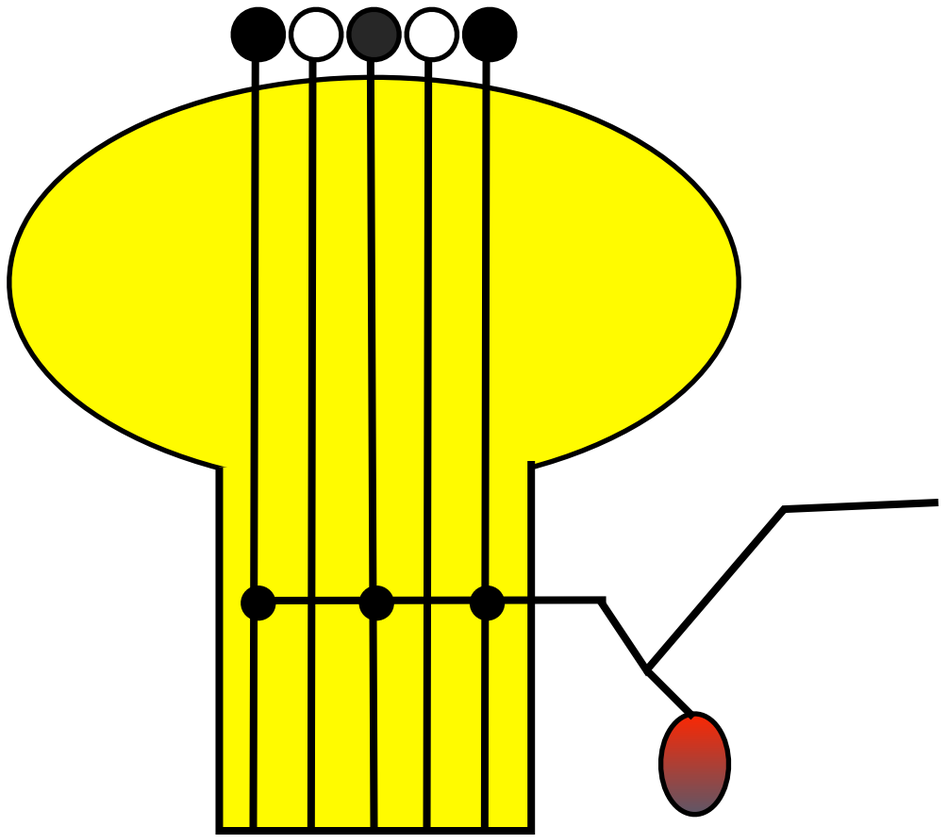


Binary MB odor response patterns

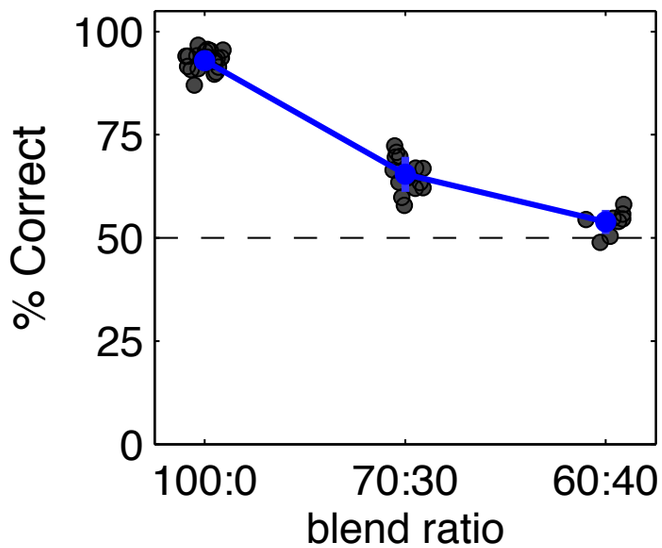


Modeling odor-specificity of learning

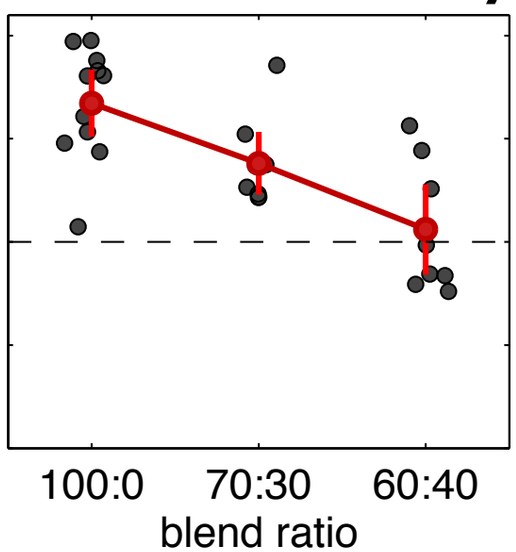
Synaptic plasticity based on binary code



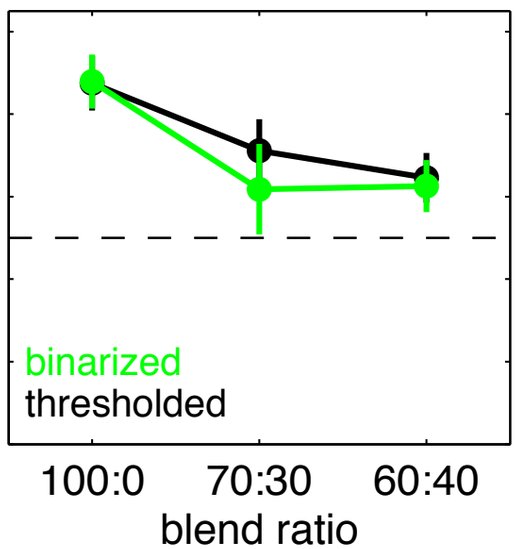
Behavior



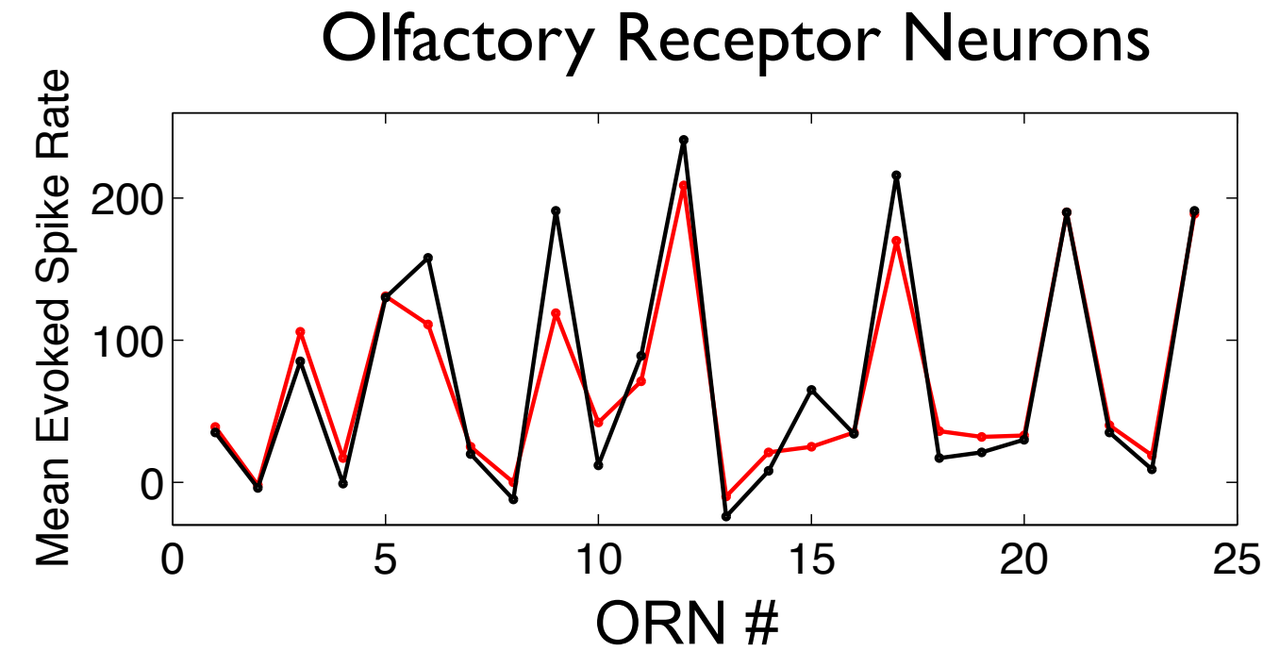
Neural activity

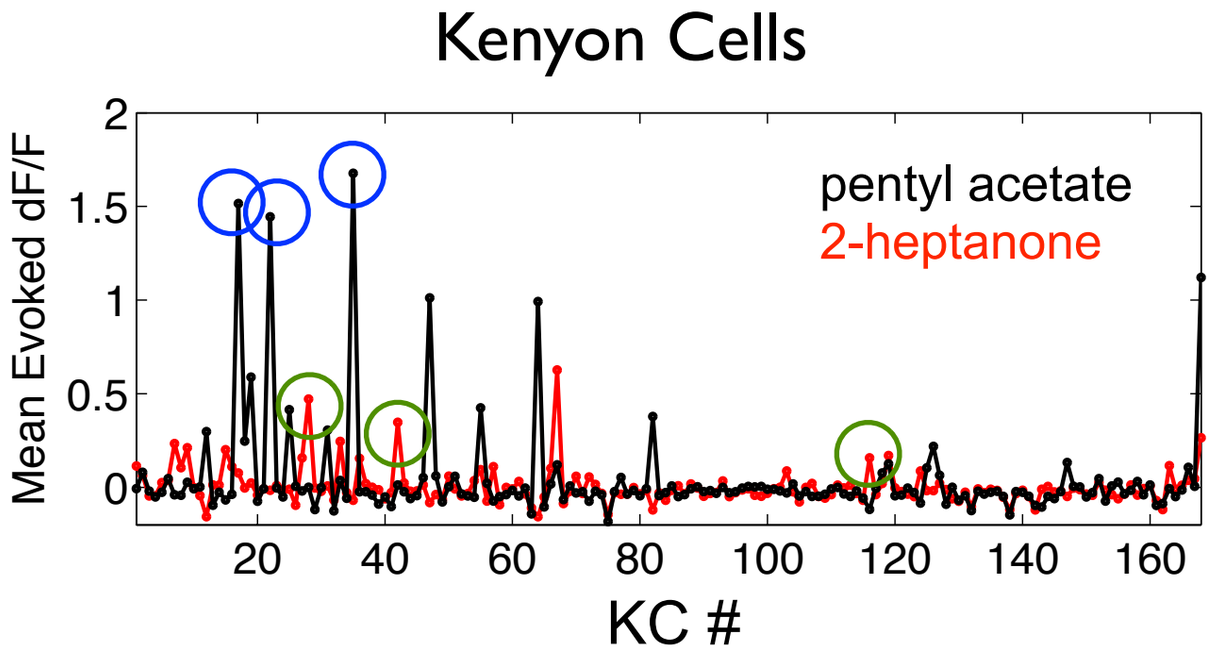


Binarized activity



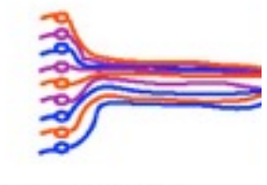
Transformation to sparse decorrelated patterns





