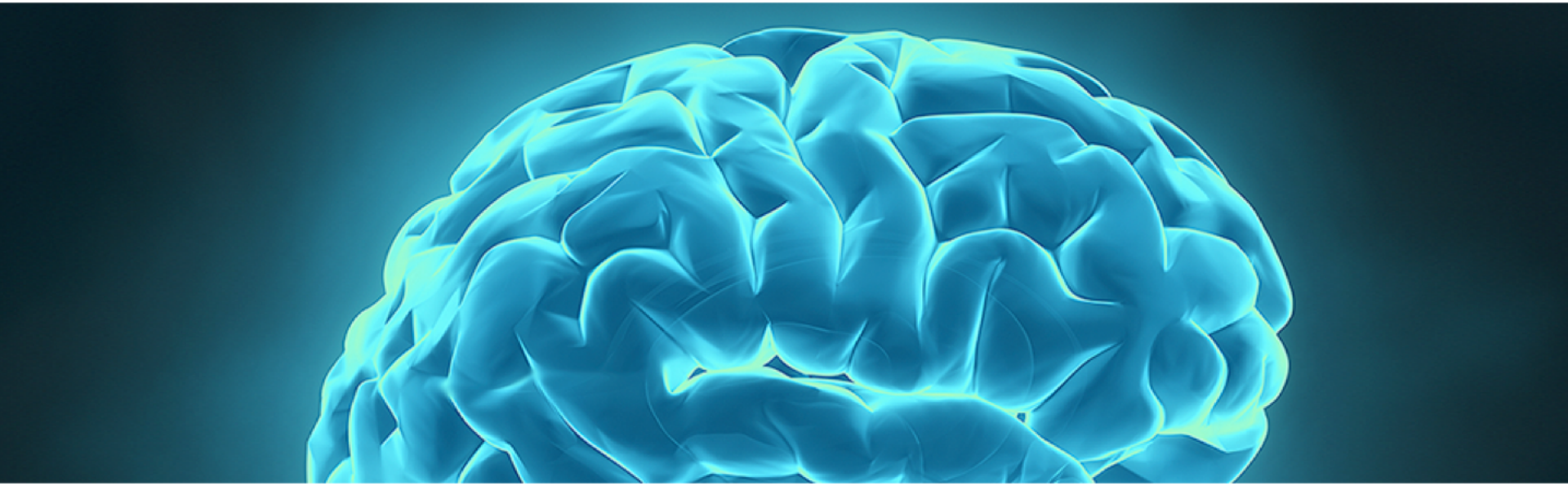
The ups and downs of Hebbian plasticity in associative fear learning



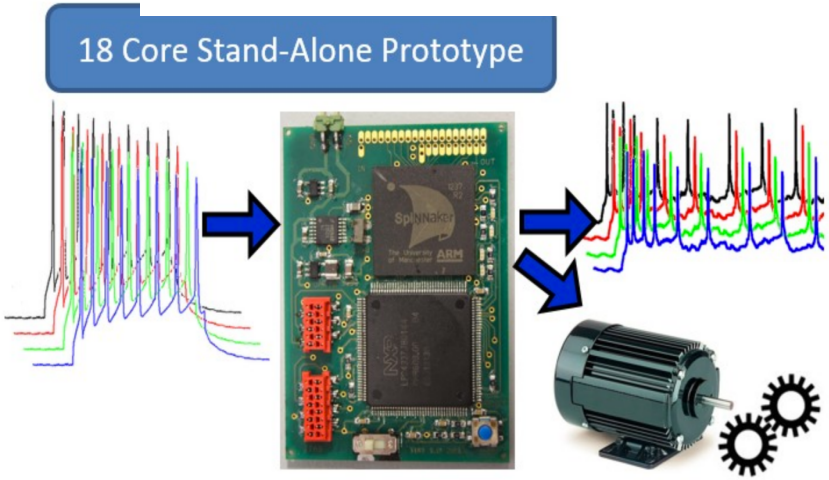
Benjamin F. Grewe, 27th June 2017 @ Leti Memory Workshop

ETH zürich

institute of neuroinformatics

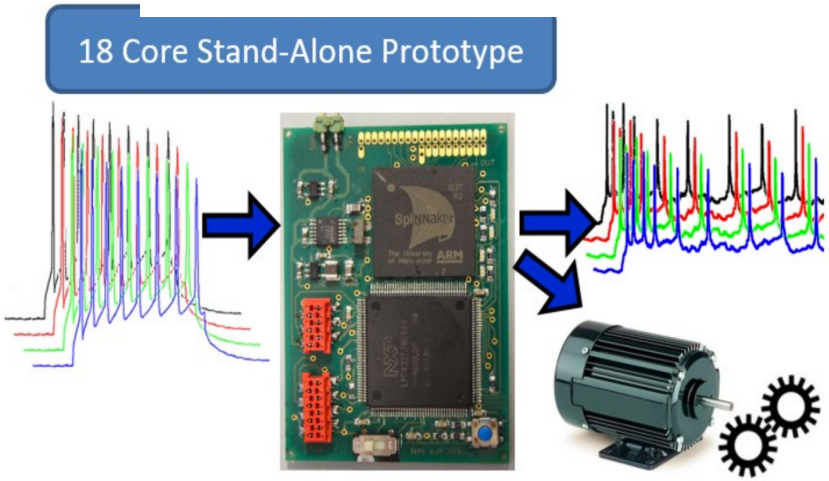
The Institute of Neuroinformatics at ETH

