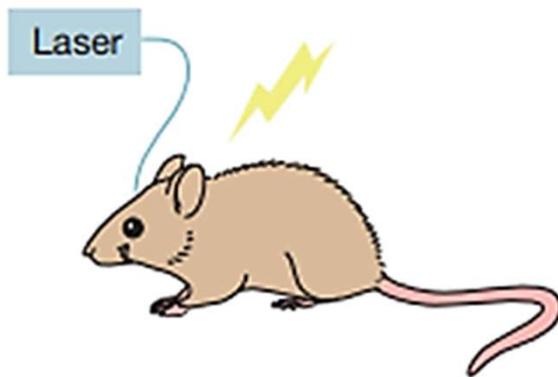
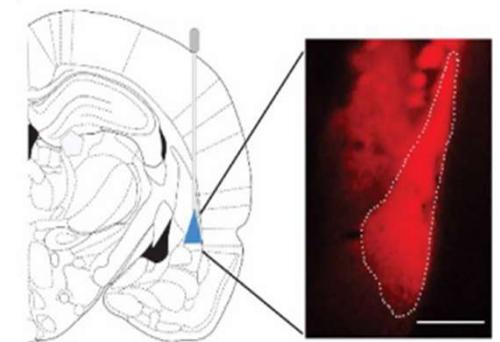


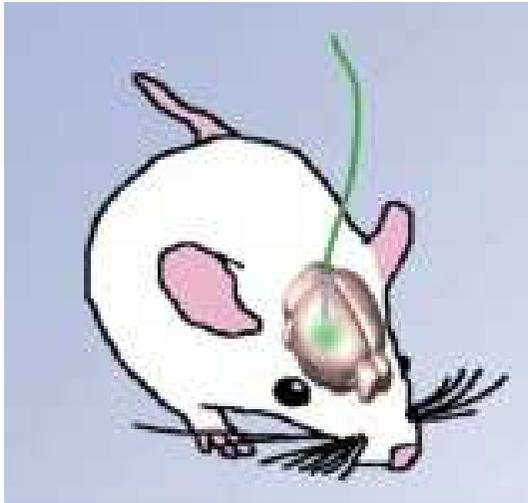
MOLECULAR NEUROPHYSIOLOGY -lesson 5-



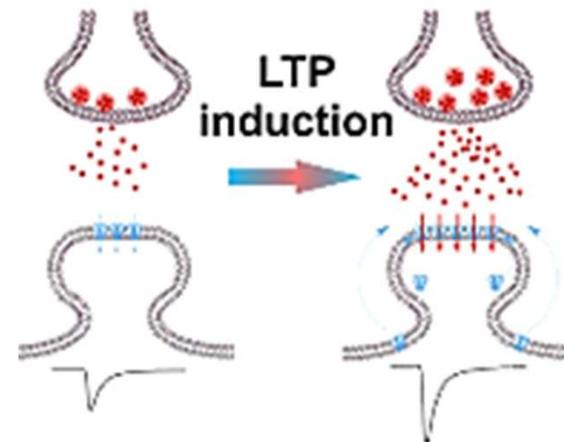
Prof. G.Cellot



To sum up...