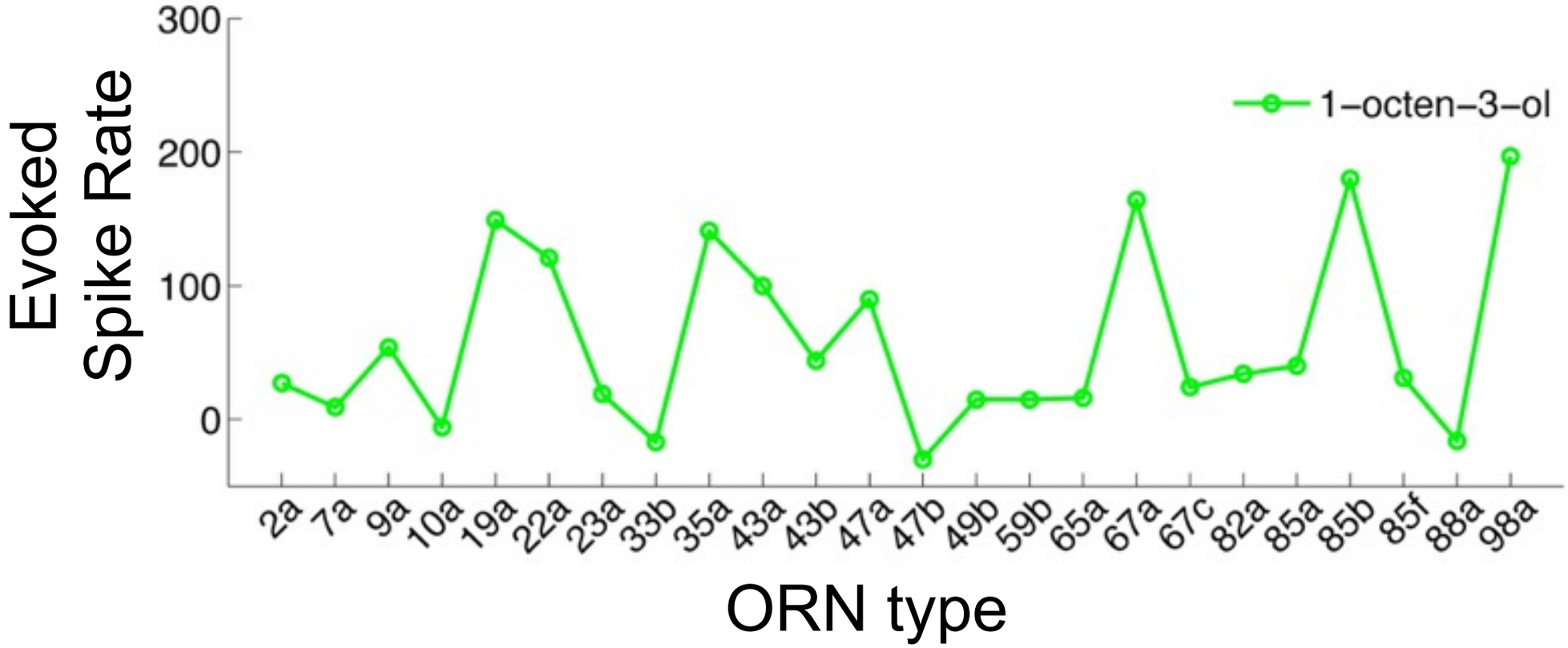
Fly can learn with a simple rule:

Change synaptic strength if KC responds



Sensory neuron representations

ORN population response (24 of 51 ORN types) to a single odor

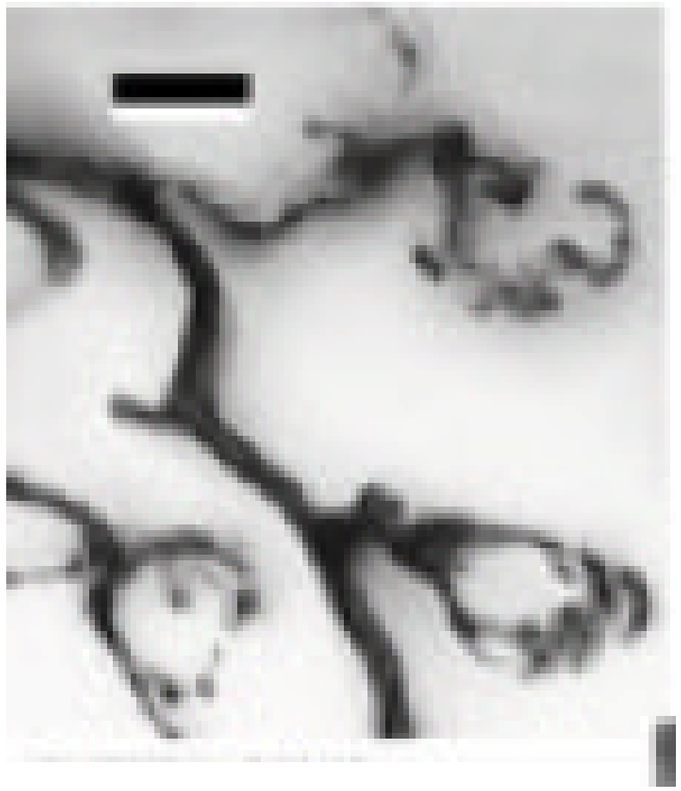


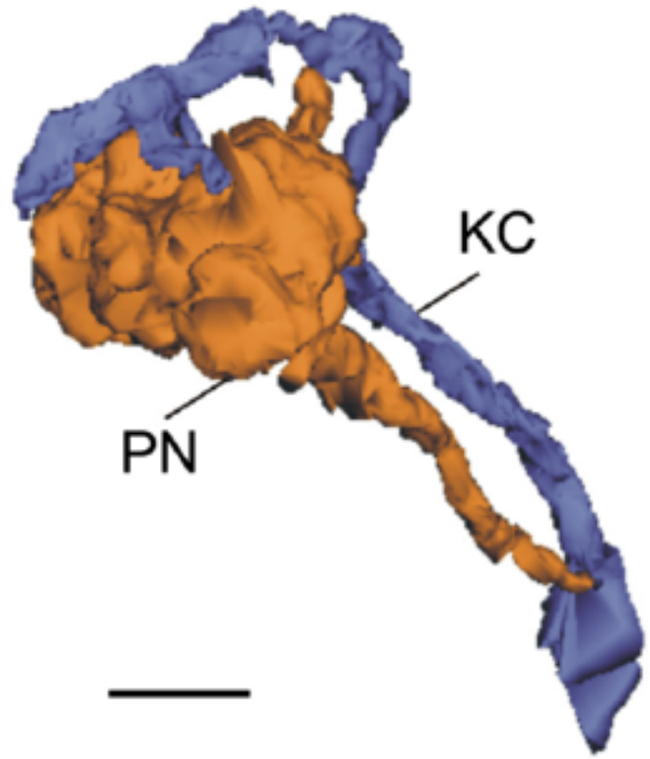
Who reads these combinations?

Hallem and Carlson *Cell* 2005

Do MB neurons read the combinatorial code?

Dendritic integration in MB neurons





Leiss et al
J Comp Neurol 2009

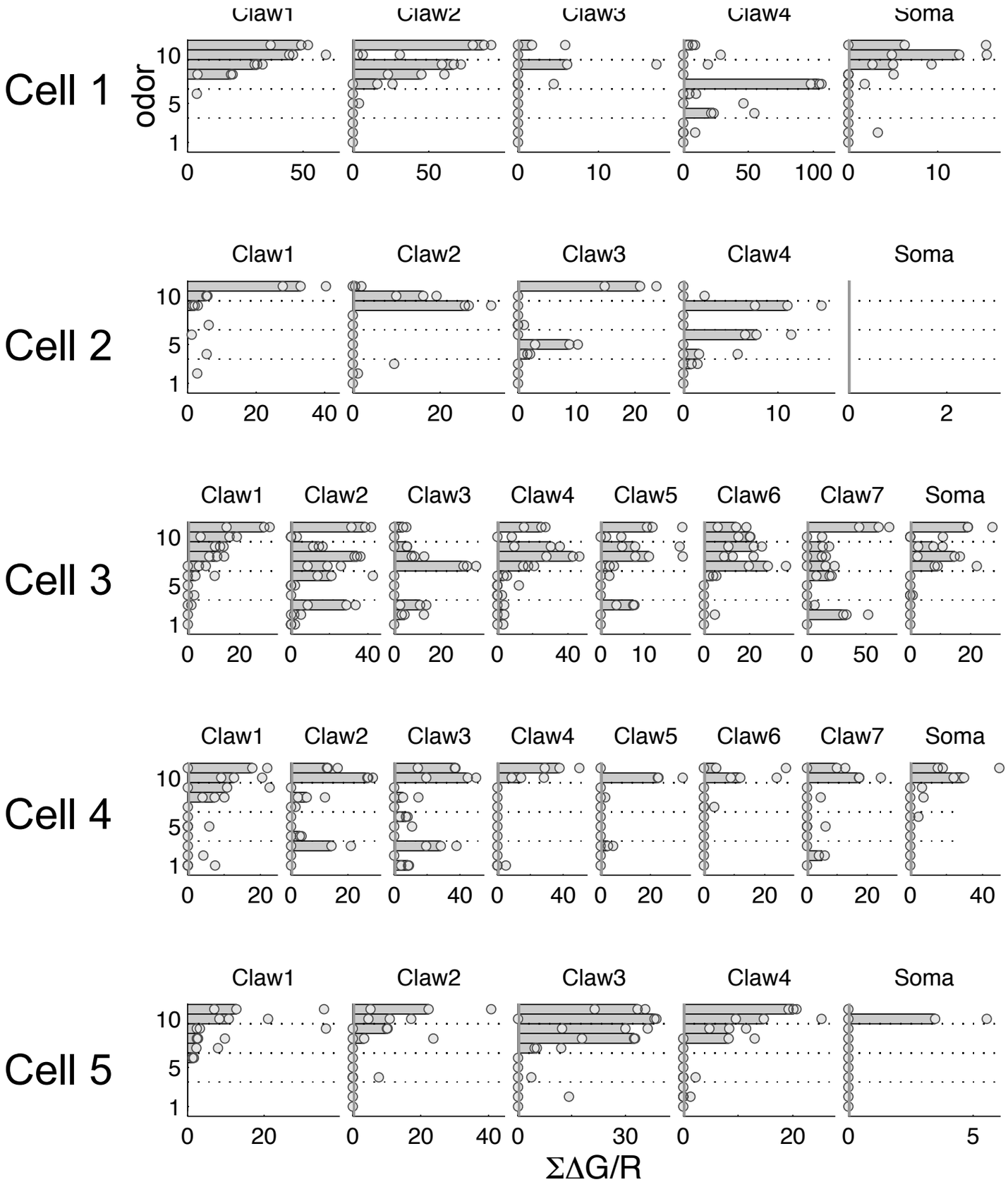
1 MB claw contacts 1 PN terminal
MB neurons have 5-7 claws on average