Neuromorphic Computer Hardware

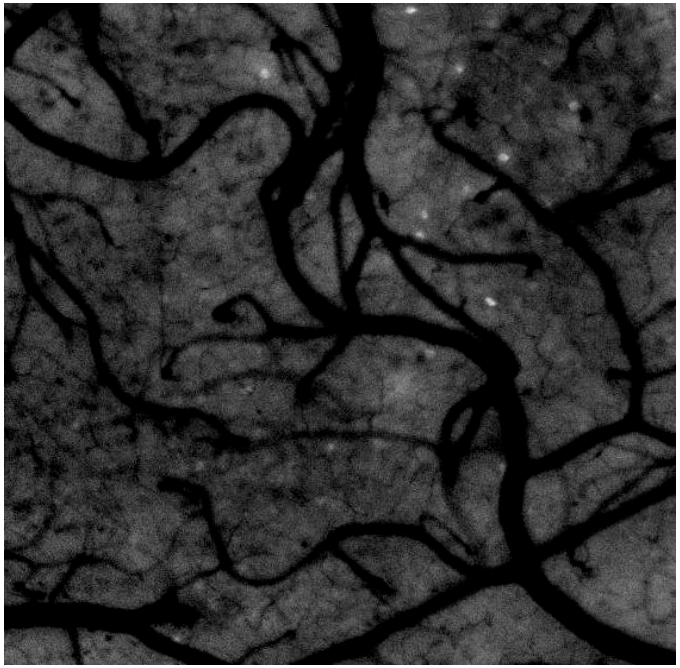


The Institute of Neuroinformatics at ETH

Neuromorphic Computer Hardware

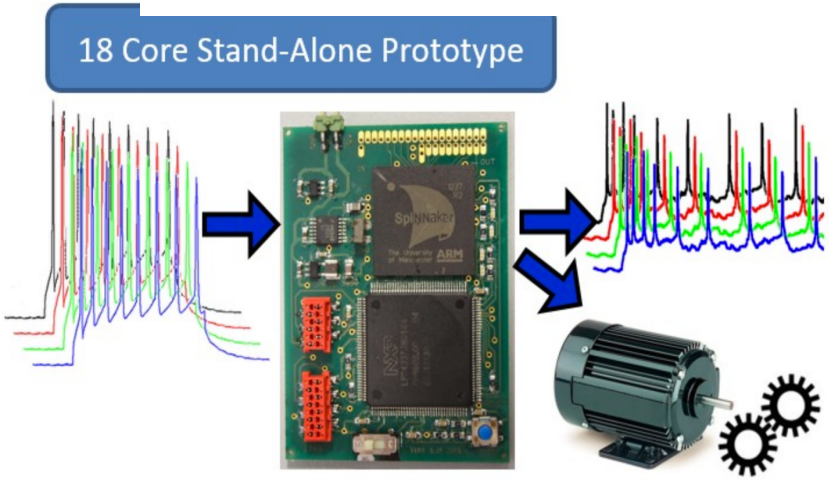


Computational & Systems Neuroscience

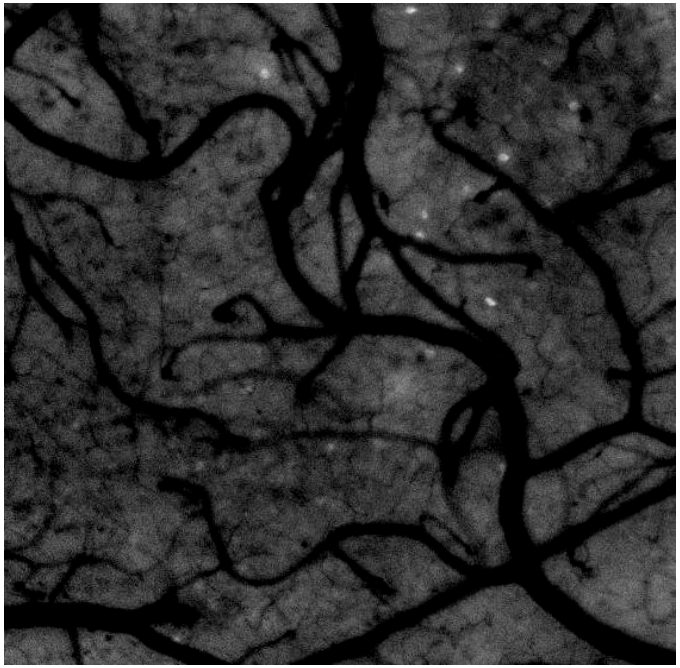


The Institute of Neuroinformatics at ETH

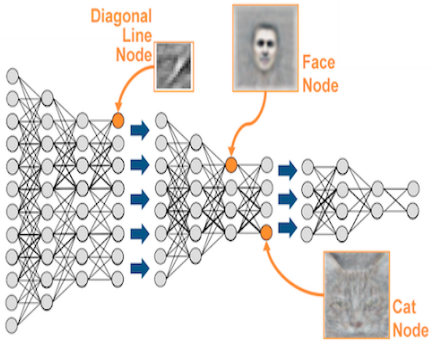
Neuromorphic Computer Hardware



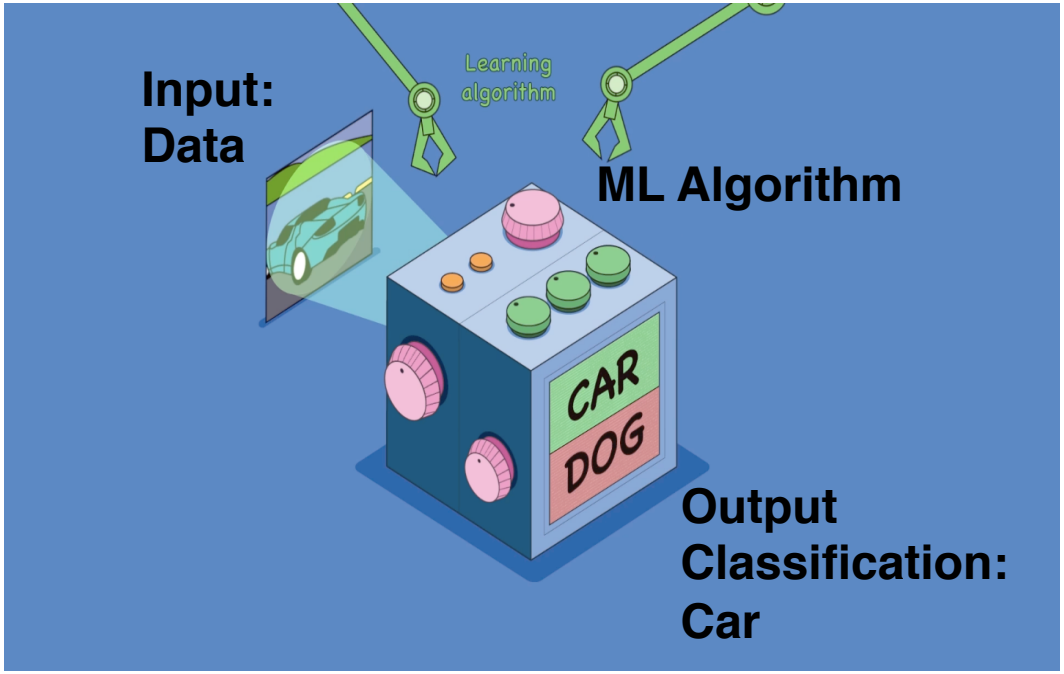
Computational & Systems Neuroscience



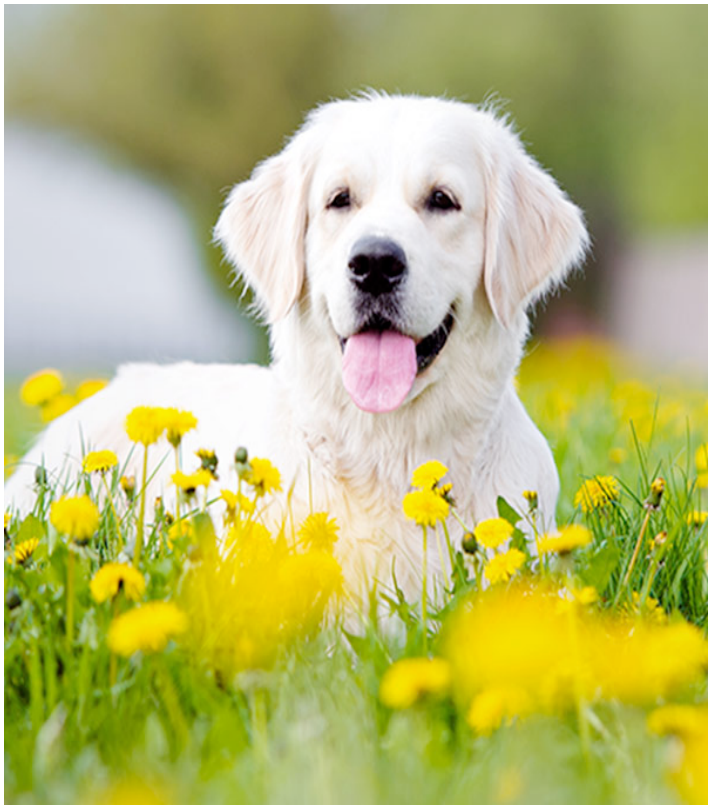
Algorithms and Machine Learning

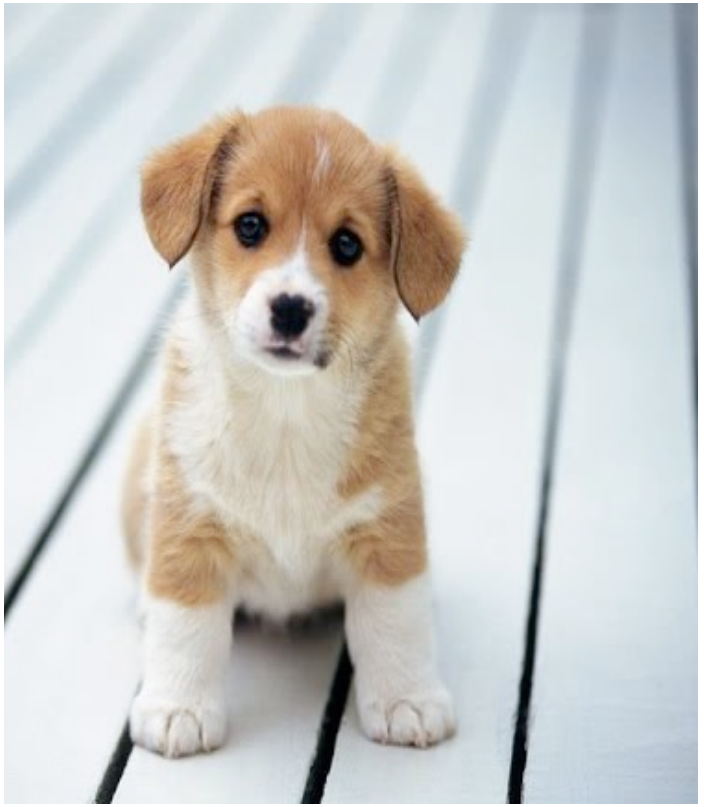


Machine Learning Allows to Reveal Hidden Structure in Complex, High-dimensional Data.



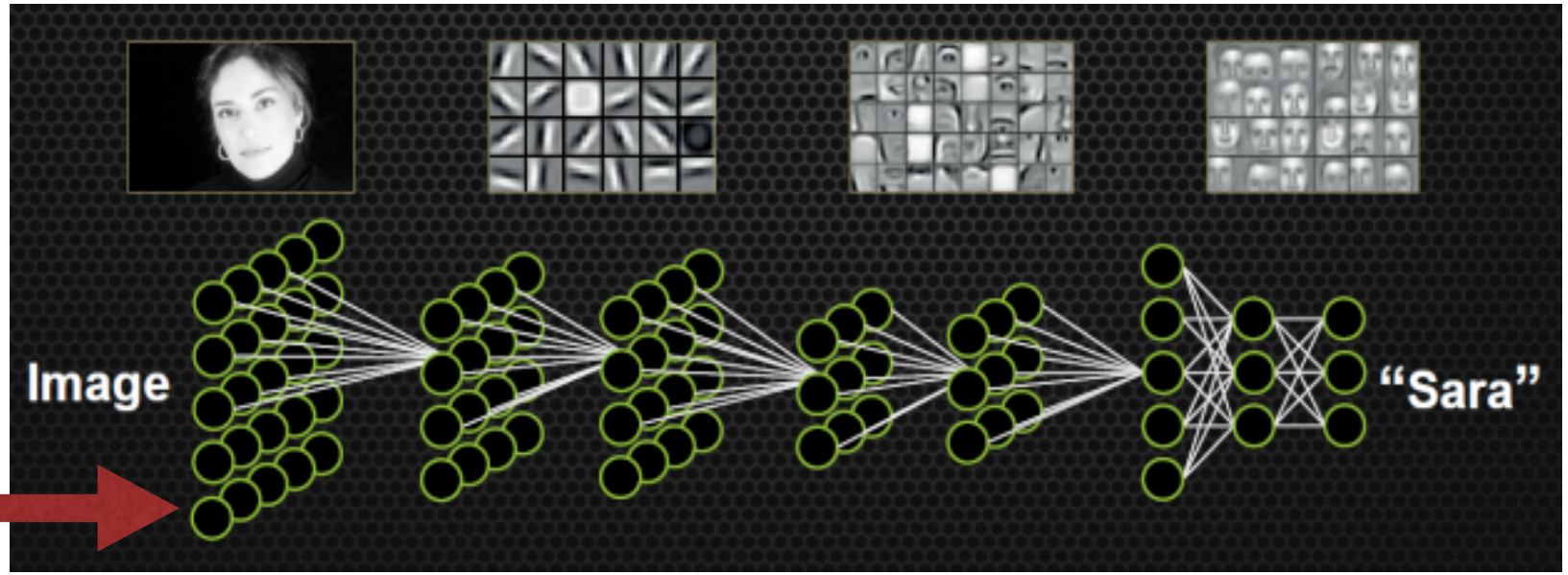
Machine Learning Allows to Reveal Hidden Structure in Complex, High-dimensional Data.





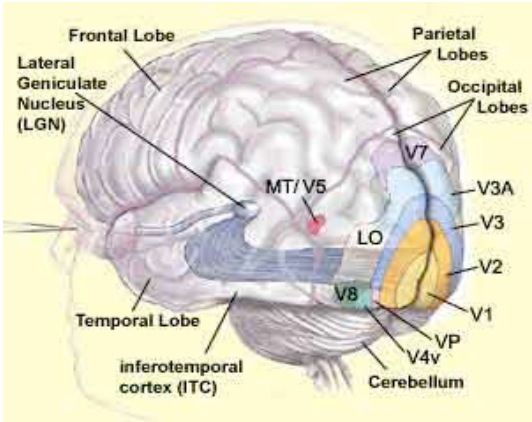
4MP = 2000 x 2000 pixel

Hierarchical Artificial Neuronal Networks have Revolutionized Machine Learning Application in Particular for Object or Speech Recognition



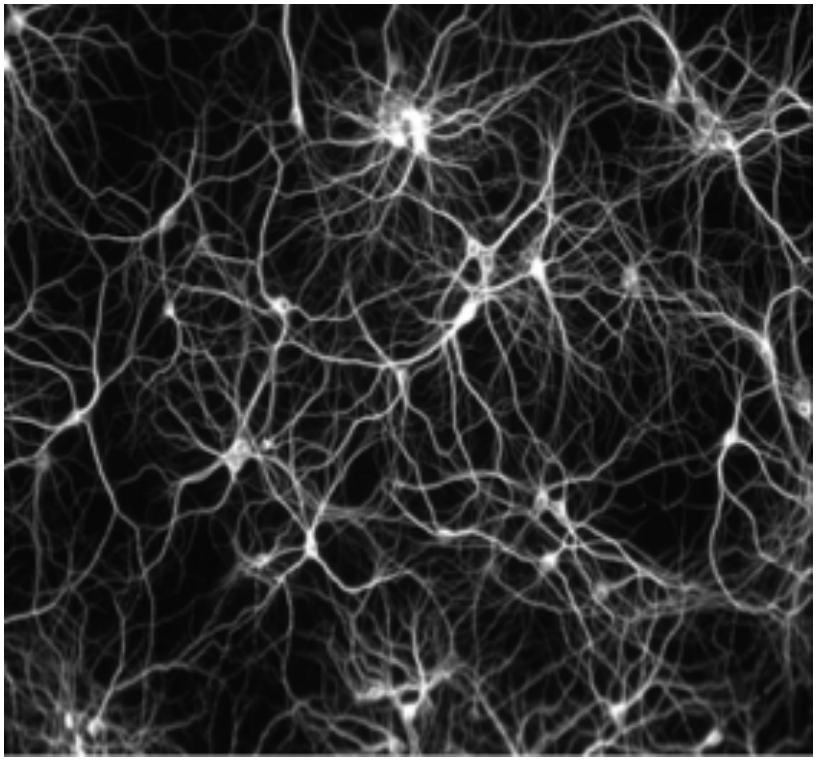
Neurons

V1——-----V2—---—V3—— -----V4-MT/V5------——IT



The Brain is an Incredibly Powerful Computational Device.

- 10^11 Neurons und 10^15 Synapses
- 150,000-180,000 km Nerve fibers
- 1200 cm^3 Volume
- 20 Watt power consumption



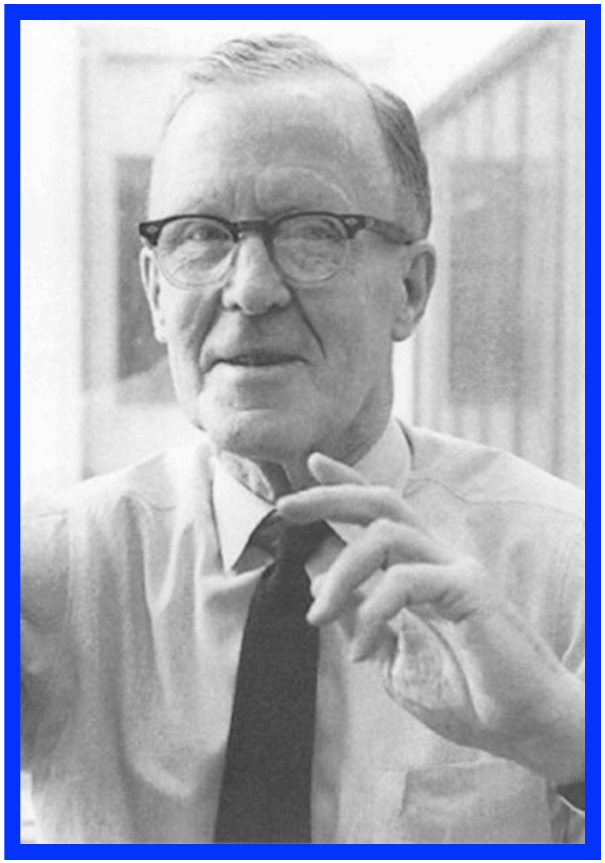
How do Neuronal Networks in the Brain form a new Memory?

Learned Associations are Basic Building Blocks for the Construction of Memories

Classical Conditioning **Hebbian Learning Rules**



Ivan Pavlov (1903)



Donald O. Hebb (1949)
Organization of Behavior

What are Biological Substrates of Long-term Associative Memories?

1. Molecular Substrates

2. Synaptic Substrates

3. Cellular Substrates

What are Biological Substrates of Long-term Associative Memories?