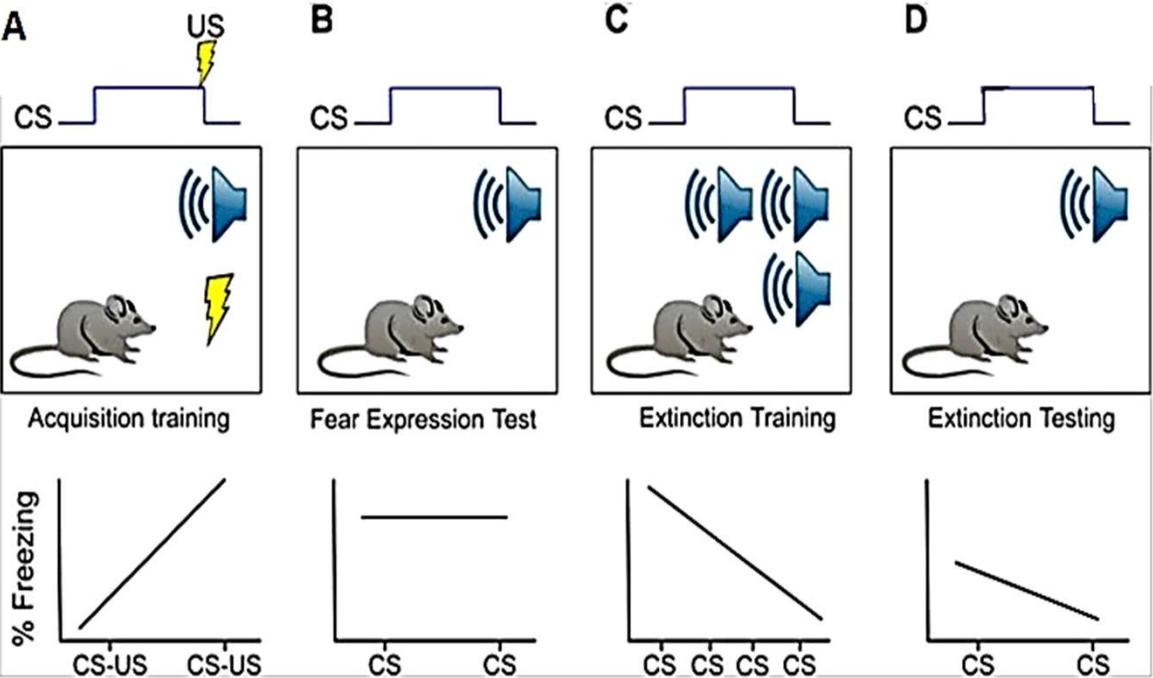


Optogenetic makes possible to (re-) activate the ENGRAM related to a fear memory



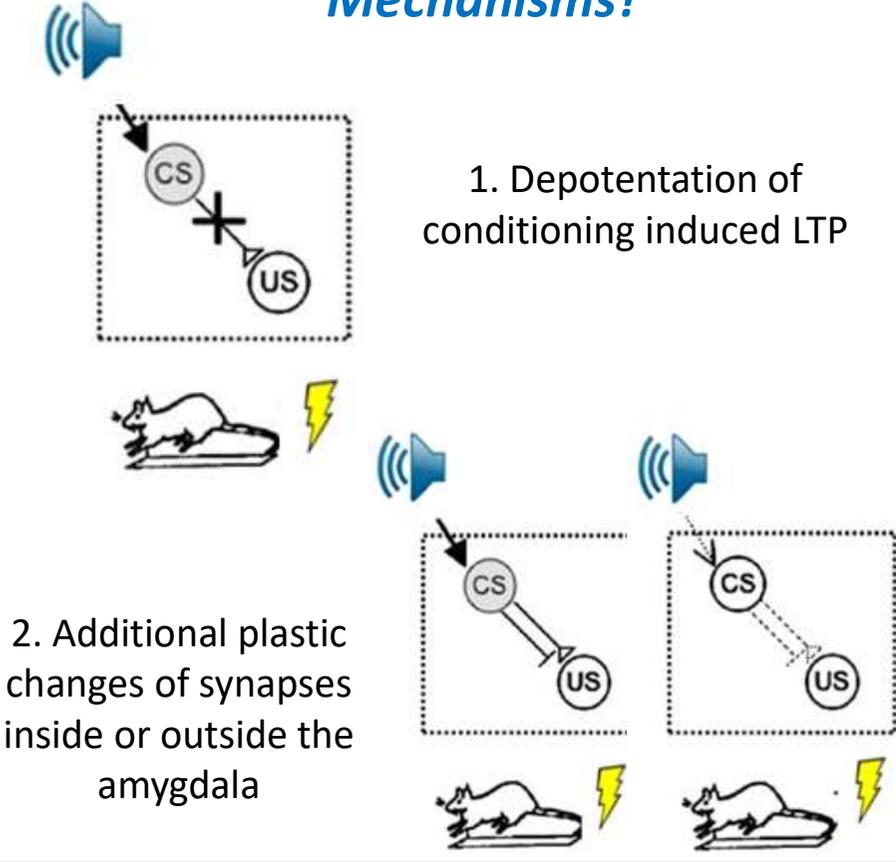
Can memory/learning be erased? An animal model for fear extinction