Do MB neurons integrate different inputs on their dendritic claws?

5µm

Gruntman & Turner
Nat. Neuro 2013

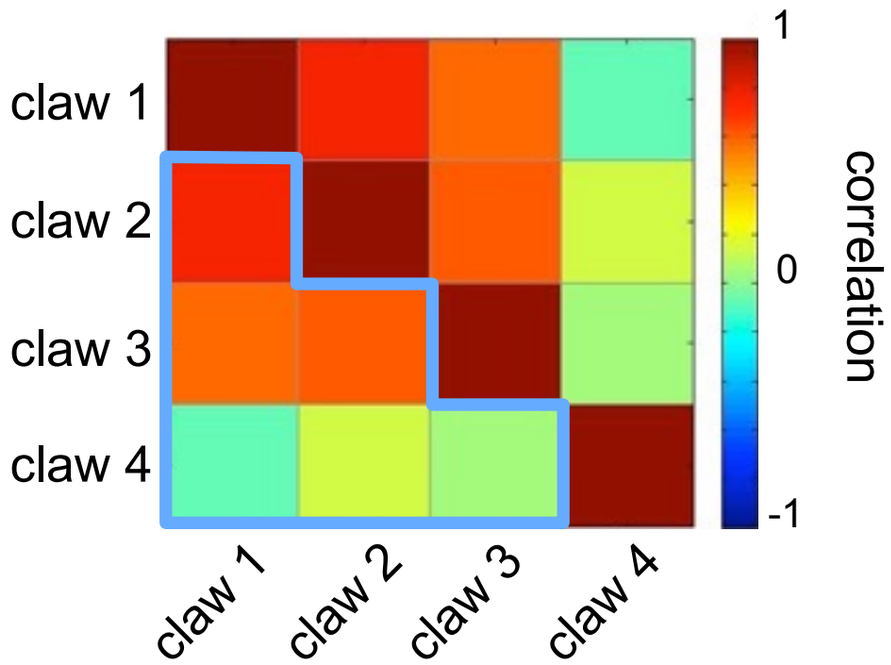
Odor tuning of MB dendritic claws

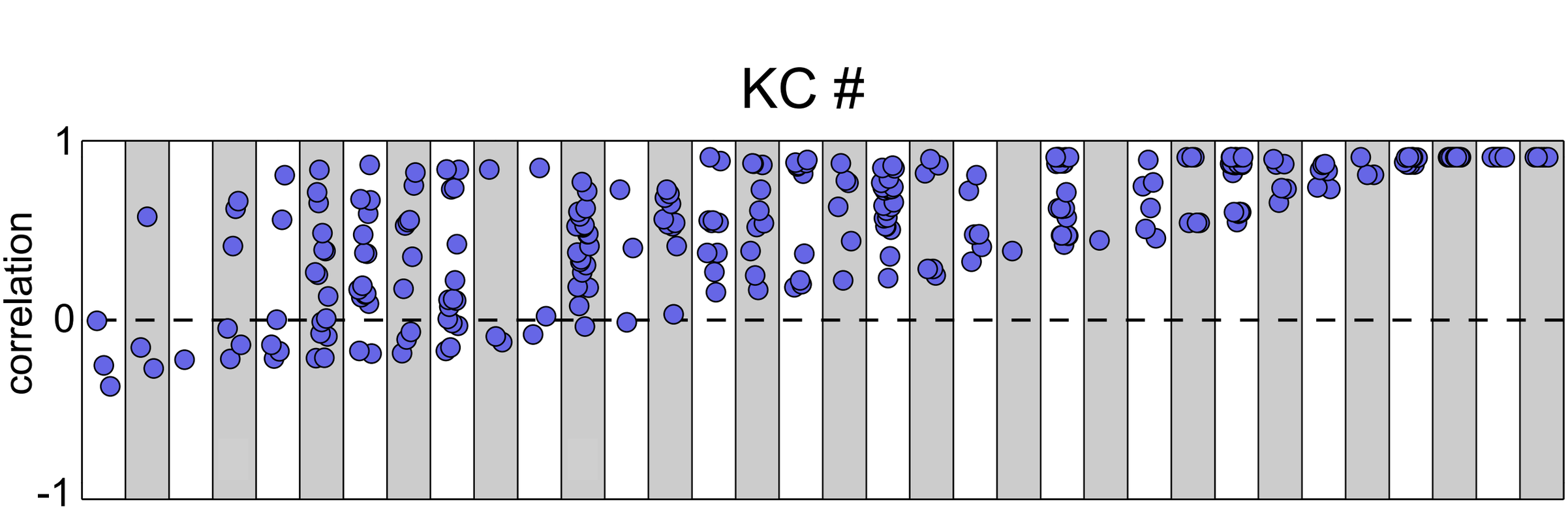


Gruntman & Turner
Nat. Neuro 2013

MB dendritic claws receive distinct inputs

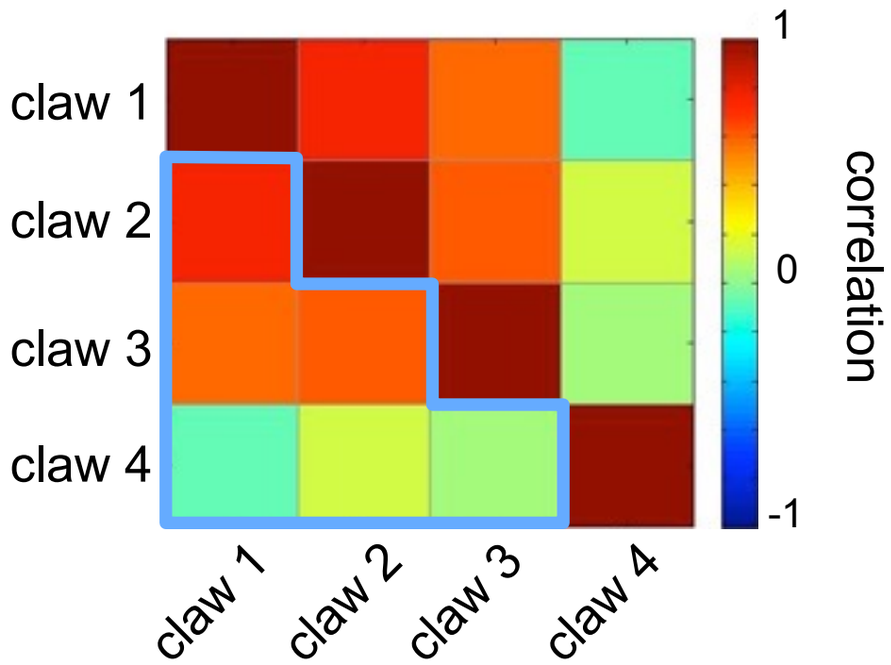
Correlations between odor tuning curves of different dendritic claws



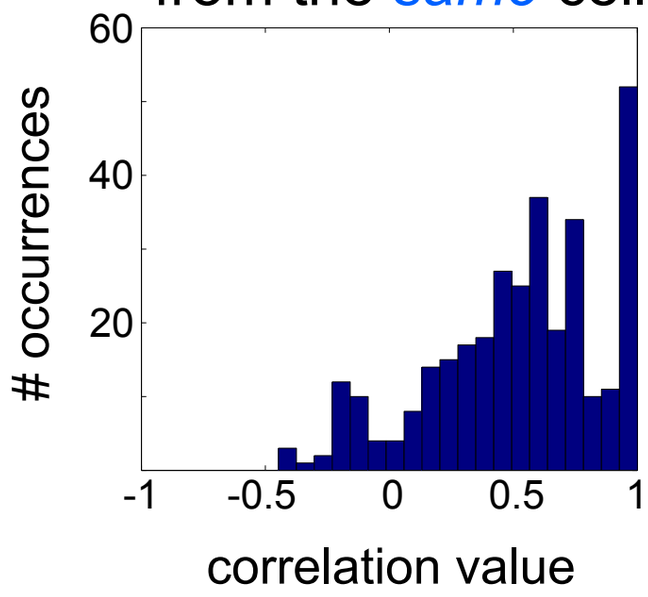


MB dendritic claws receive distinct inputs

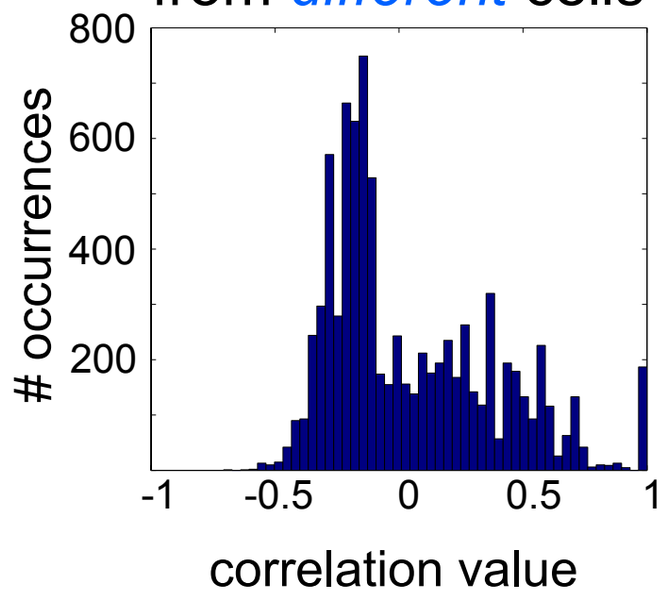
Correlations between odor tuning curves of different dendritic claws