1. Molecular Substrates
2. Synaptic Substrates
3. Cellular Substrates
4. Network Level Substrates

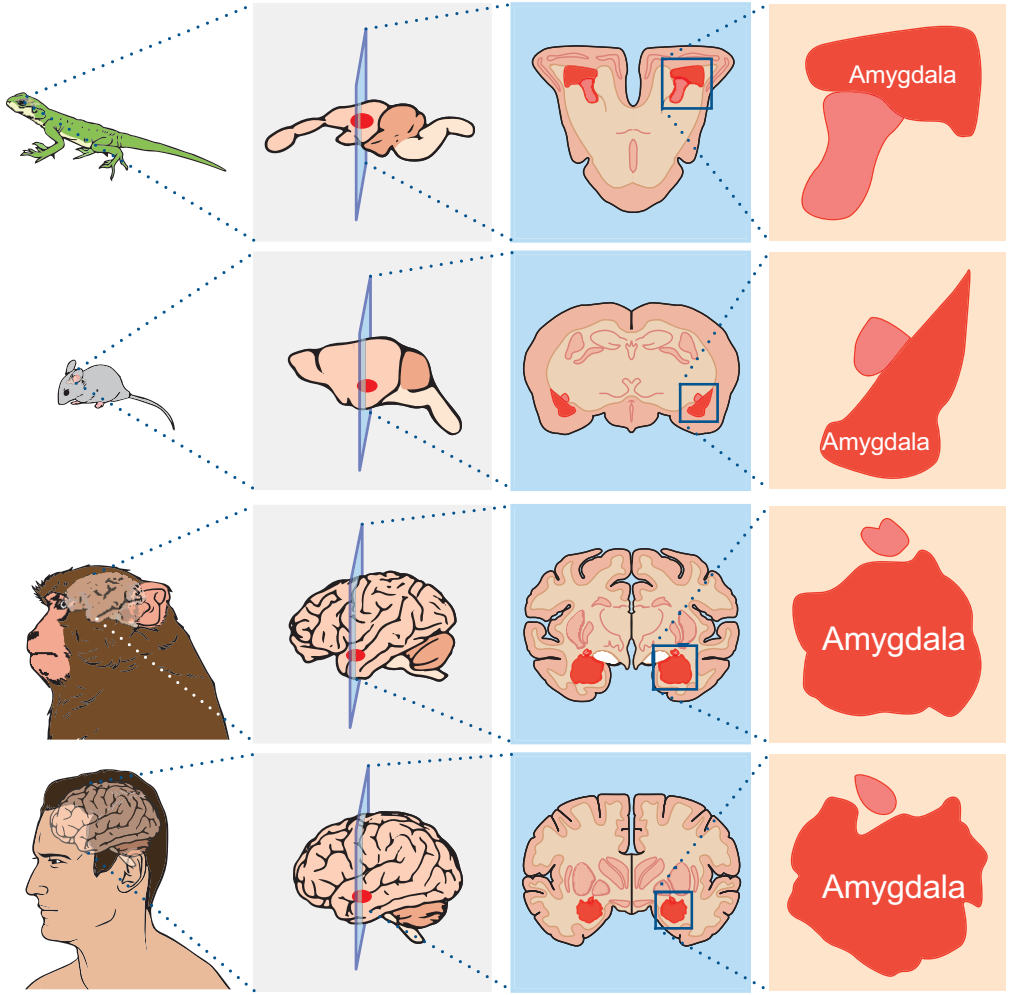
Fear Learning as Model System to Study Memory in the Brain

Fear!



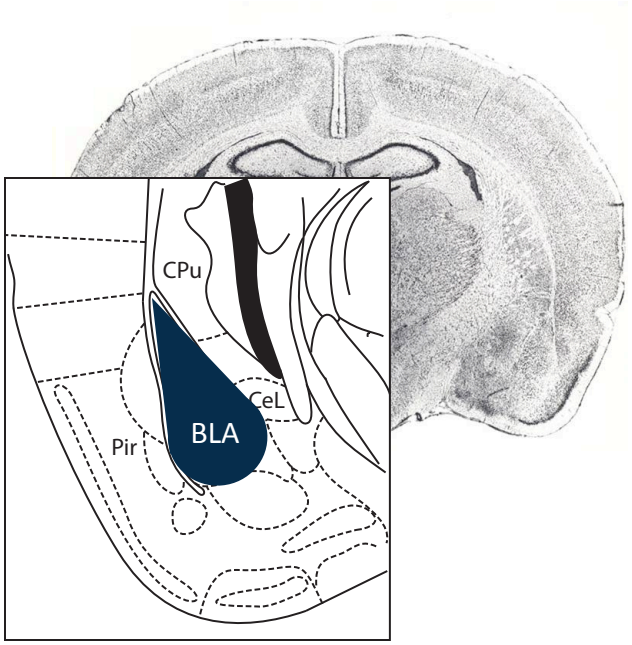
…help us to survive and to predict danger!

The Amygdala is Crucial for Emotional Learning and is Conserved Across Species



Adapted from Janak et al. 2015

The Mouse Amygdala for Investigating Associative Memory Formation in the Brain



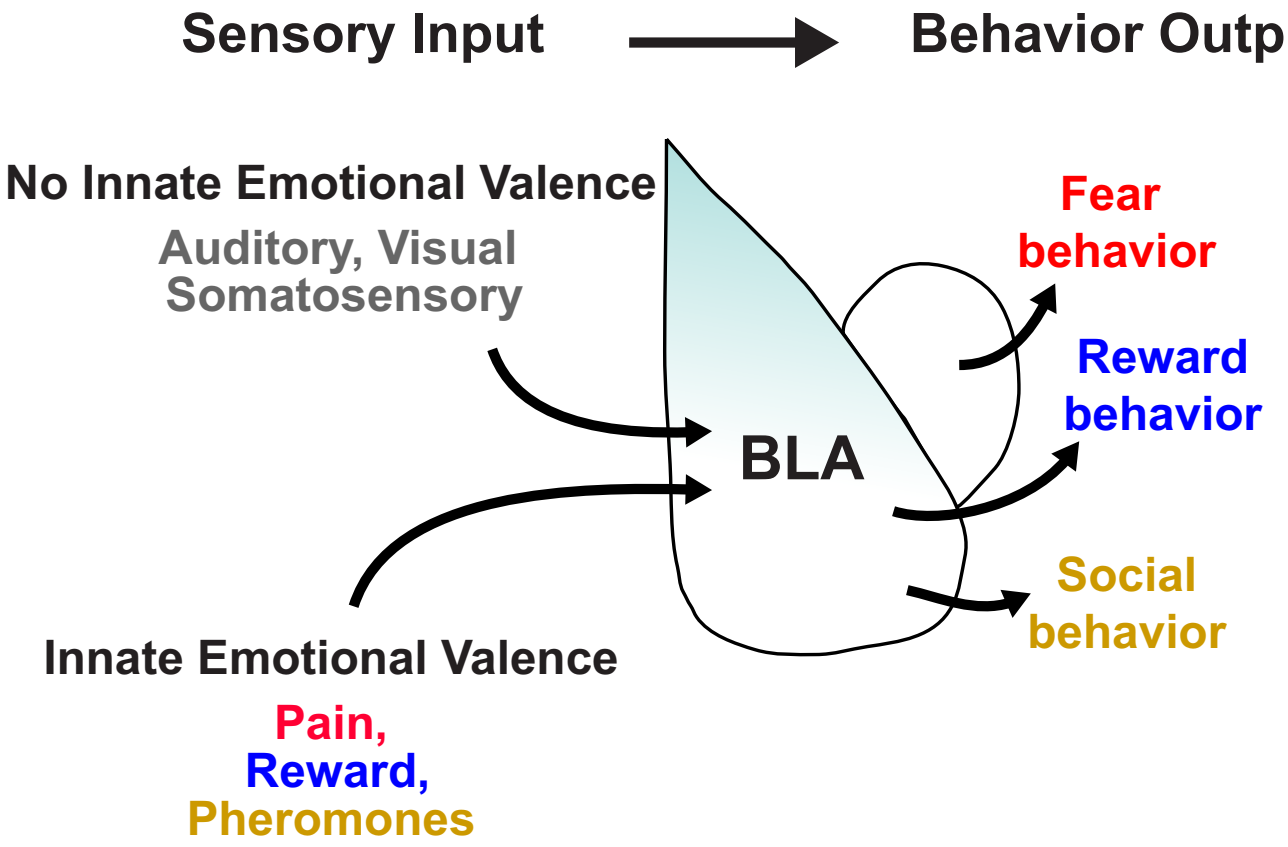
Baso-Lateral Amygdala (BLA)

The BLA is necessary for fear conditioning

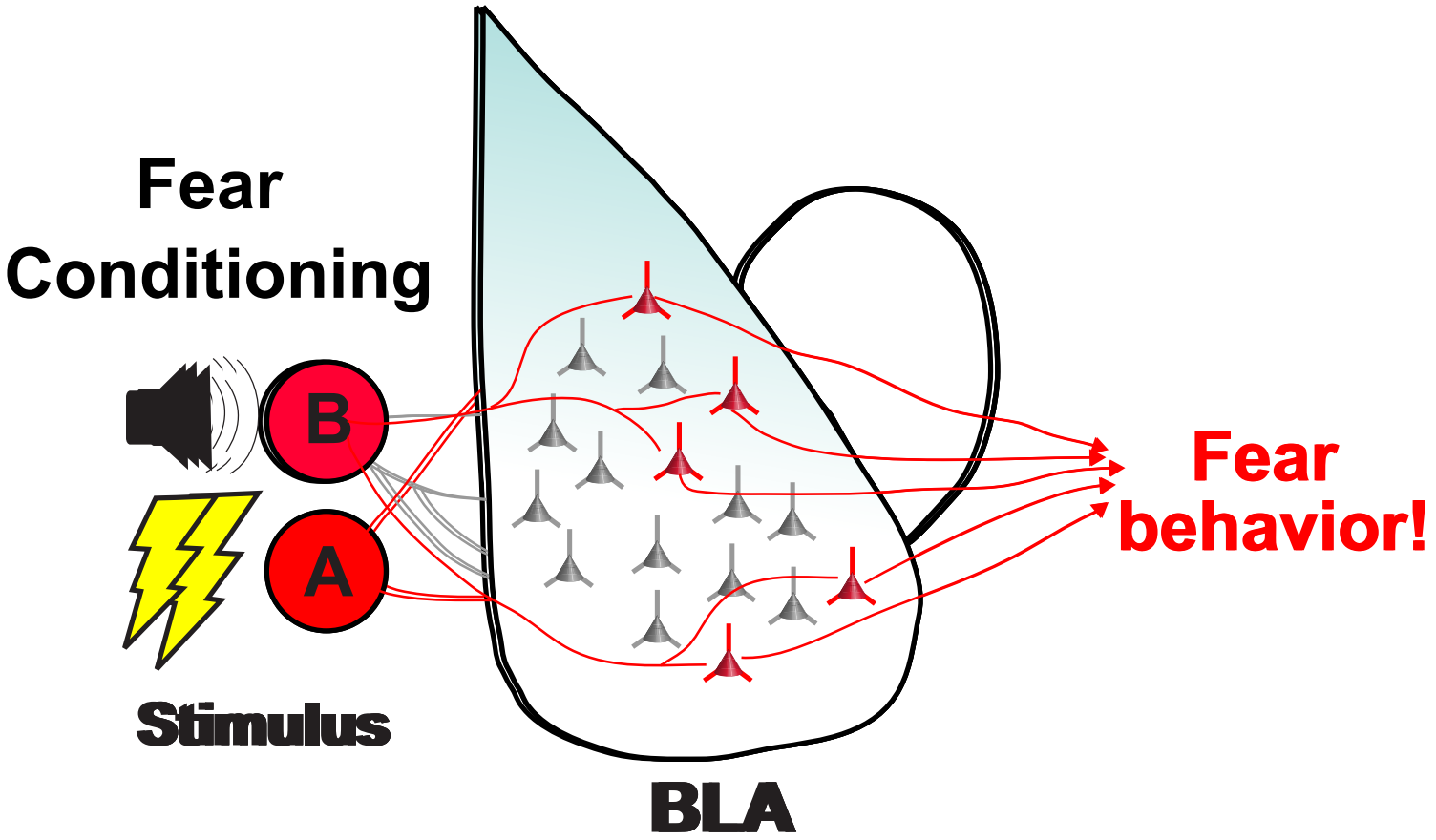
(Maren et al. 1999 and others)

The Amygdala is Uniquely Positioned in the Brain to Mediate Emotional Processing…

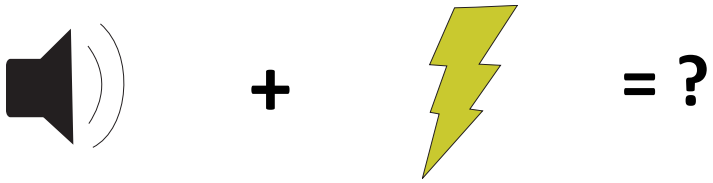
…because it Links Sensory Input to Behavioral Output!



How does the BLA Encode Emotional Information ?