The repetitive exposure to the CS in the absence of UC trains the animal to extinguish fear conditioning



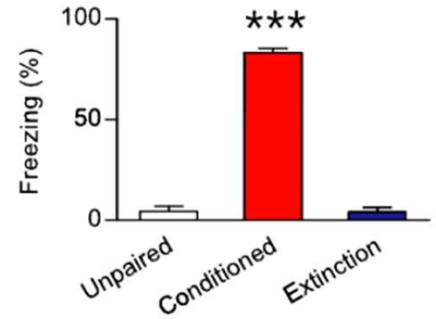
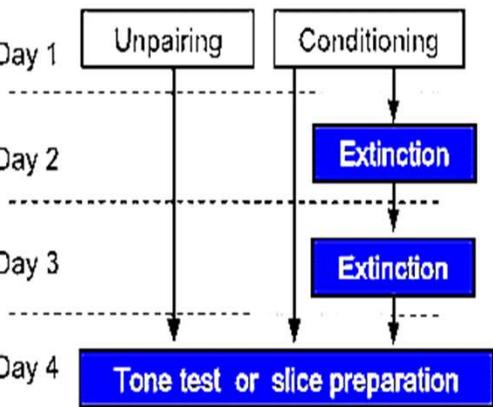
Fear extinction can be thought as a new learning process wherein animals learn that the CS is no longer predictive of the US

Mechanisms?

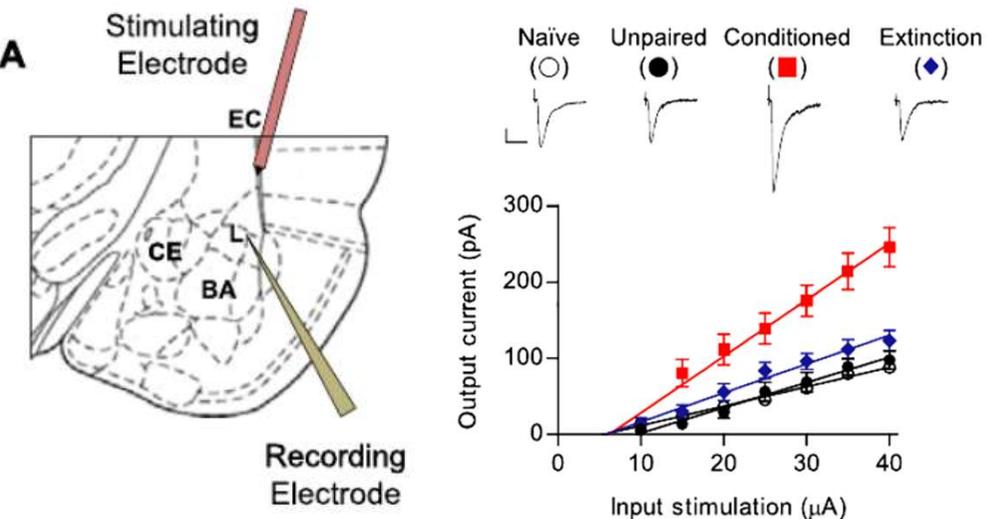


As in some cognitive behavioral therapies against phobias...

Mechanisms underlying fear extinction: DEPOTENTIATION of the conditioning induced plastic changes?