Tuning curve correlation of claws from the *same* cell



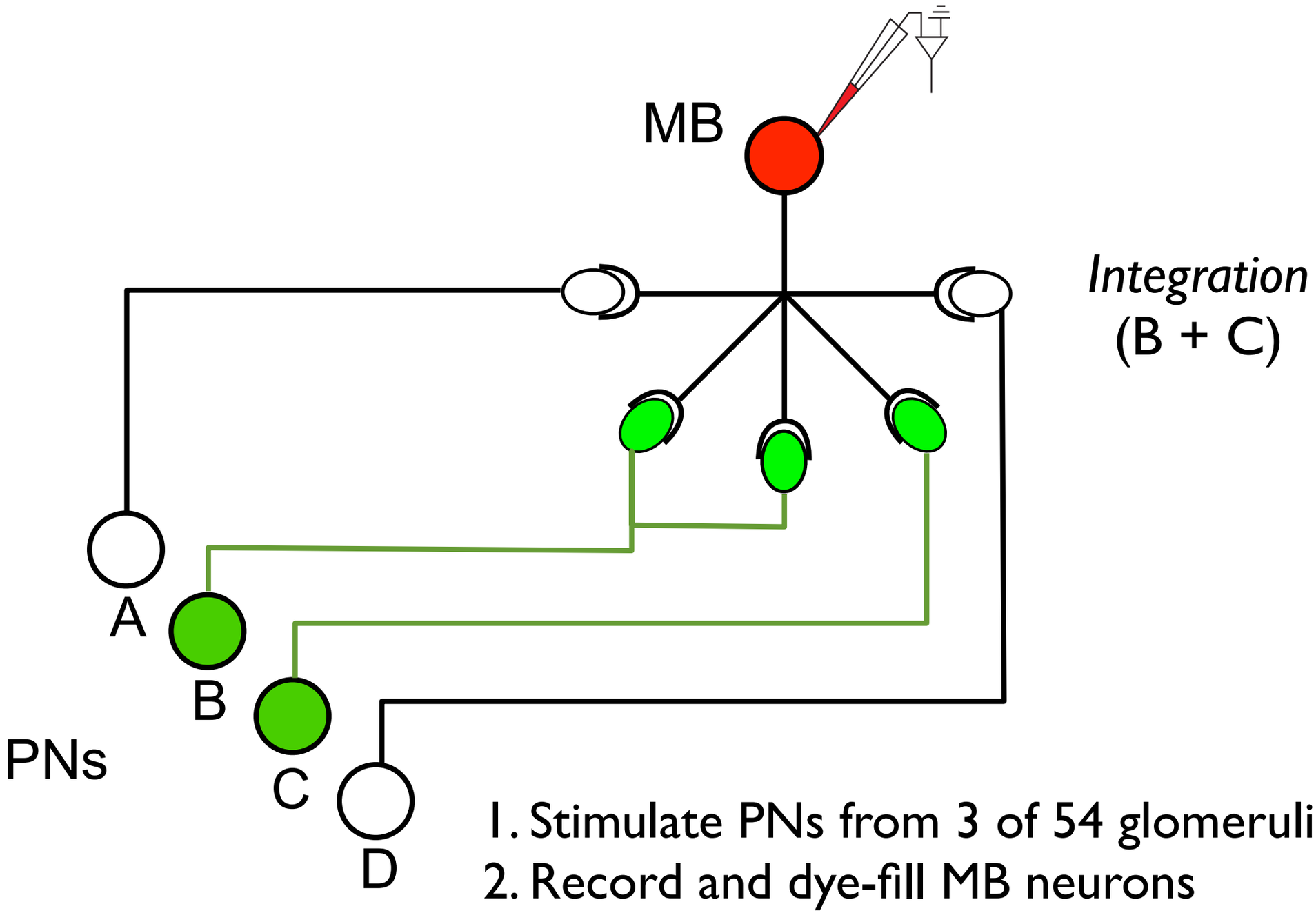
Tuning curve correlation of claws from *different* cells



Distinct... but similar

Synaptic Integration in MB Neurons

What level of input from how many claws is needed for a MB neuron to spike?

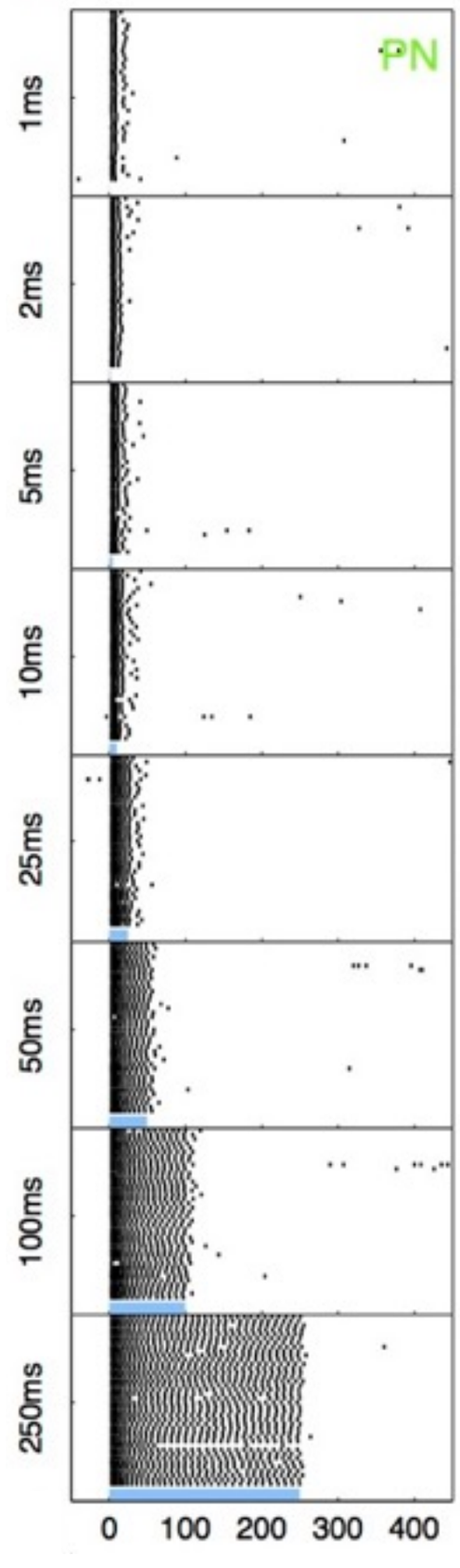


Integration
(B + C)

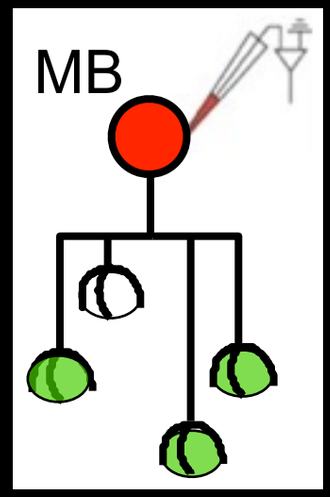
1. Stimulate PNs from 3 of 54 glomeruli with ChR2-YFP
2. Record and dye-fill MB neurons

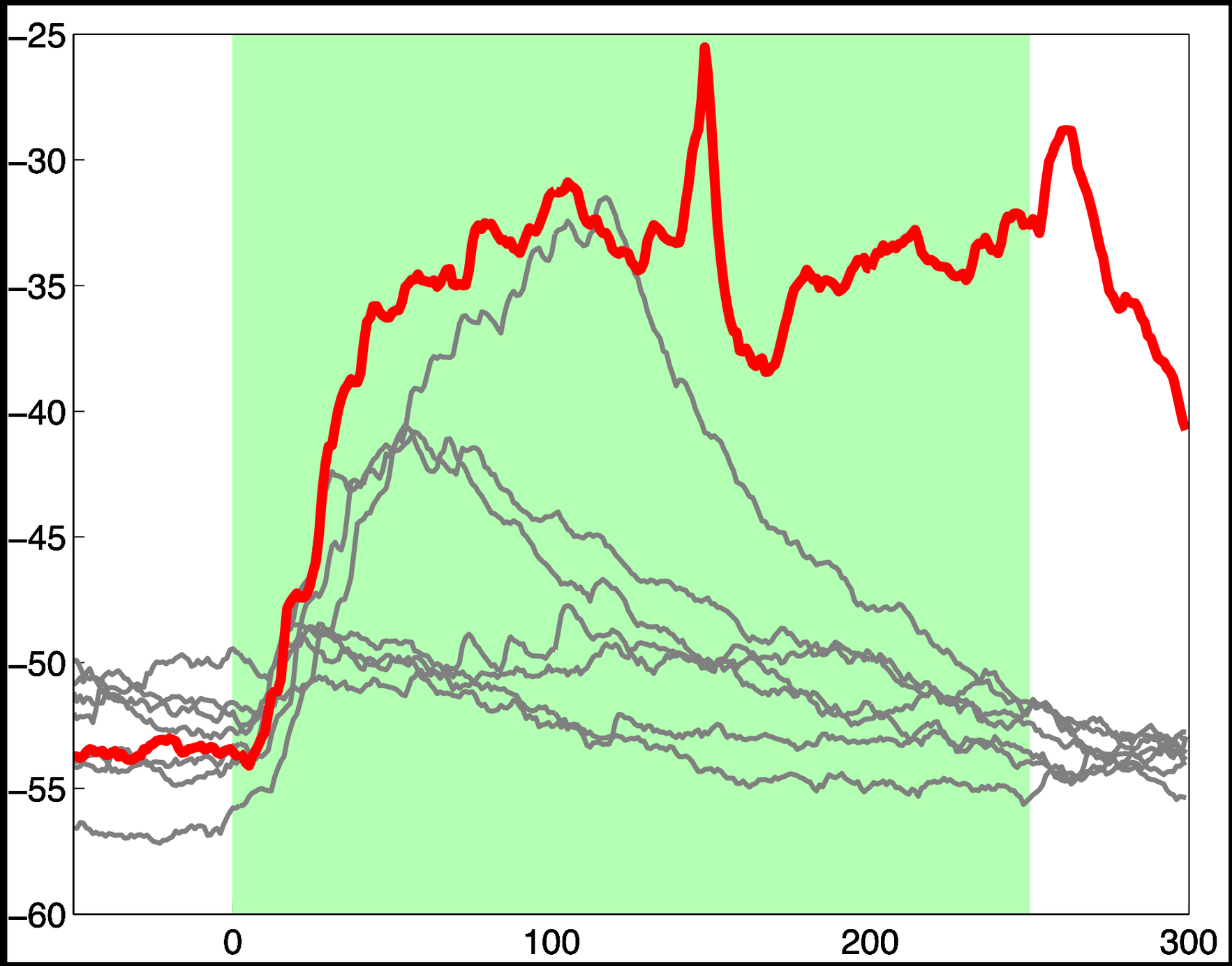
→ **Relate MB response to # claws stimulated**