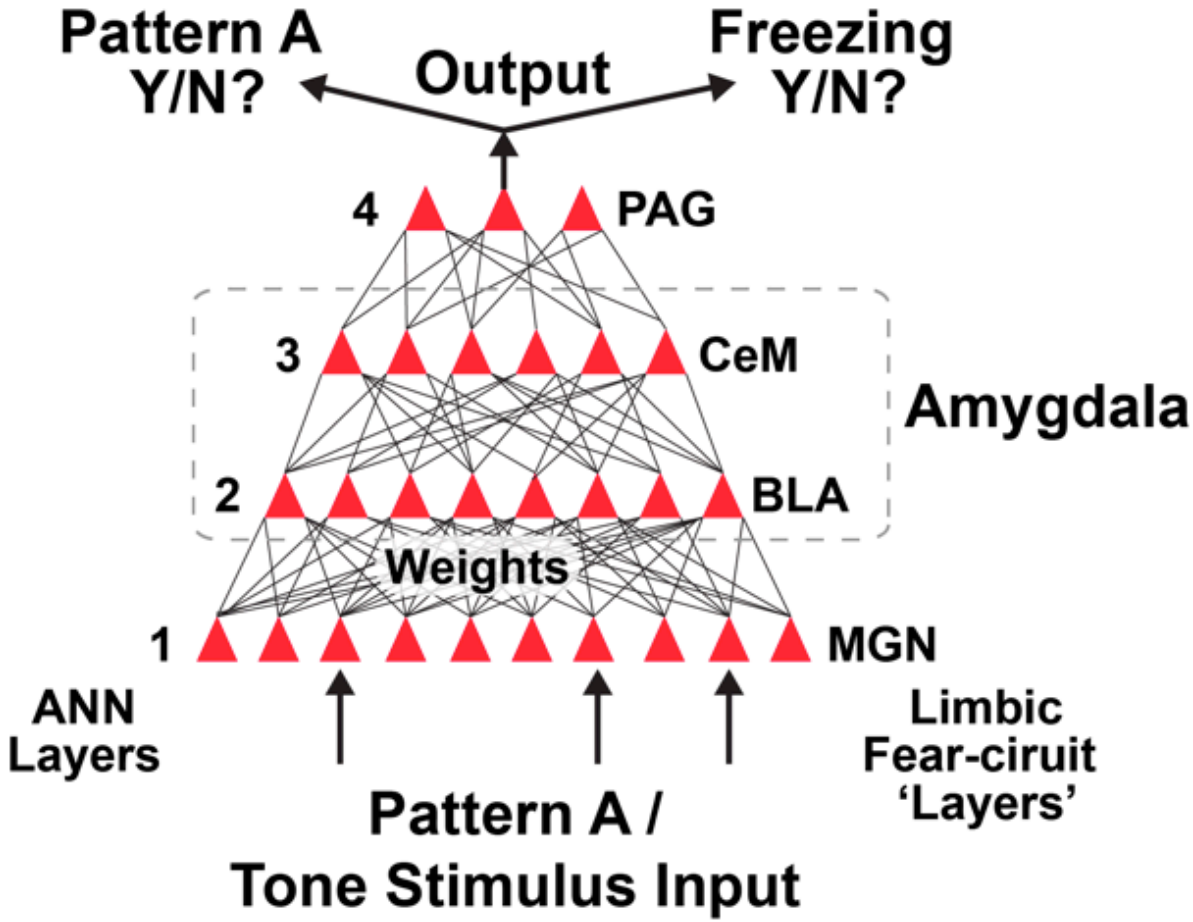
Auditory Fear Conditioning is a Model System For the Study of Associative Learning



CS
Conditioned Stimulus

US
Unconditioned Stimulus

The Hierarchical Processing of Fear



Questions:

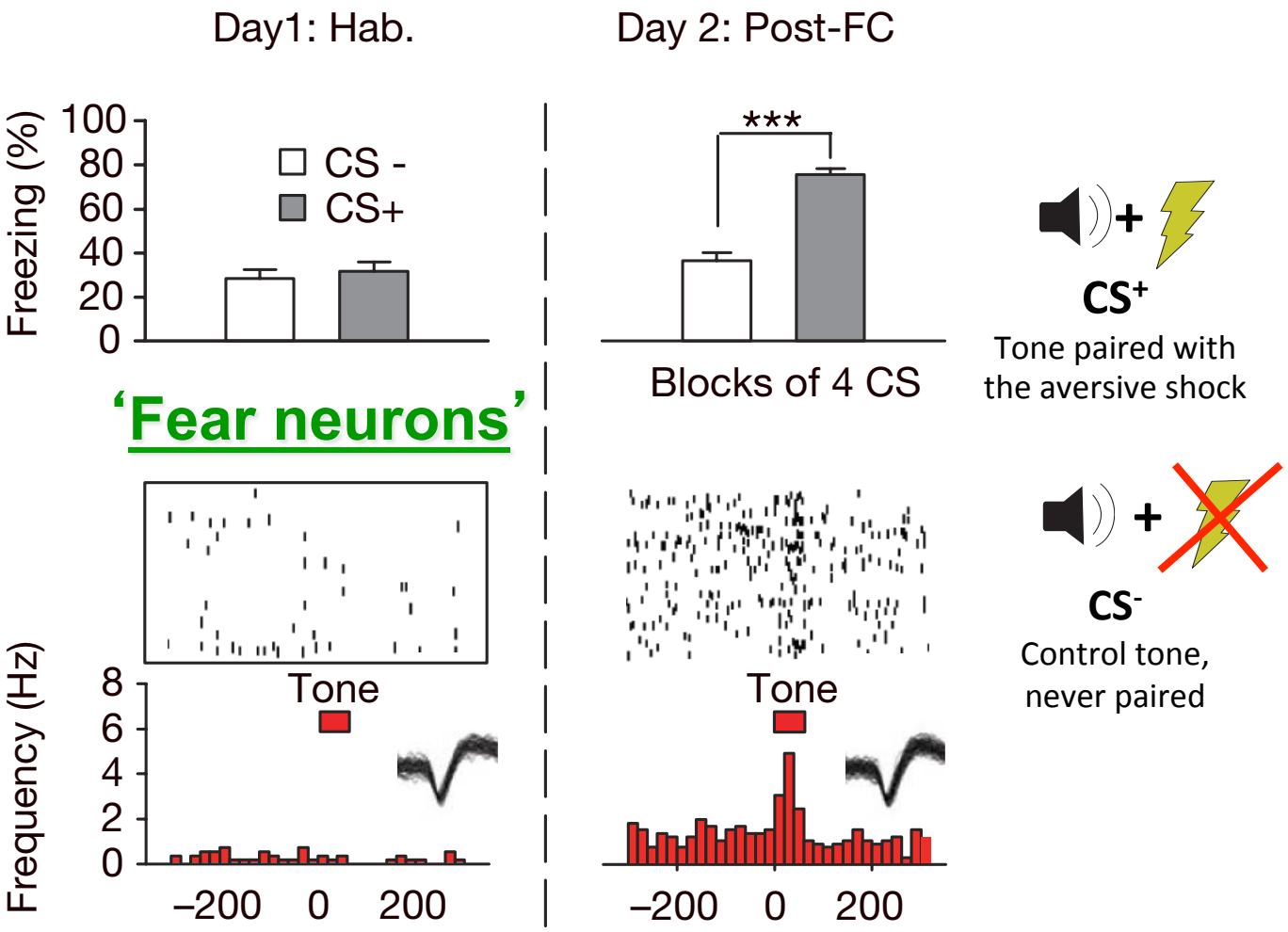
1. How is a CS or a US encoded in the BLA ?

2. How does fear conditioning change the neural ensemble representation of a CS ?

3. How is association between the CS and the US implemented in the BLA ?

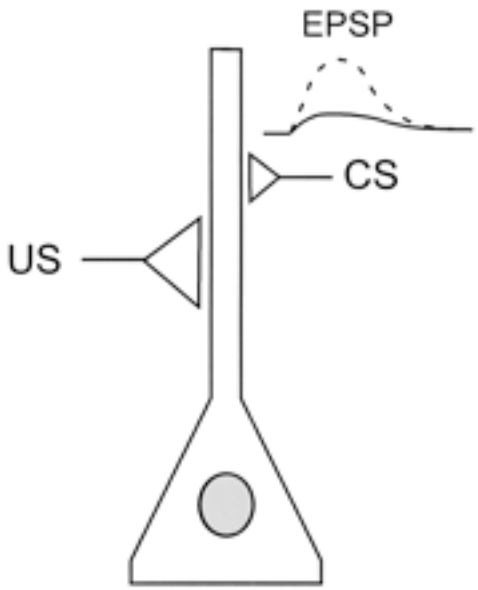
4. What does the change in the representation of the CS tell us about the representation of emotion in the brain ?

Cellular Substrates of an Associative Fear Memory in the BLA



(Herry et al. 2008, Nature)

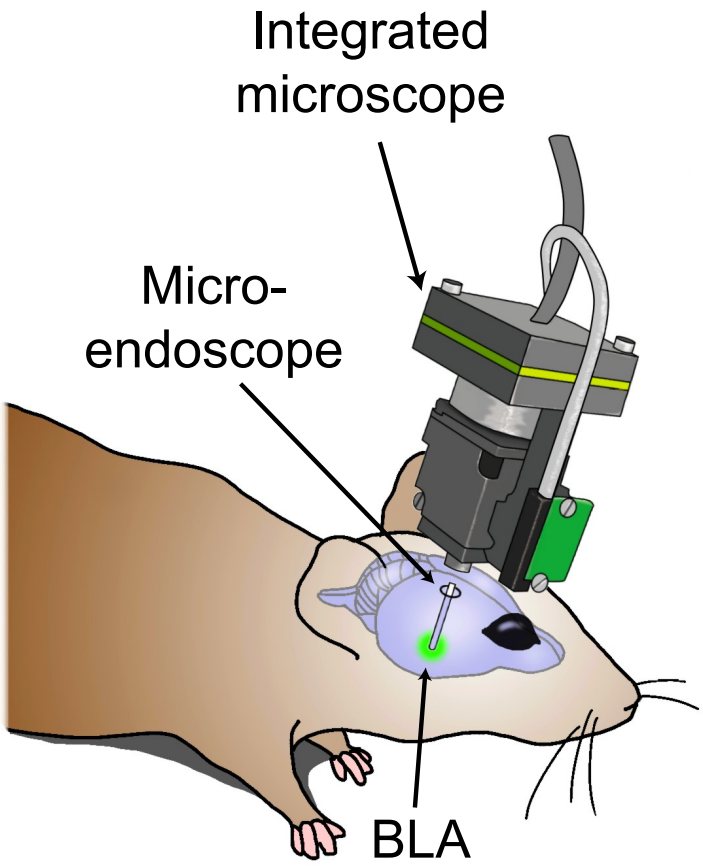
The Cellular Hypothesis of Hebbian Associative Learning

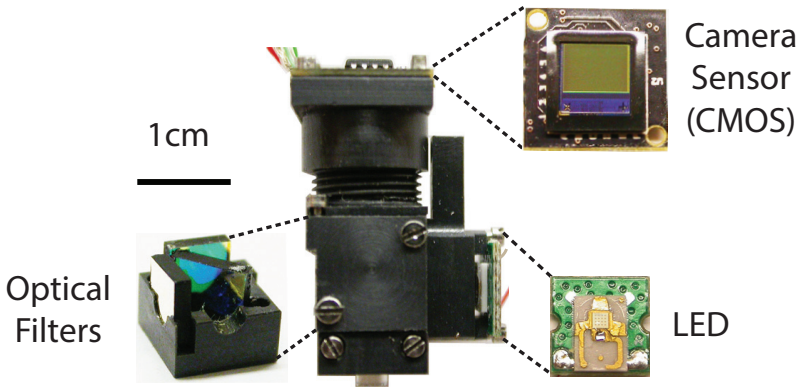


Blair et al., 2001

Hypothesis: "Neurons that potentiate to the CS are activated by the US"

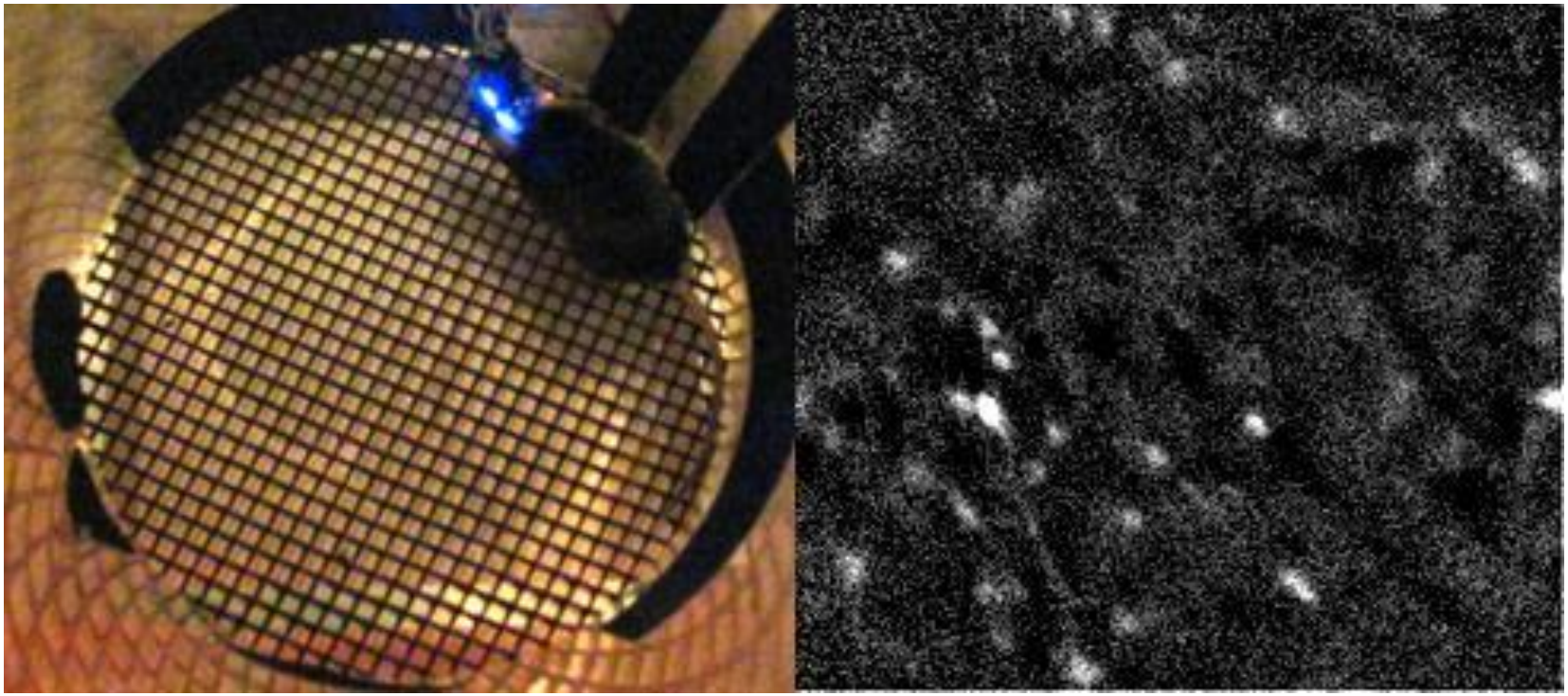
The Method: Population Calcium Imaging in Freely Moving Mice