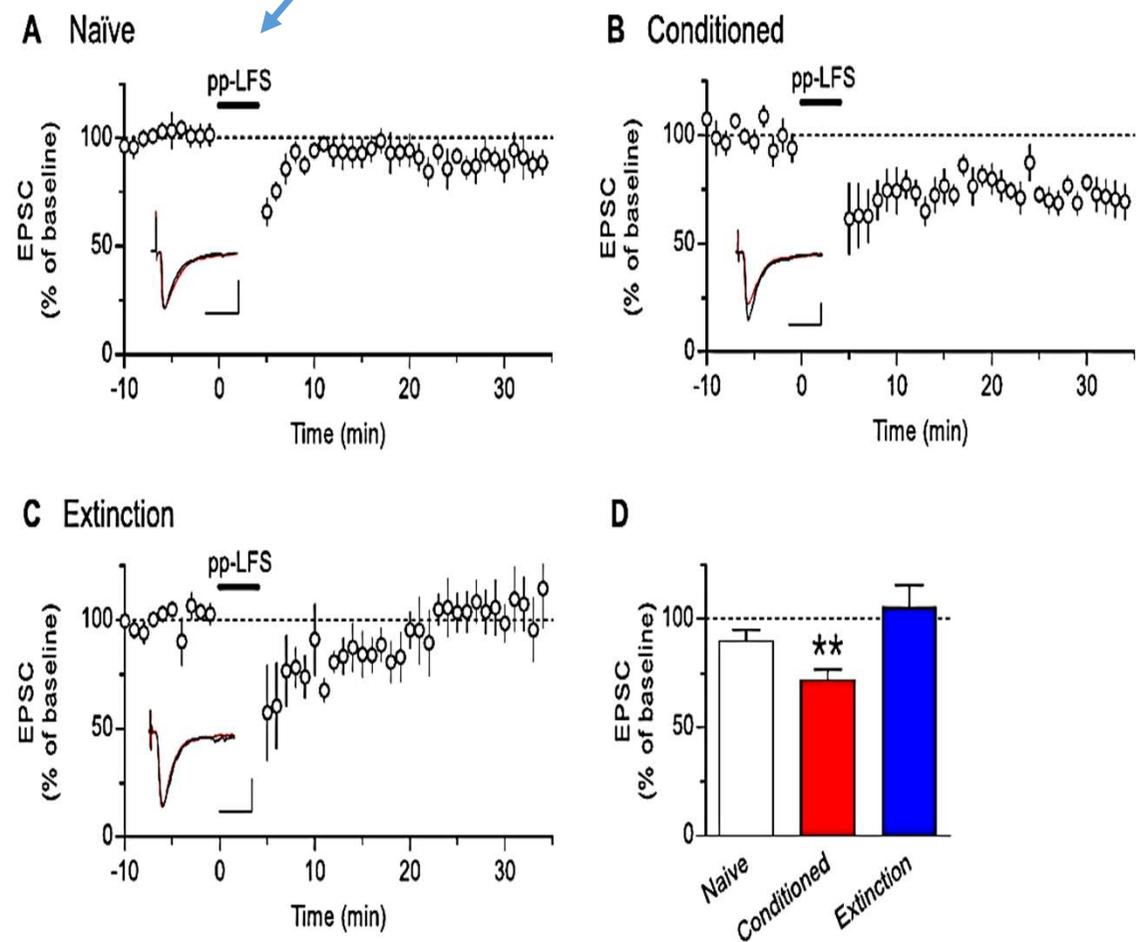


Stimulation of cortical inputs



Paired-pulse low-frequency stimulation

2 stimuli (50-ms inter-stimulus interval) at 1 Hz for 5 min

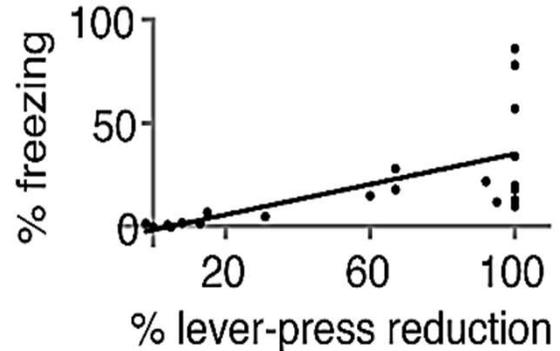
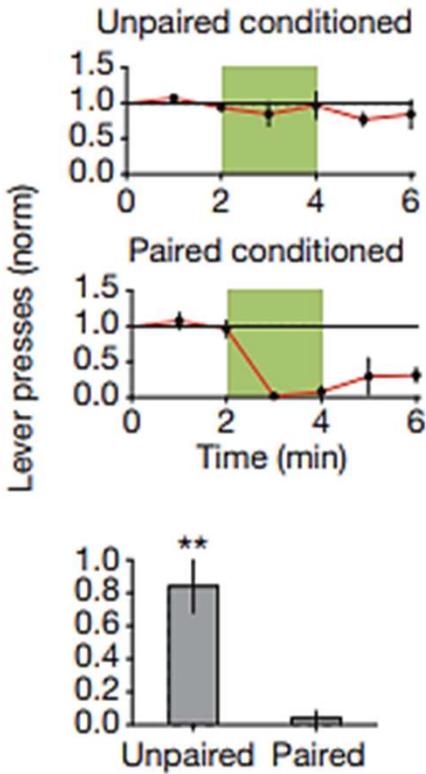