Optogenetically dialing up PN input

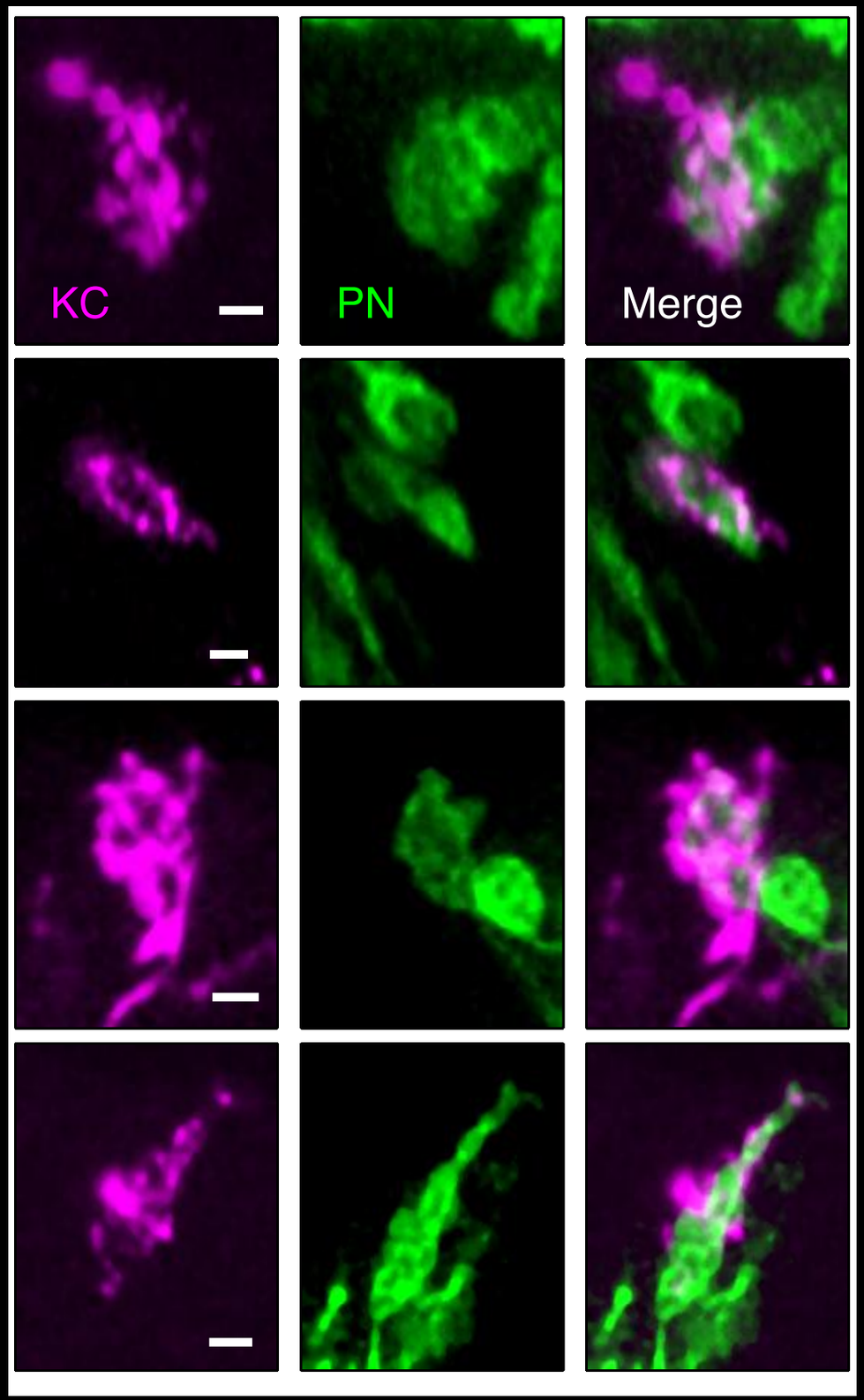


Optogenetically testing synaptic integration

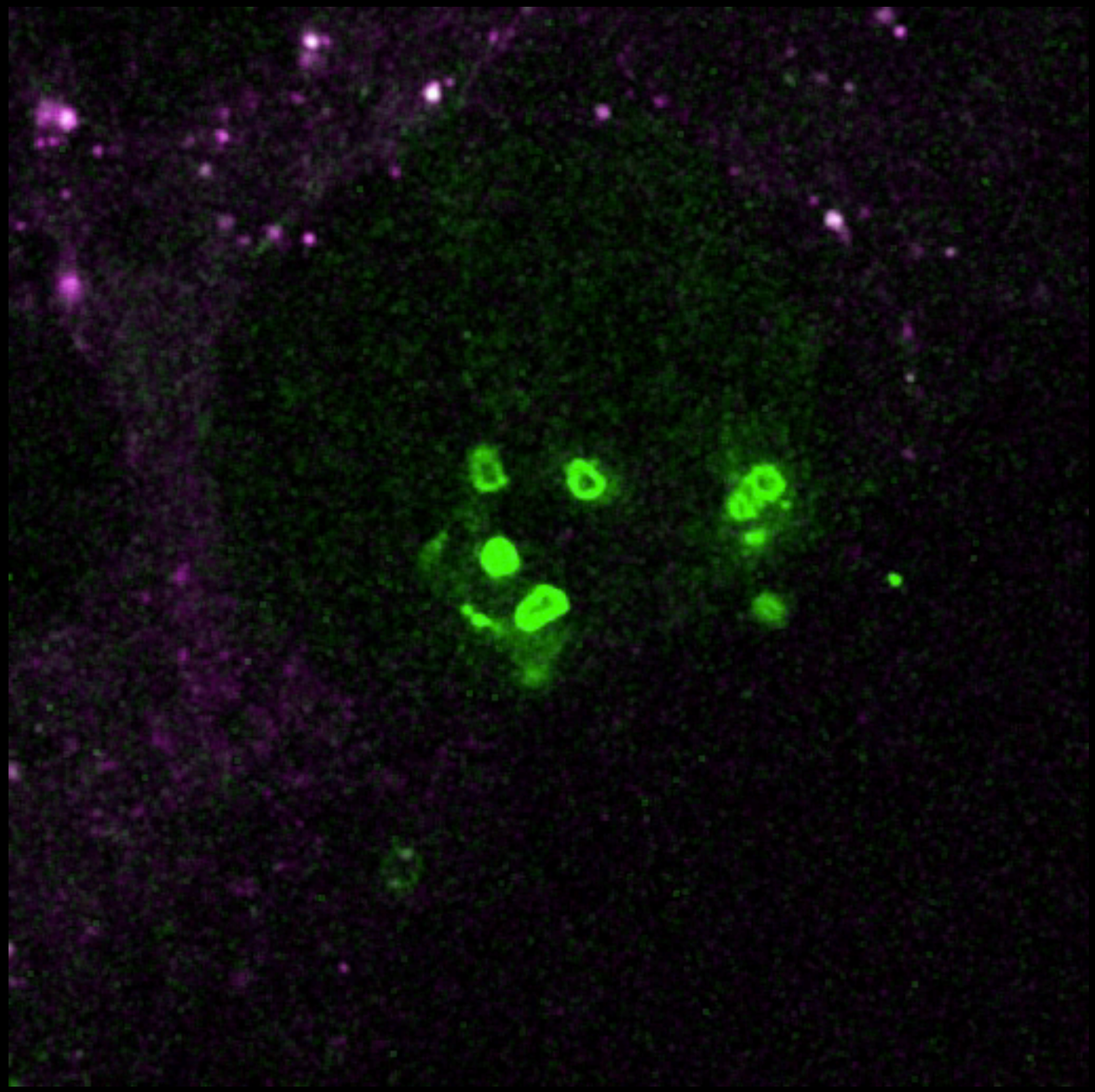




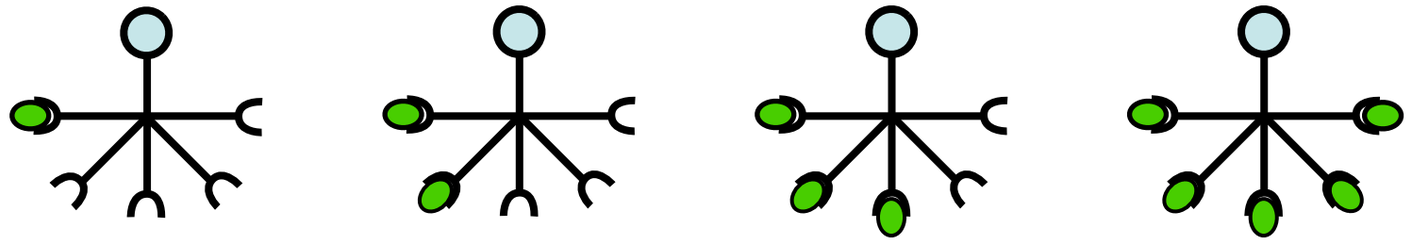
Claw-Bouton synaptic connections



Five bouton-claw contacts on one MB cell



Anatomical Connectivity Levels