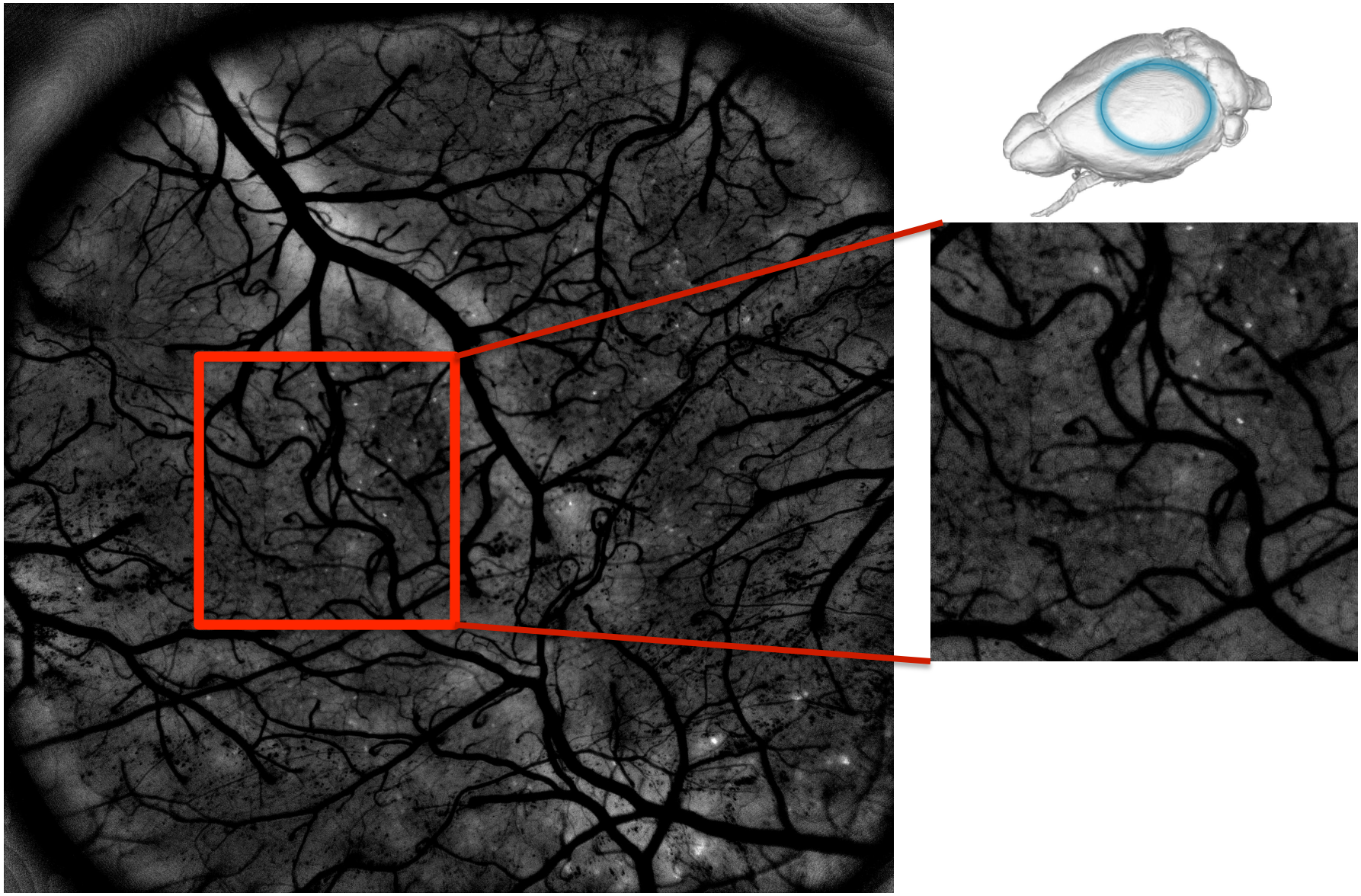


Ghosh *et al.*, 2011

Mini-scope Imaging of PrL Ensemble Activity in Freely Moving Mice

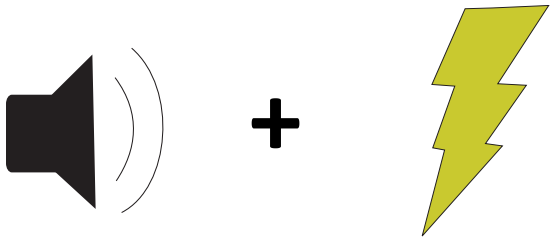


Large FOV Calcium Imaging Allows to Record from Thousands of Neurons Across Neocortical Networks.



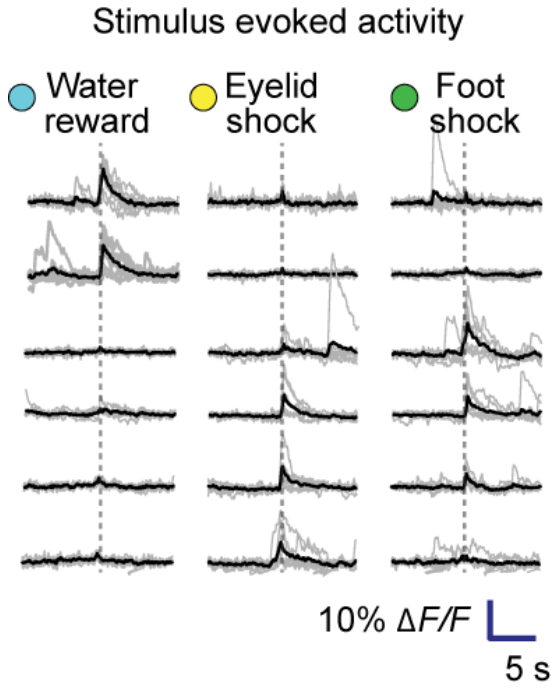
To Understand the how the BLA Assigns Emotional Valence we Need to Understand the Baseline Representations of a CS and a US

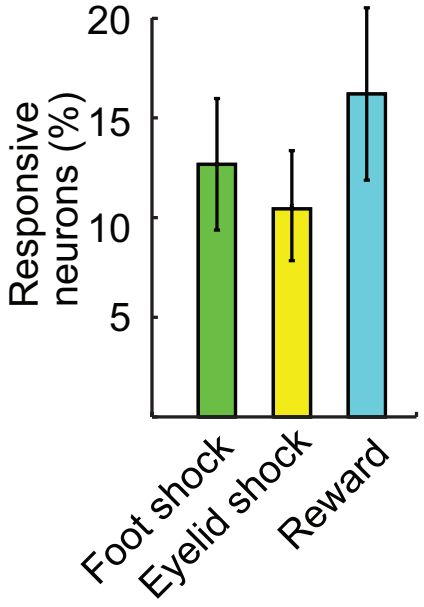
Fear Conditioning

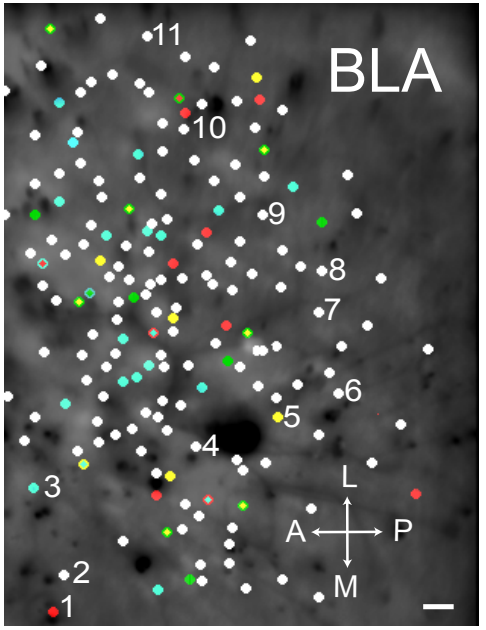


CS US

Emotional Relevant Stimuli Activate Sparse, Intermingled Neuronal Subsets in the BLA



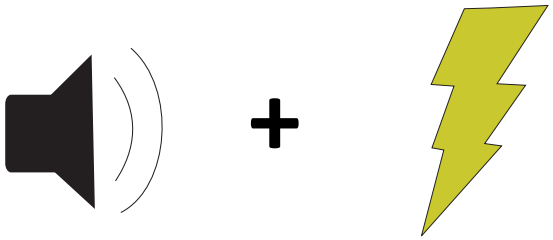




- Water reward
- Foot shock
- Eyelid shock
- Tone
- Not responsive

To Understand the how the BLA Assigns Emotional Valence we Need to Understand the Baseline Representations of a CS and a US

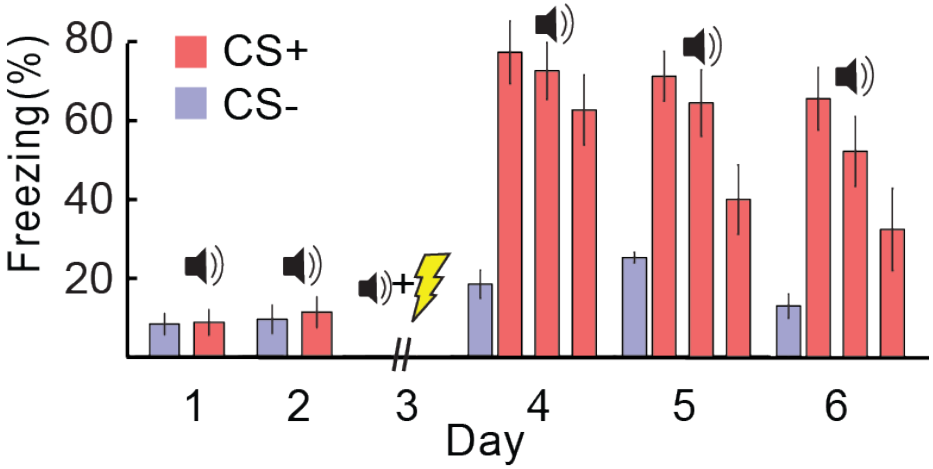
Fear Conditioning



CS US

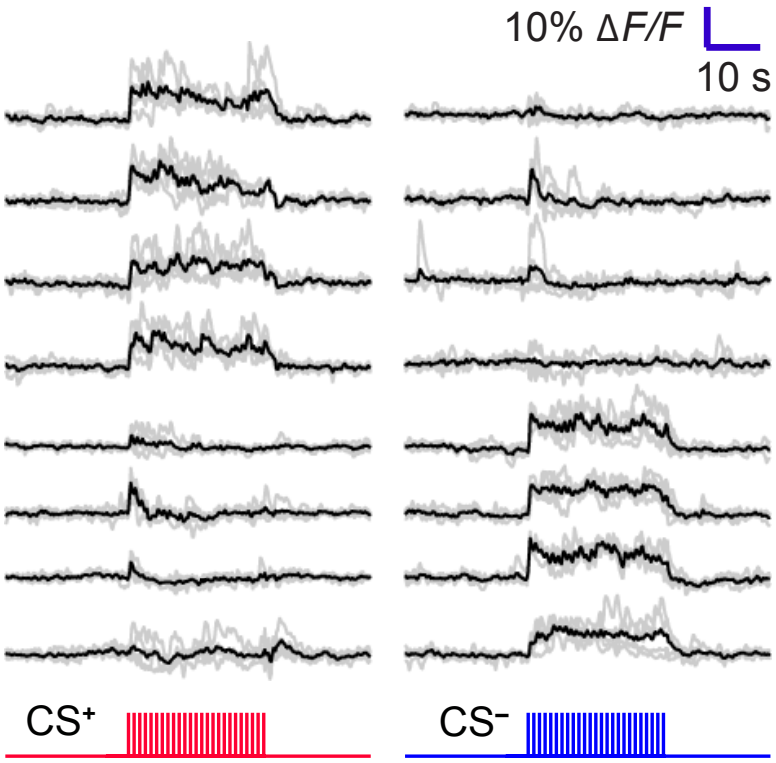
The Conditioning Paradigm

	Habituation		FC	Fear testing		
Day	**1**	**2**	**3**	**4**	**5**	**6**
# CS⁻	5	5	5	4	4	4
# CS⁺	5	5	5+	12	12	12