Hong et al., European Journal of Neuroscience, 2009, doi:10.1111/j.1460-9568.2009.07004.x

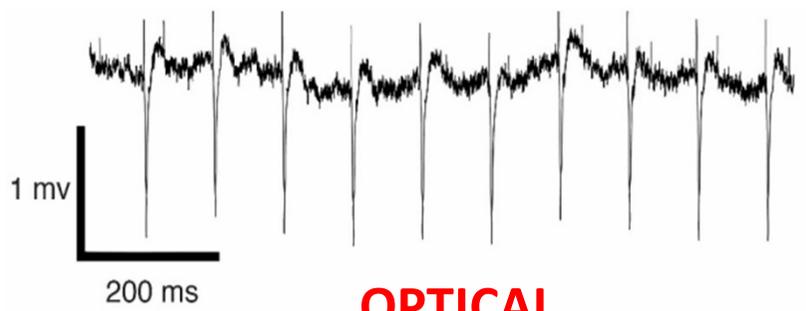
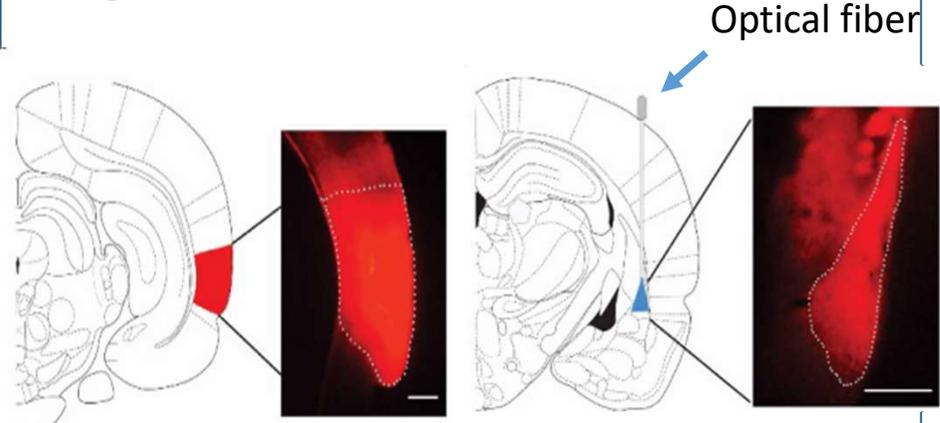
Optogenetic manipulation of circuit involved in fear extinction