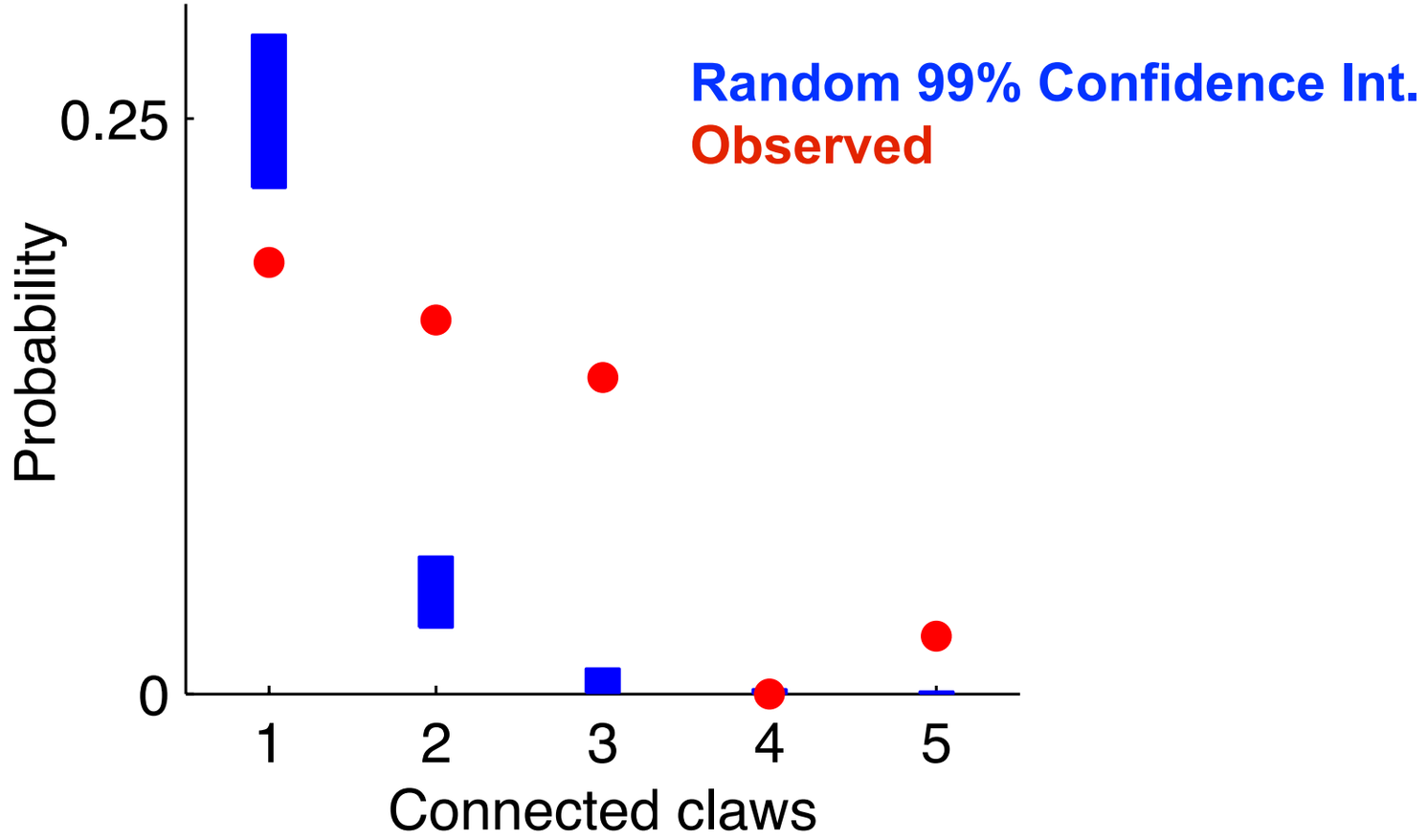


n=17
1 Connected Claw

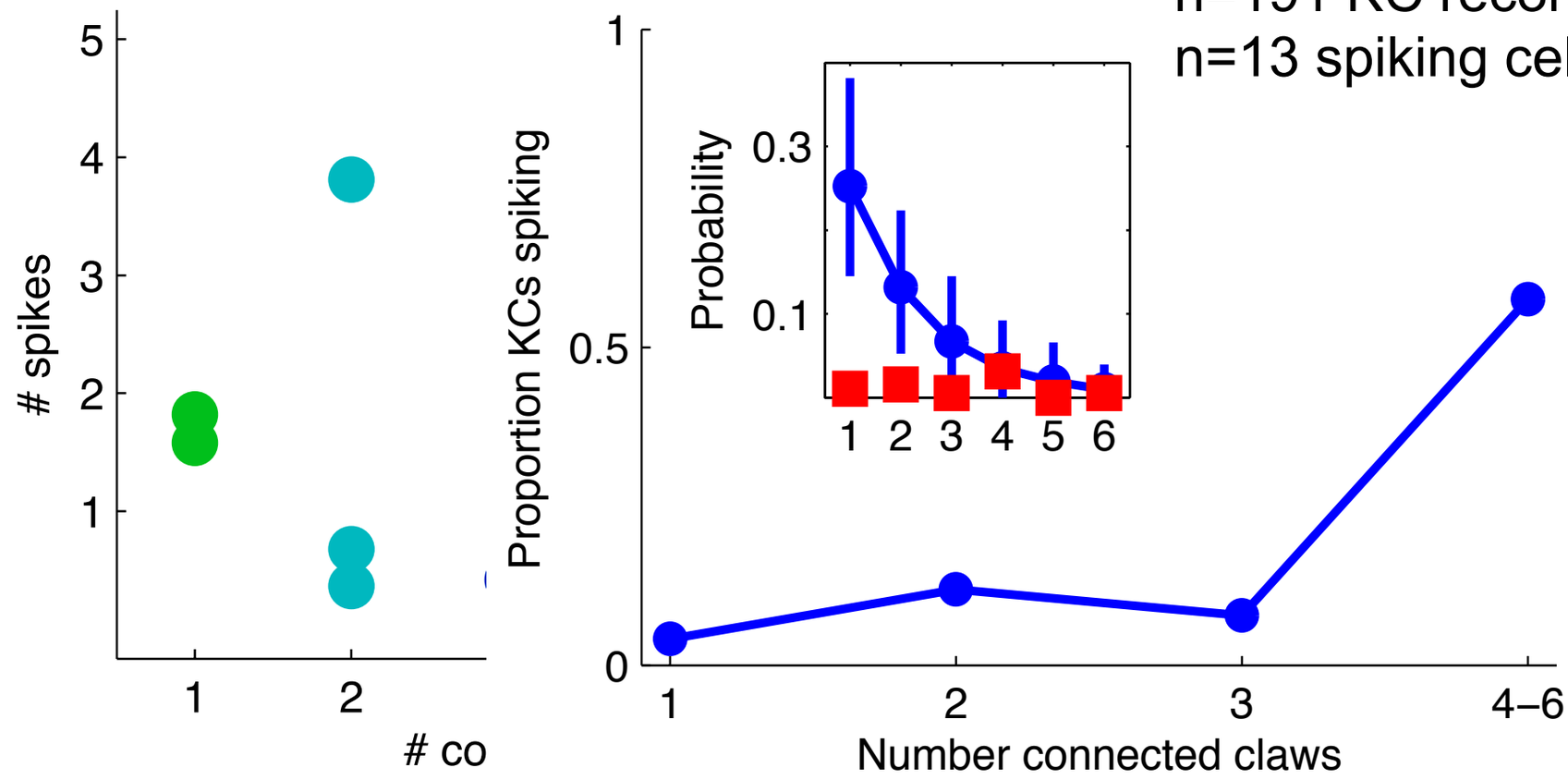
n=14
2 CC

n=6
3 CC

n=2
5 CC



MB spiking requires activation of multiple claws



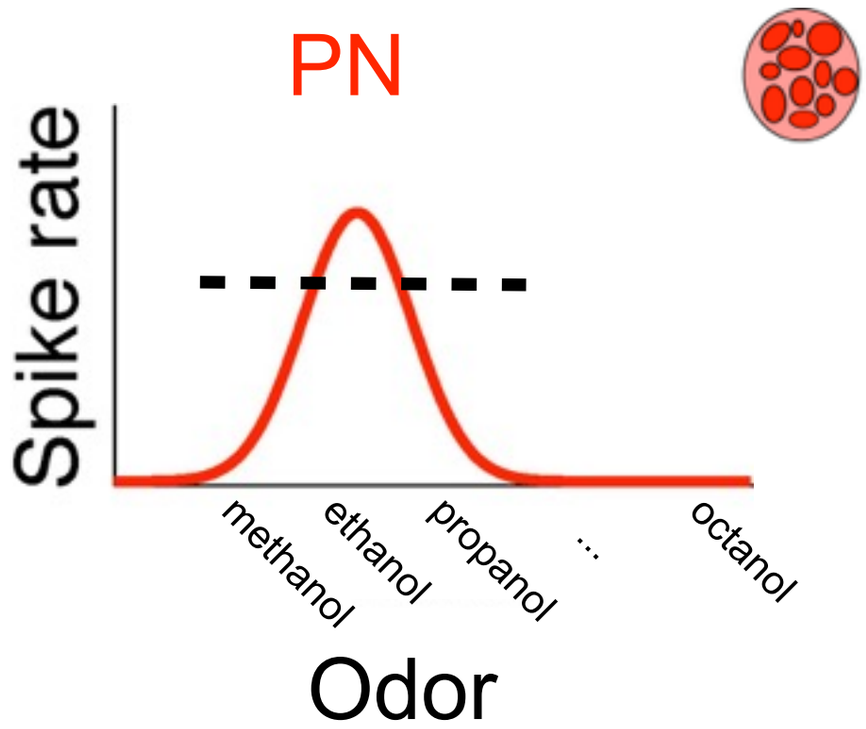
spikes not strongly dependent on # claws
P(response) is strongly dependent on # claws