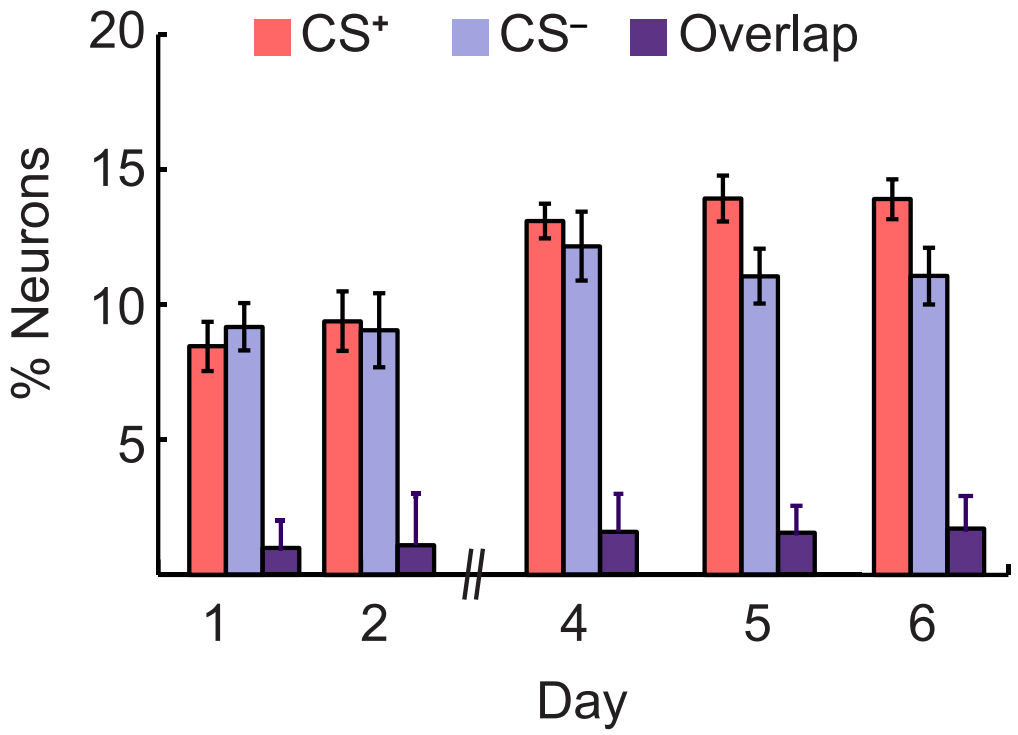


Mice that have not been implanted with the microendoscope show the same fear learning behavior

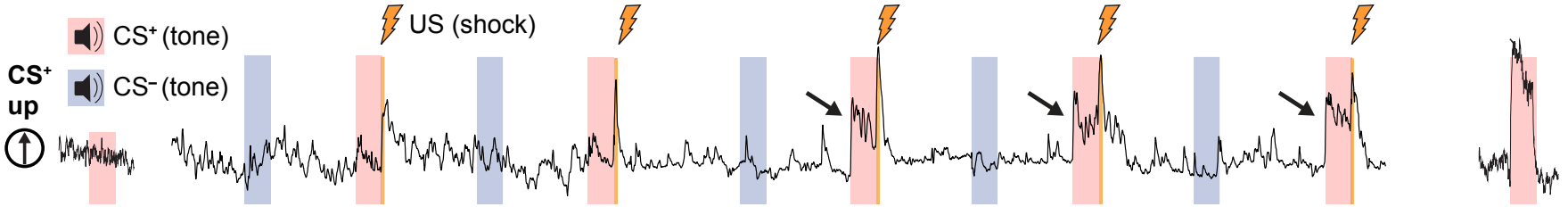
Even Before Fear Learning Neutral Auditory Stimuli Activate Individual BLA Neurons

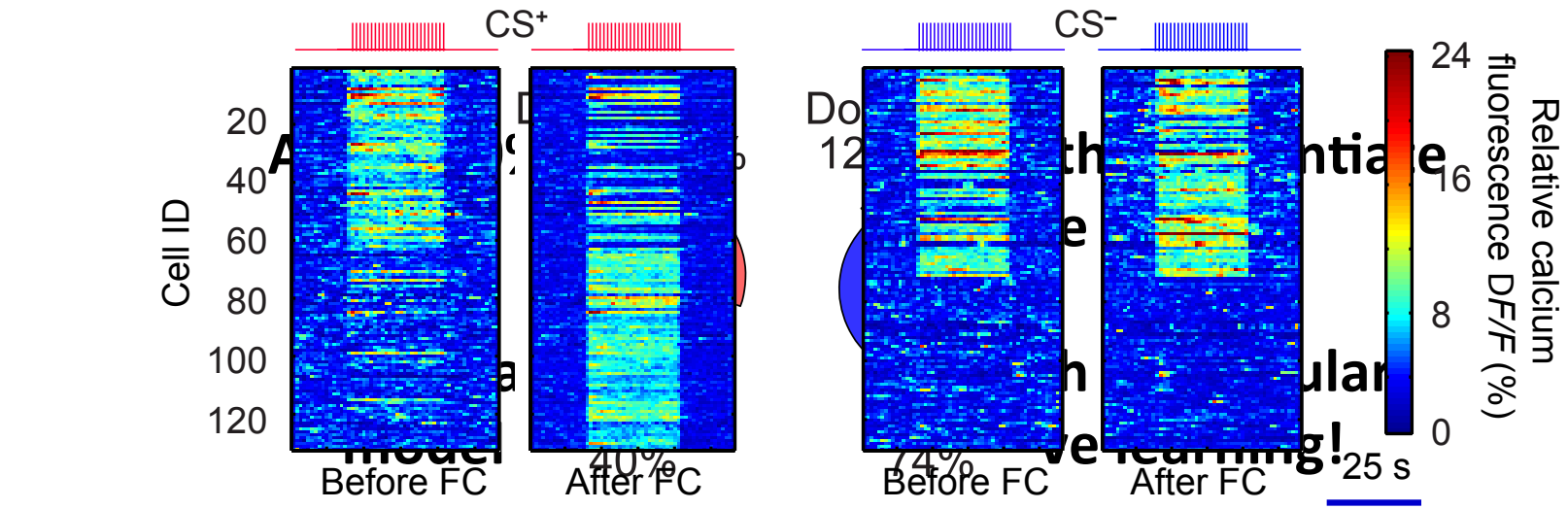


CS Tone Stimuli Activate Sparse, Intermingled Neuronal Subsets in the BLA

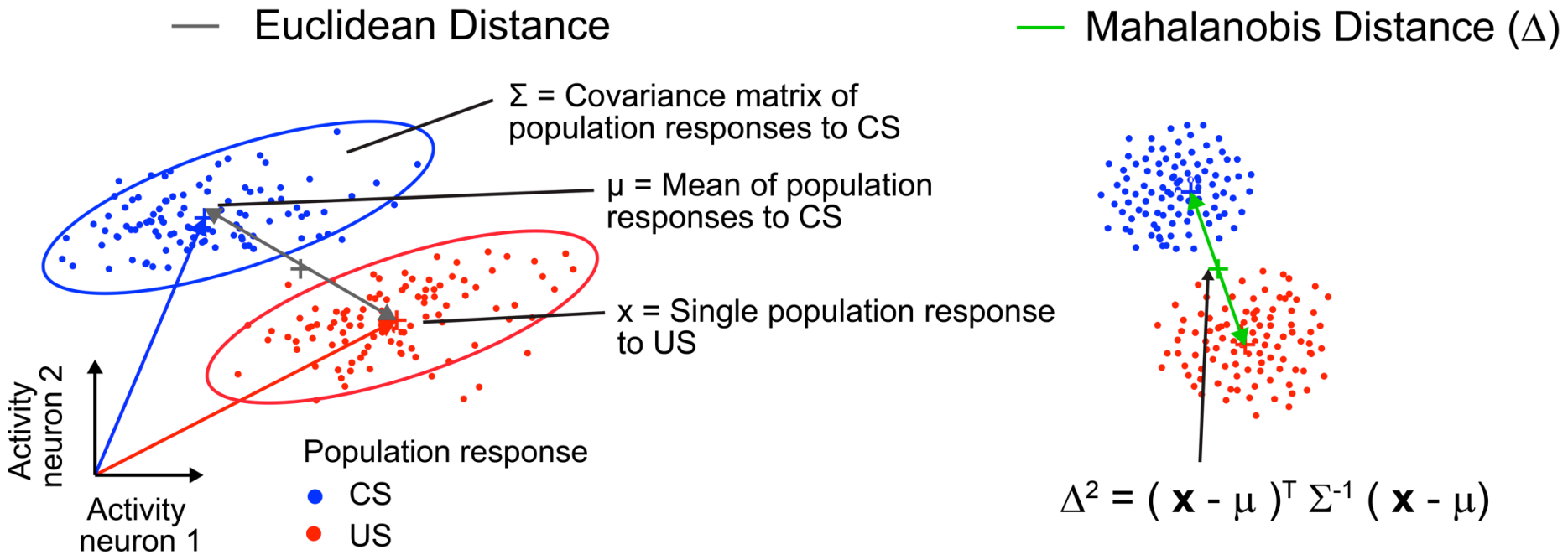


Fear Conditioning Initiates Up- , but also Down-Regulation of Single-Neuron CS Responses in the BLA



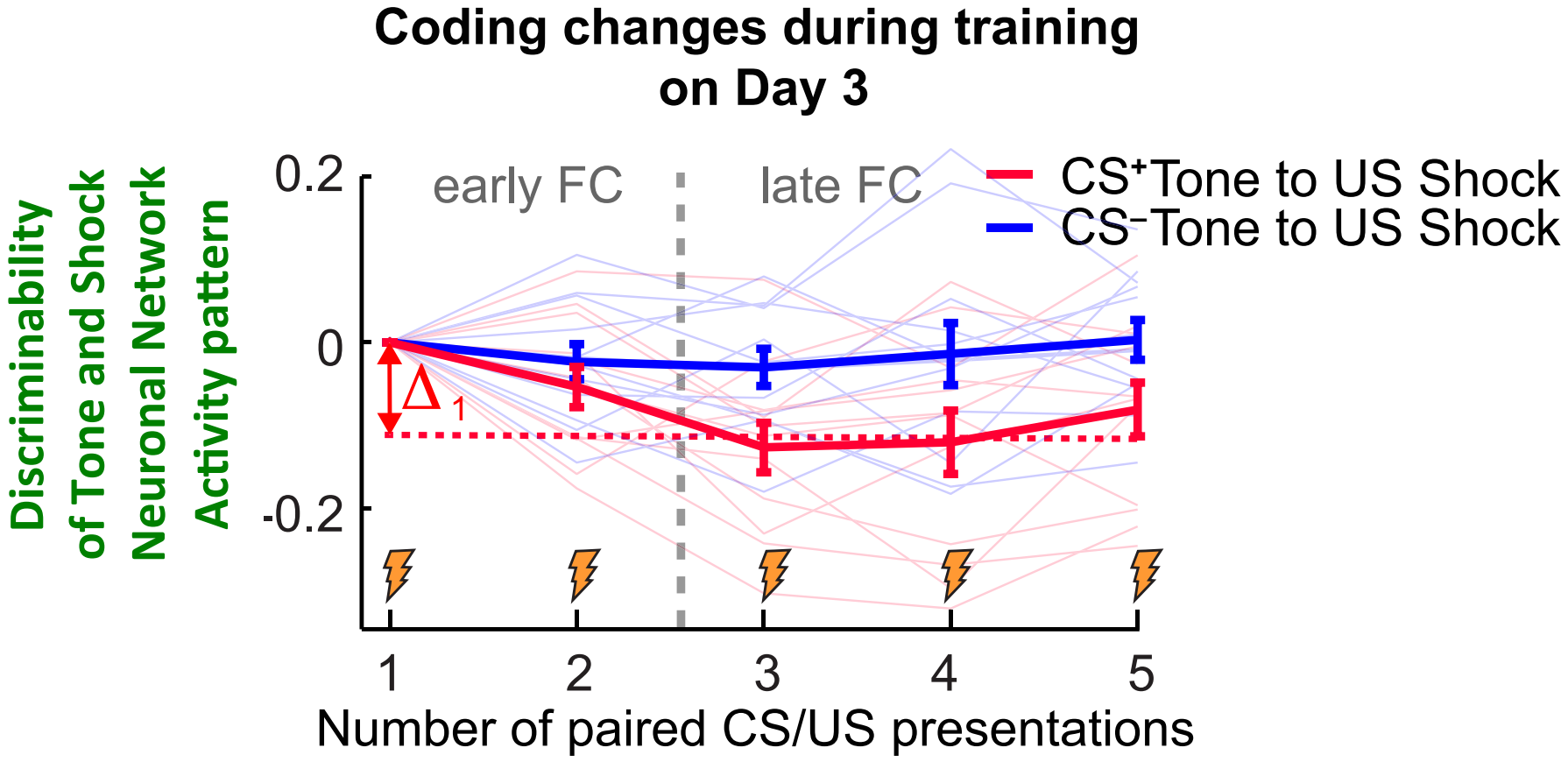


The Mahalanobis Distance Allows us to Track and to Compare Similarities between Neuronal Activity Patterns

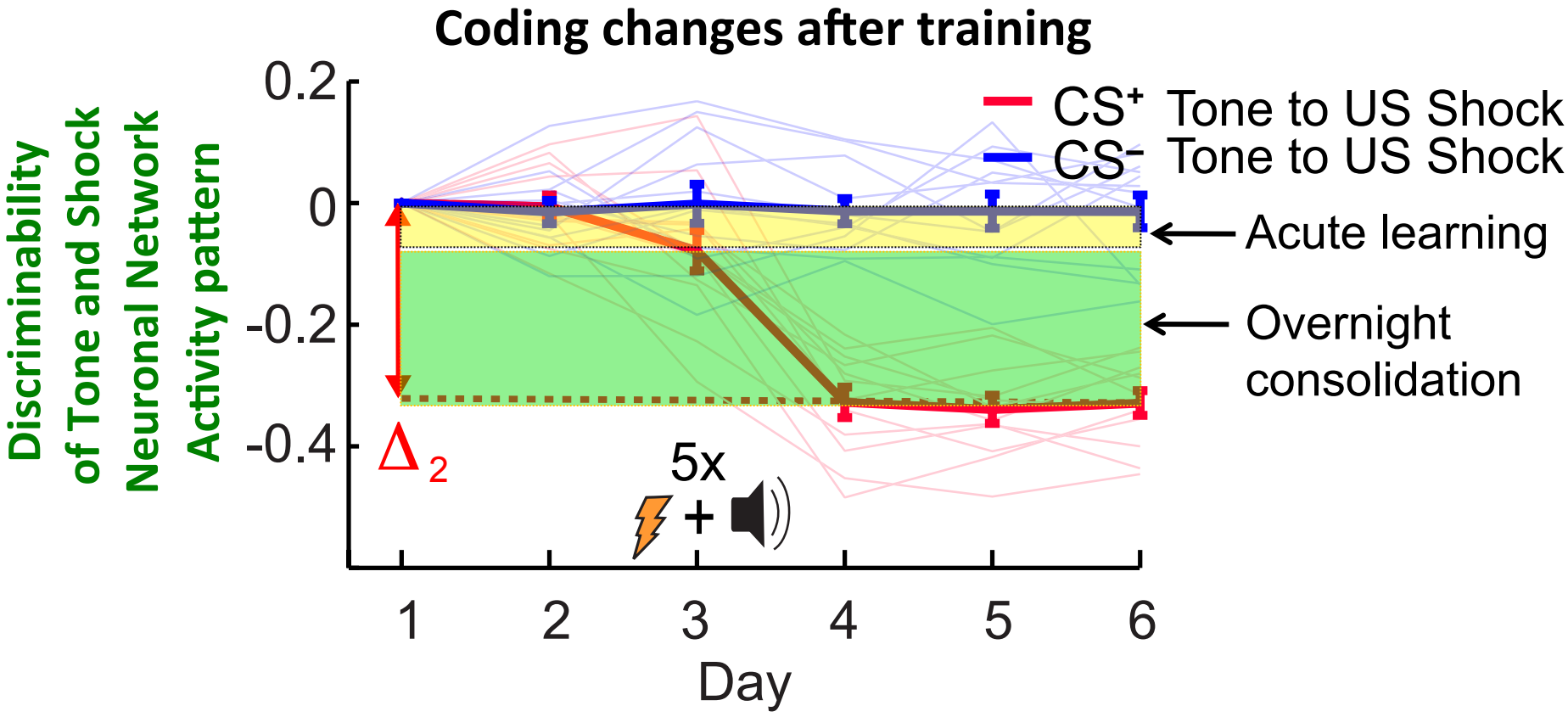


The Mahalanobis distance metric accounts for differences in cells's mean activity rates and multivariate correlations between cells.

Aversive Fear Learning Transforms Tone-evoked Network Responses to Mimic the Shock-driven Response



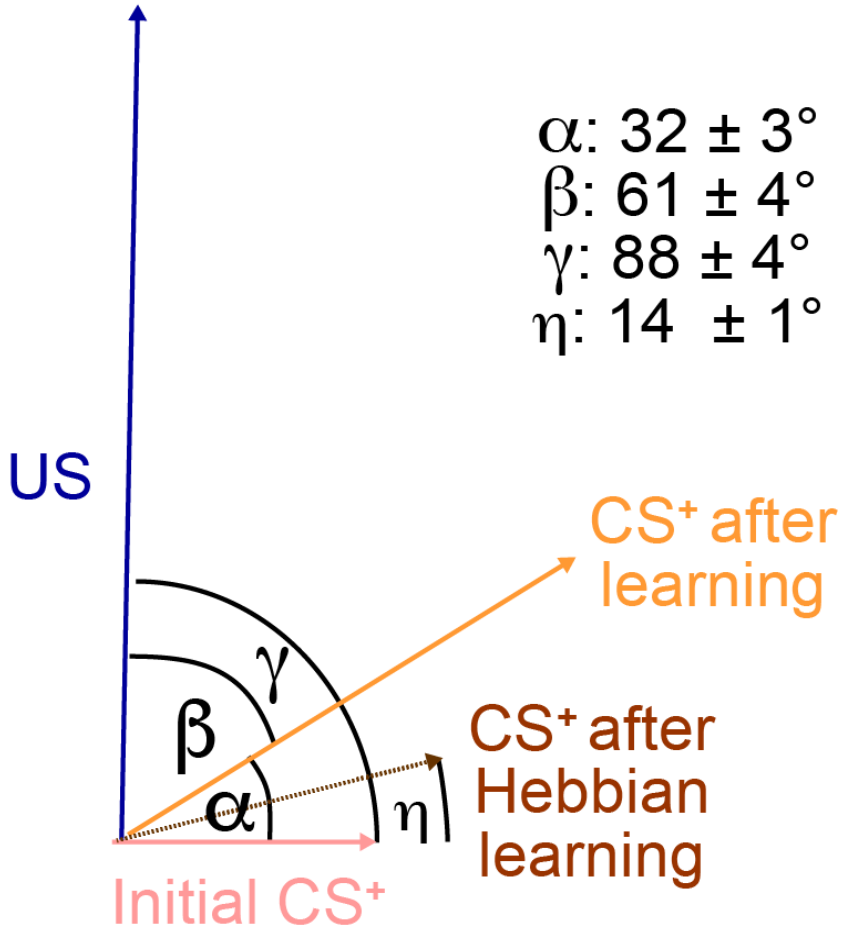
Overnight, the Tone-evoked Network Response Becomes even more Similar to the Shock Response



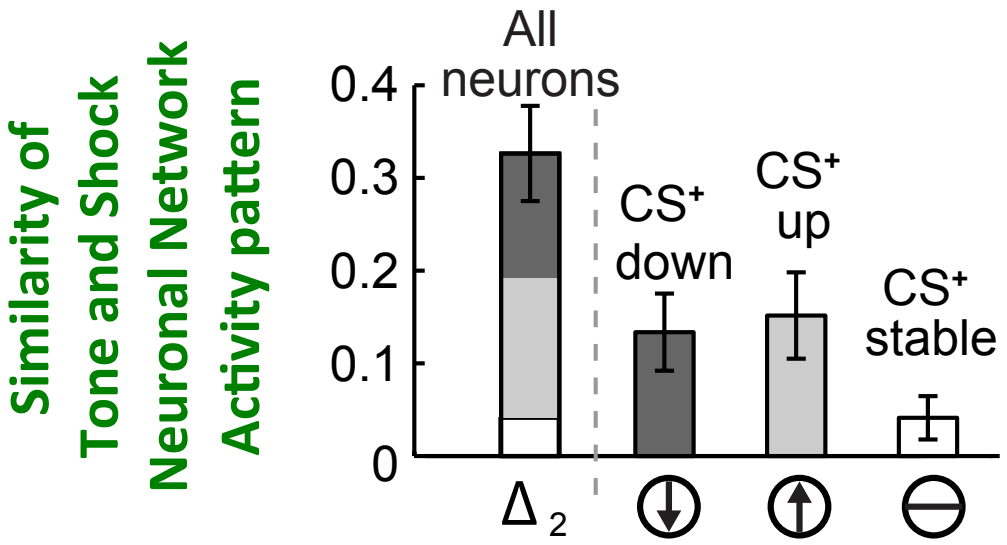
~20% of the network changes occur during learning

~80% of the changes occur overnight

During Conditioning, the US representation Guides the Rotation of the CS Population Vector Towards the US Population Vector



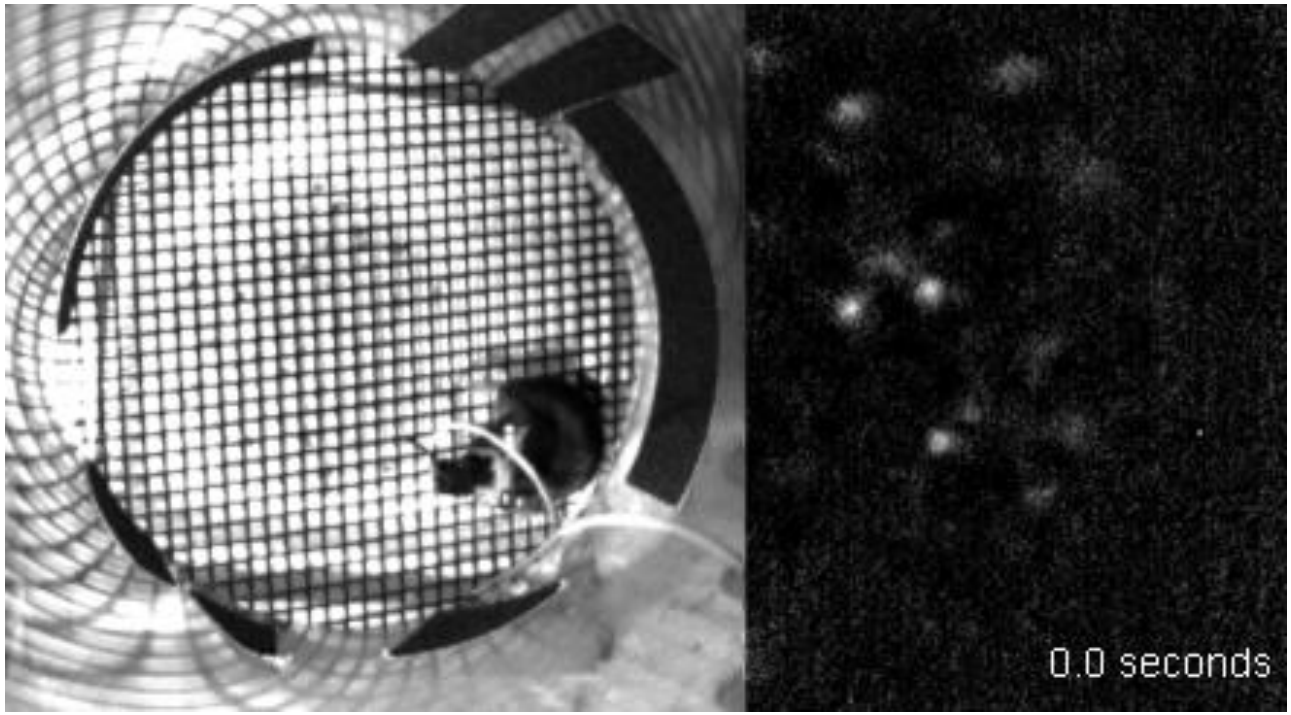
Neurons with Depressed and Potentiated Tone Responses Have Nearly Equal Roles in Transforming the Tone-evoked Network Response.