Gruntman & Turner Nature Neurosci 2013

Integration & Capacity in Sparse Representations

Potential costs of sparseness:

- lack of reliability given small # spikes
- loss of information from thresholding



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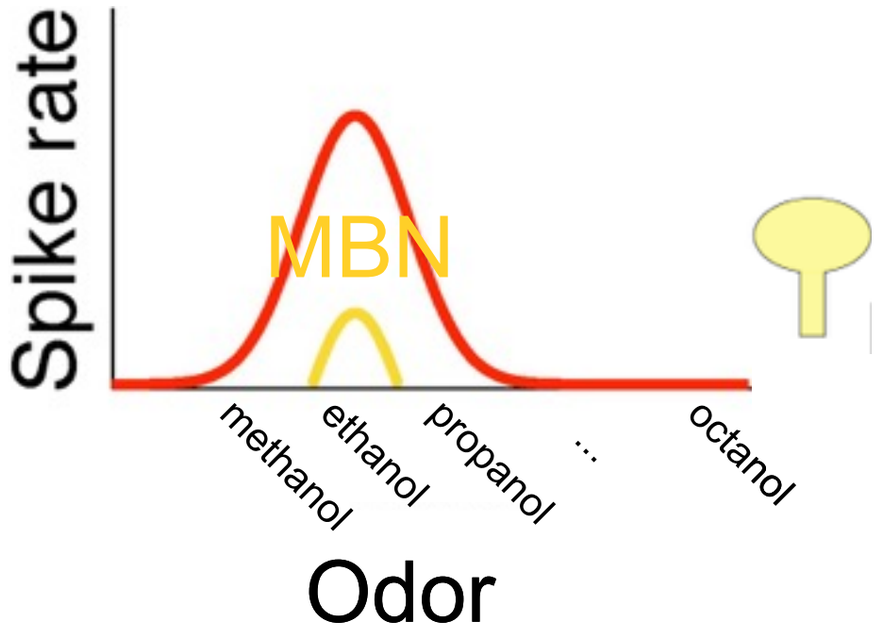

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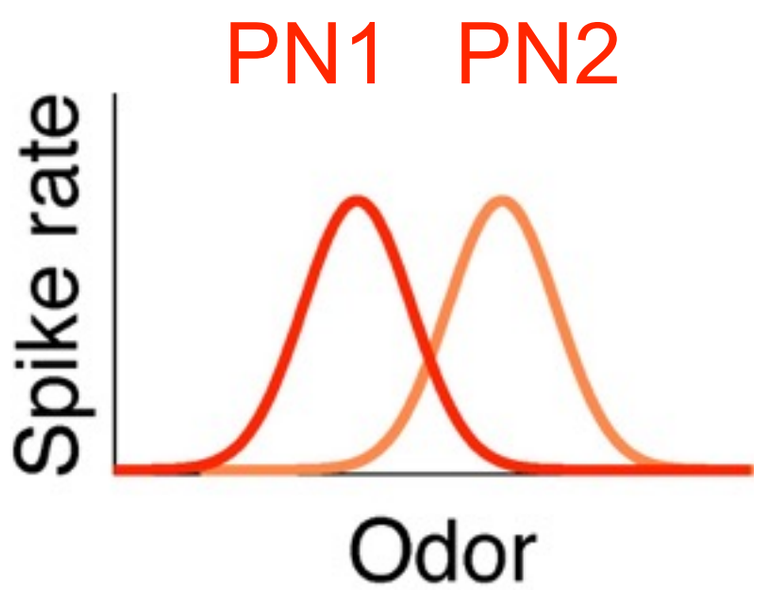

Integration & Capacity in Sparse Representations

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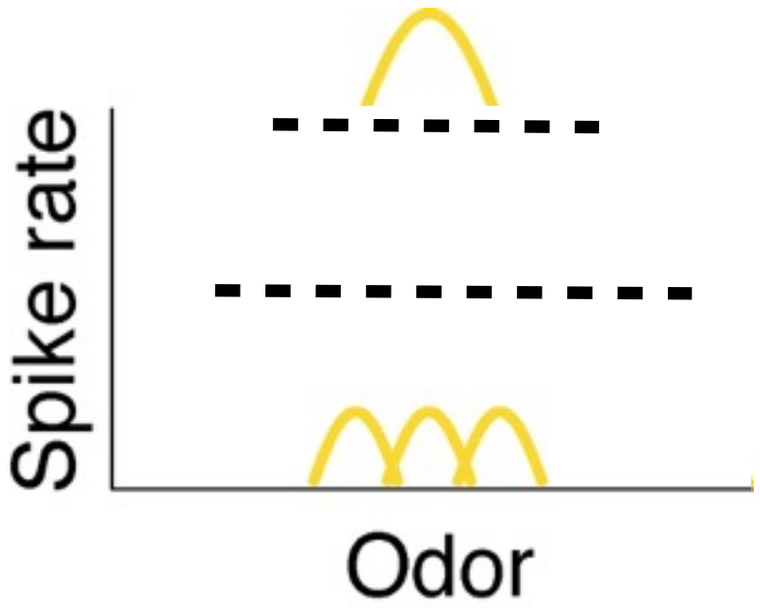


Integrating combinations of different PN inputs helps maintain overall capacity

MB neurons integrate the combinatorial code

- MB neurons *receive* different inputs
- *Require* multiple inputs to spike
  - Synaptic summation plateaus over time
  - Multiple inputs add sublinearly

Correlated tuning - Convergent connections

Fire together - Wire together

Thanks to:

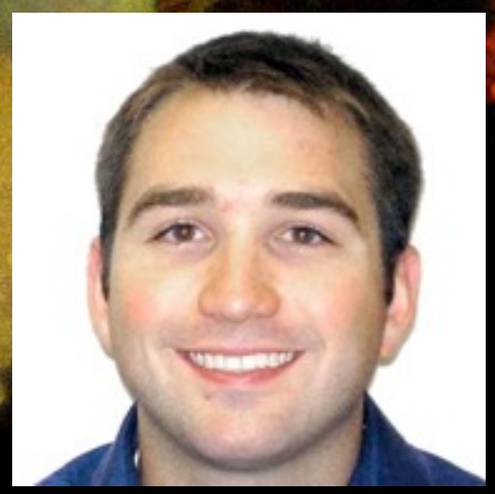
Yoshi Aso
Janelia Farm

Toshihide Hige
MB Output Neurons
Postdoc

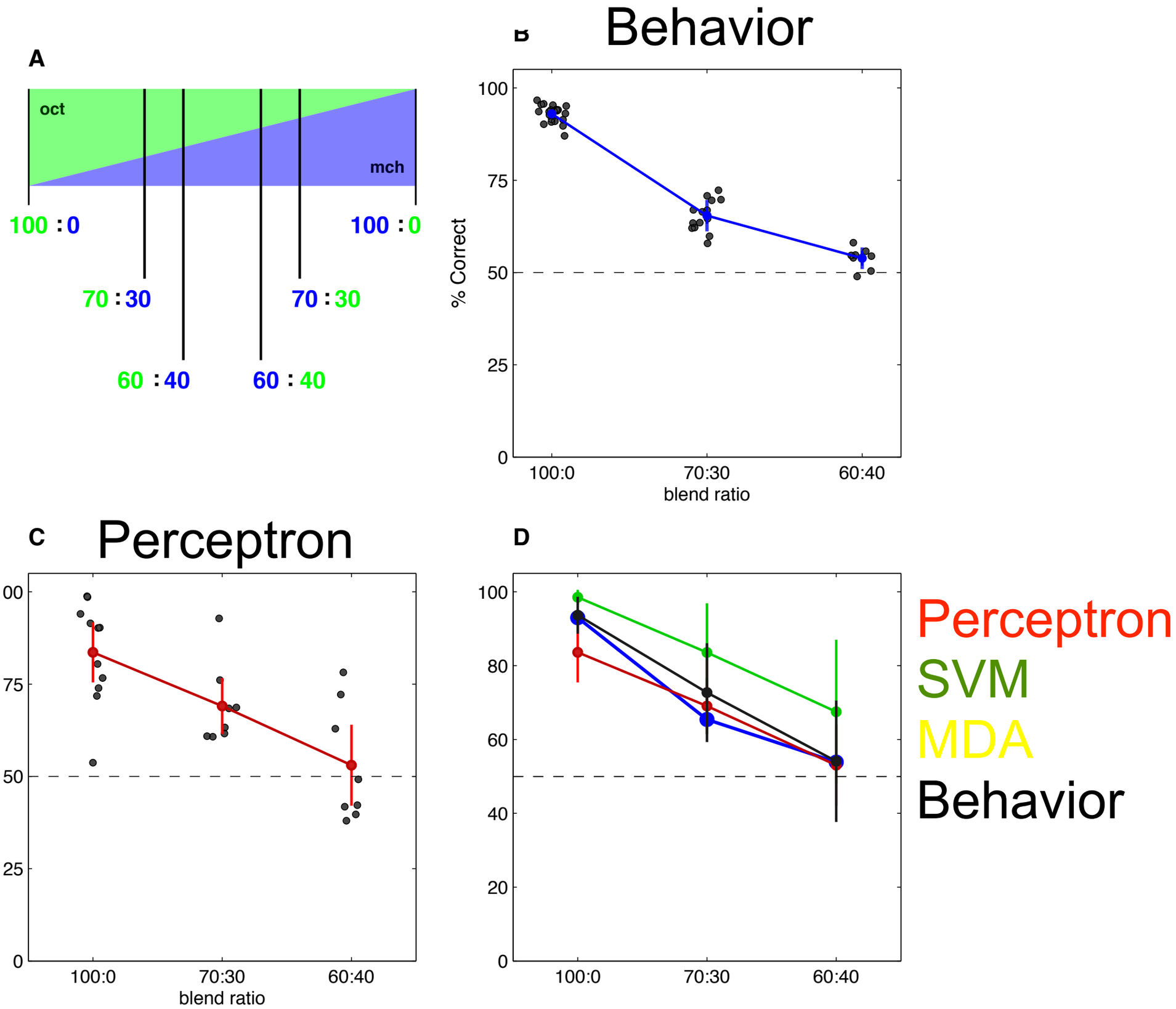
Gerry Rubin
Janelia Farm

Eyal Gruntman
Dendritic Claws
WSBS

Rob Campbell
MB population activity
Postdoc



Kyle Honegger
MB population activity
WSBS

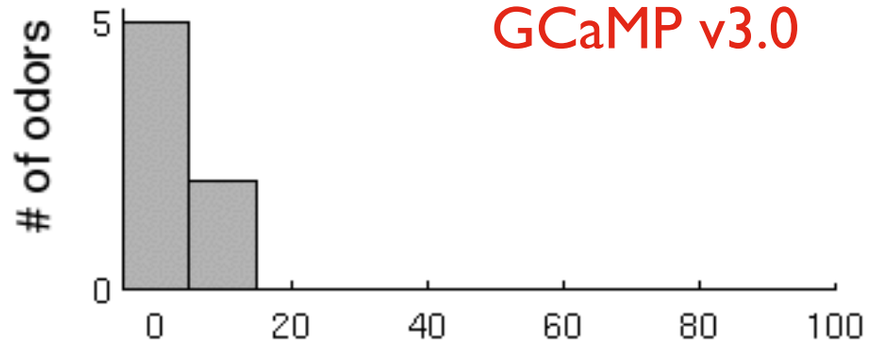

A
oct
mch
100 : 0
100 : 0
70 : 30
70 : 30
60 : 40
60 : 40
B
Behavior
% Correct
100
75
50
25
0
100:0
70:30
60:40
blend ratio
C
Perceptron
100
75
50
25
0
100:0
70:30
60:40
blend ratio
D
100
80
60
40
20
0
100:0
70:30
60:40
Perceptron
SVM
MDA
Behavior

Tracking population activity in the Mushroom Body with genetically encoded calcium indicators

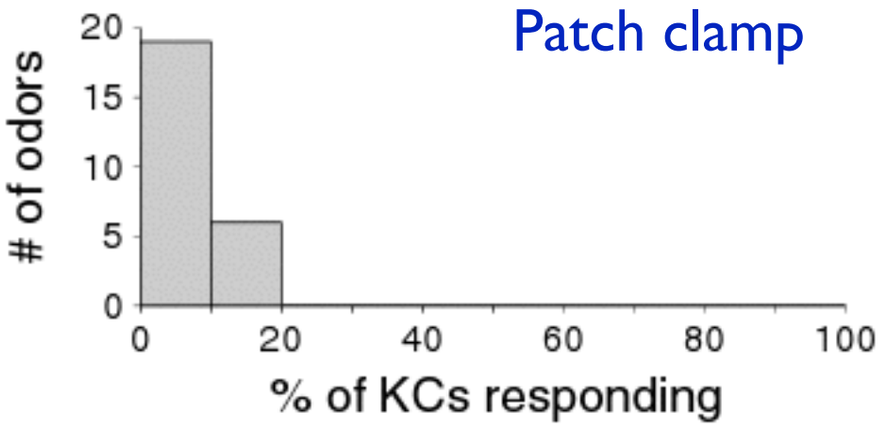
GCaMP v3.0 sensitivity is similar to electrophysiology

Fraction of responding cells

GCaMP v3.0

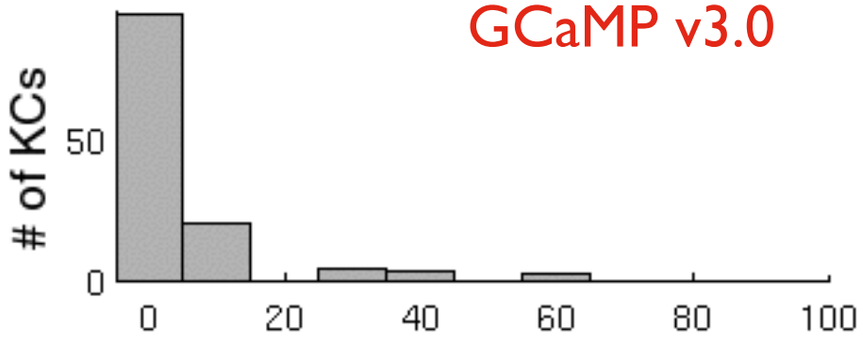


Patch clamp

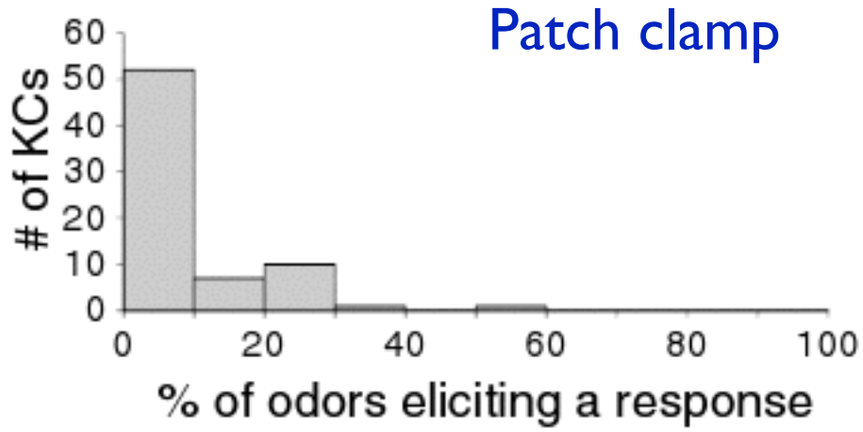


Tuning Width

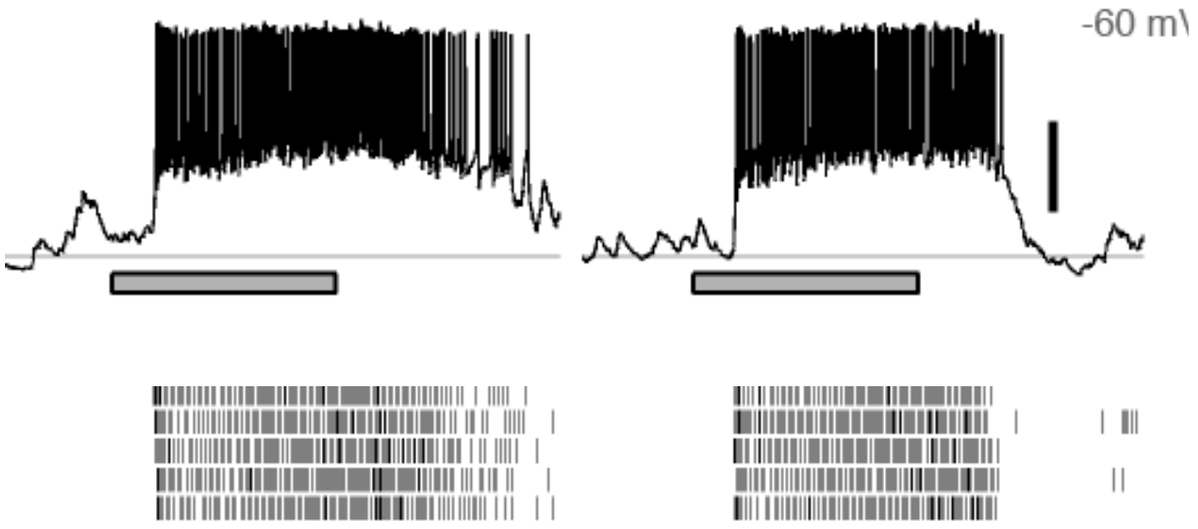
GCaMP v3.0

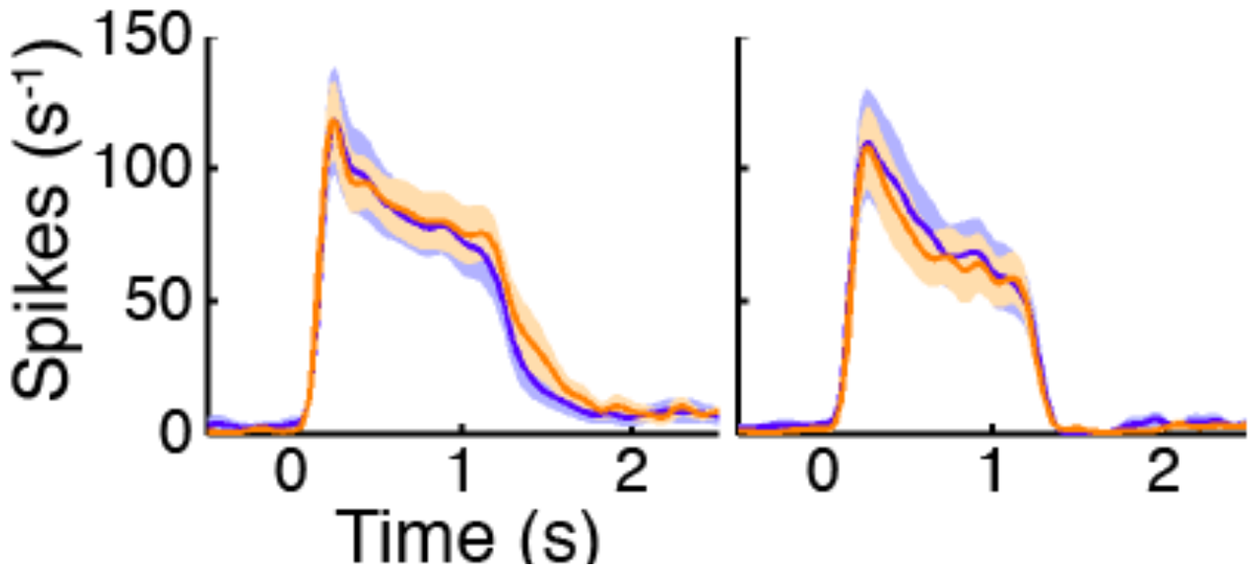


Patch clamp



Rob Campbell & Kyle Honegger


-60 m\


Spikes (s-1)
150
100
50
0
0
1
2
Time (s)
0
1
2