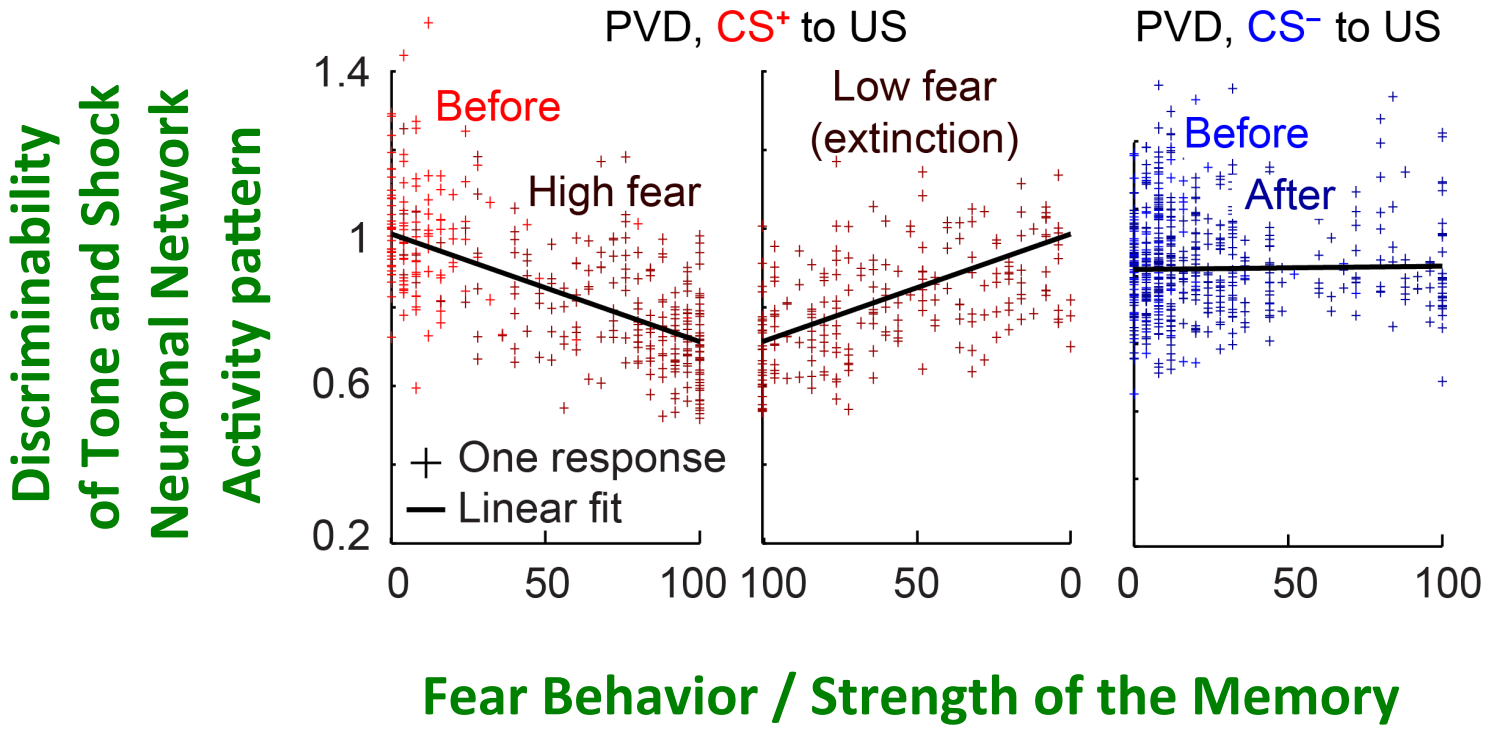
Depression of Tone-evoked neuronal responses play a substantial role in associative fear learning!

Again our data is not consistent with the cellular model of Hebbian associative learning!

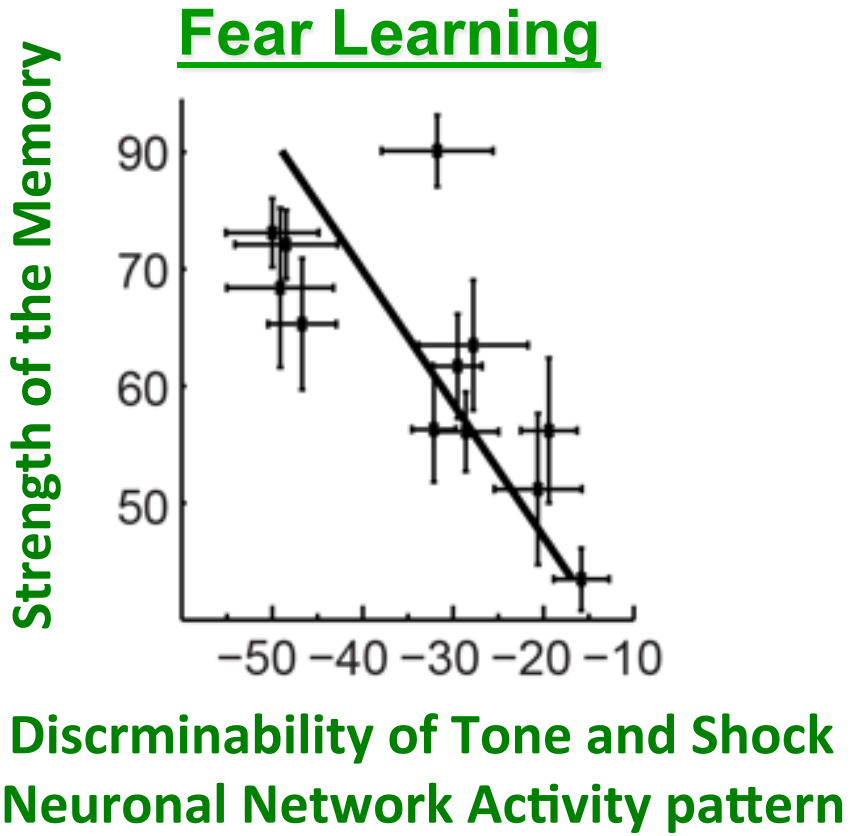
Aversive CS Coding Correlates with Freezing Behavior After Learning



Tone-evoked Network Responses Correlate with Fear Behavior After Learning



The Strength of the Tone-Shock Association Predicts the Overall Level of Learned Fear for Individual Mice



Summary

1. The neural activity patterns for different CS and US stimuli are sparse and largely distinct before learning.

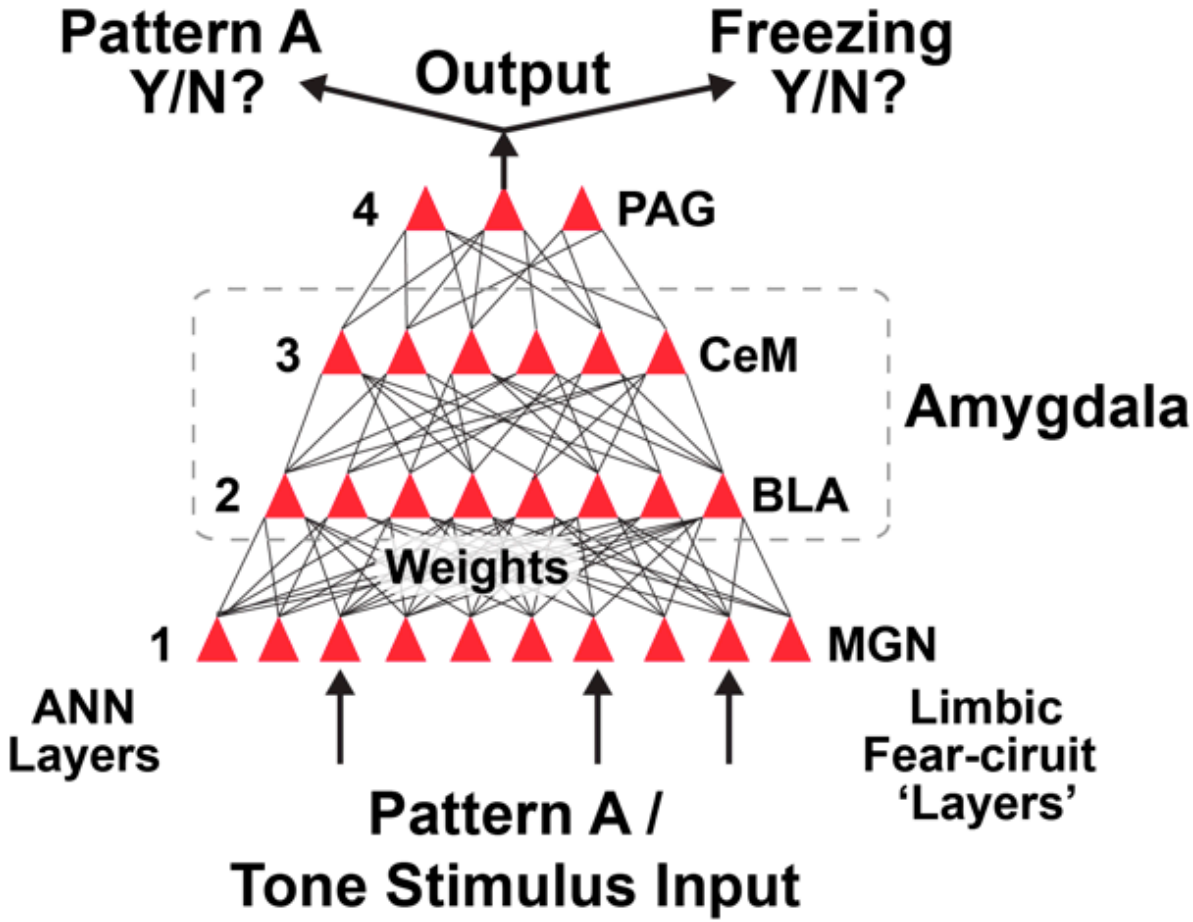
2. Pairing a tone CS and shock US during fear conditioning initiates up-, but also down regulation of CS responses in individual BLA neurons.

3. Pairing a neutral tone (CS) with an aversive shock (US) transforms tone ensemble coding to mimic that of the aversive shock.

4. The majority of this ensemble transformation occurs during post-learning consolidation, not during training.

5. The overall amount of ensemble transformation correlates with the learning performance of the mouse.

The Hierarchical Processing of Fear

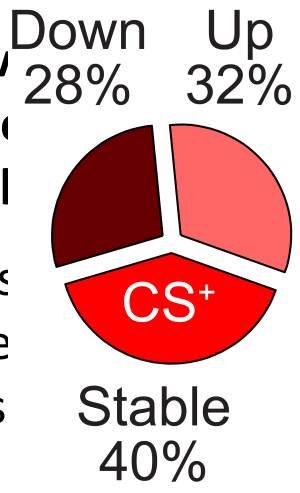


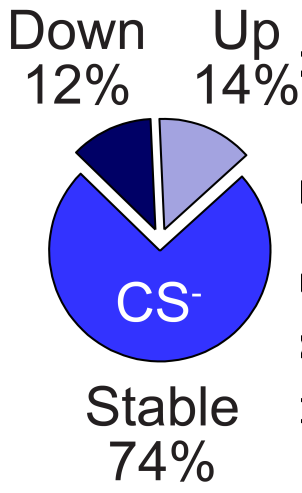
Implications for Systems Neuroscience

1. Our data is inconsistent with the *cellular hypothesis* of Hebbian associative learning, due to multiple contrary results.

2. Instead our data support an ensemble model of associative learning. In this new model the ensemble representation of the US serves as a supervision signal for re-shaping the neural ensemble representation of the CS^{+}.

Implications for Systems Neuroscience Research

3. How is the superv 

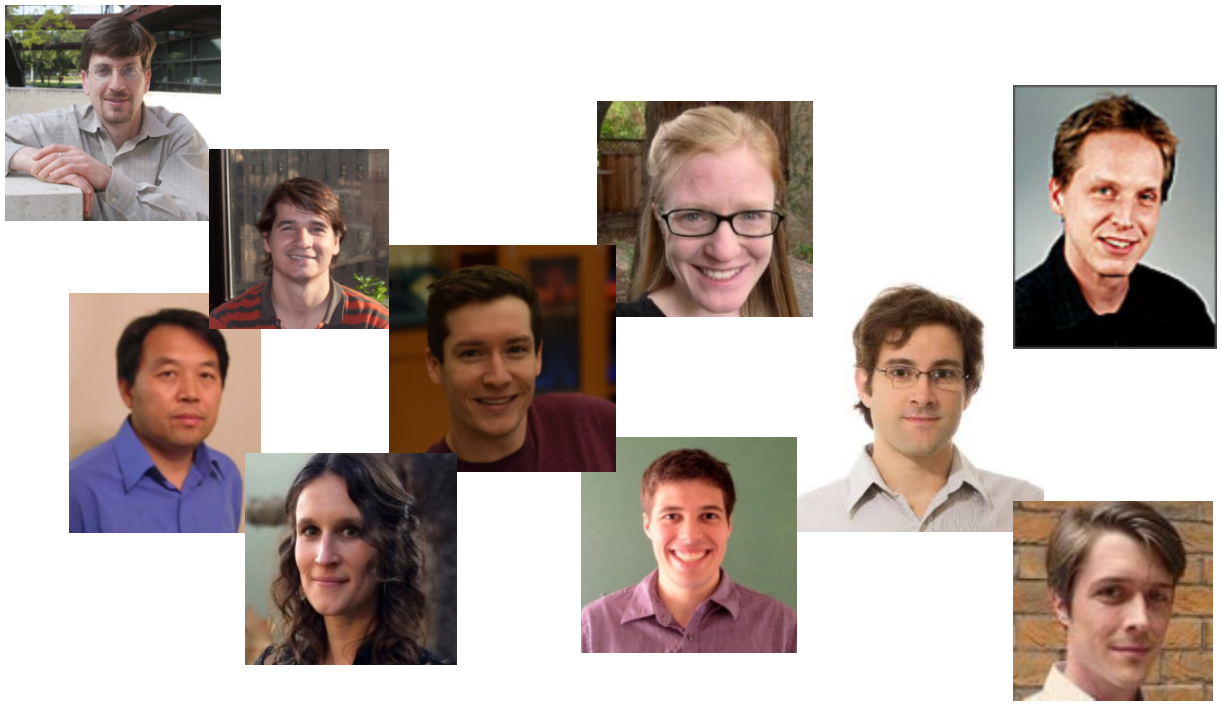


he cellular level? While the simplest model es not fit the data, the next simplest model oes.

(1) Stable CS respons ~~odulator~~, ~~US input~~
(2) Potentiated CS re odulator, US input
(3) Depressed CS res odulator, ~~US input~~

Thanks to:

Mark Schnitzer, Jerome Lecoq, Jones Parker, Pablo Jercog, Thomas Rogerson, Jesse Marshall, Lacey Kitch, Jin-Zhong Li, Maggie Carr-Larkin
(Stanford University)
Jan Grundemann & Andreas Luthi
(FMI Basel)




Thank you for your Attention!