1. Pre-training:

Rats were trained to associate lever press for a reward



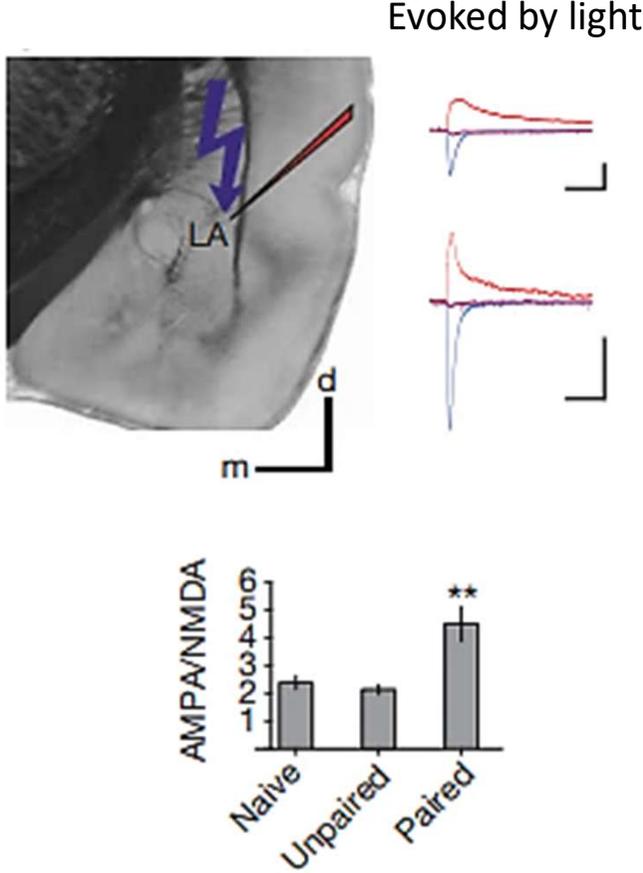
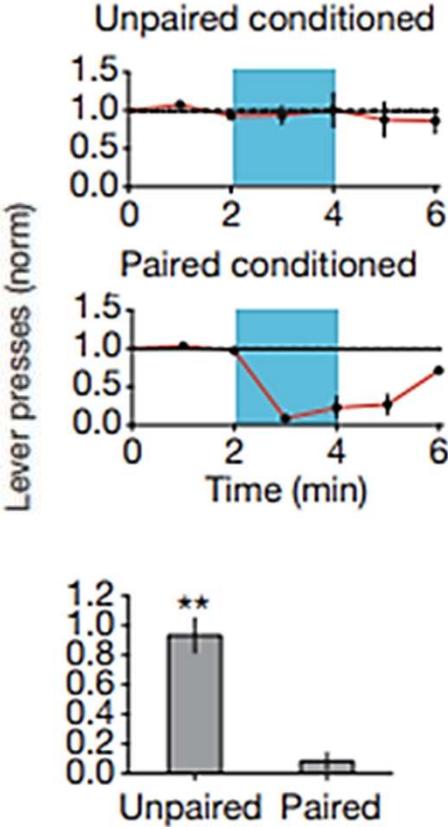
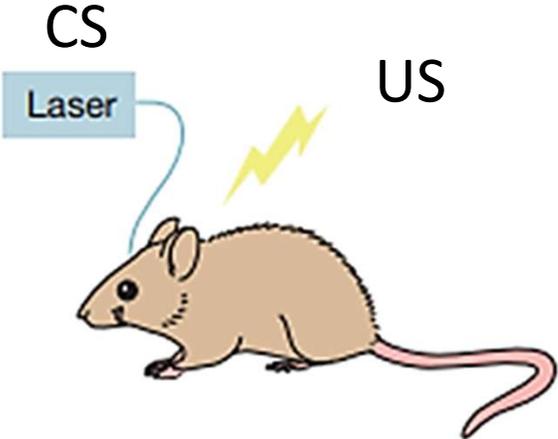
2. Injection in auditory cortex of an adeno associated vector carrying light-activated channel ChR2



OPTICAL STIMULATION=CS

Optogenetic manipulation of circuit involved in fear extinction

3. Pairing optogenetic stimulation of CS with footshock (US) results in fear learning

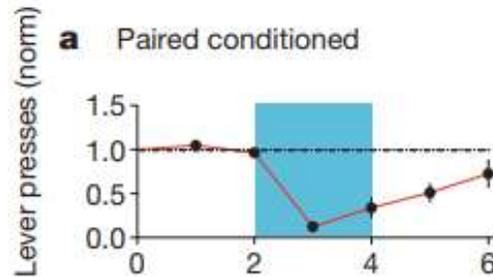


And in LTP in the lateral amygdala

Can memories be inactivated through optogenetic manipulation?

Optical LTD: 900 pulses of light (@1 Hz)

Optical LTP: 5 trains of light (each train 100 pulses, @ 100 Hz; 3 min interval)



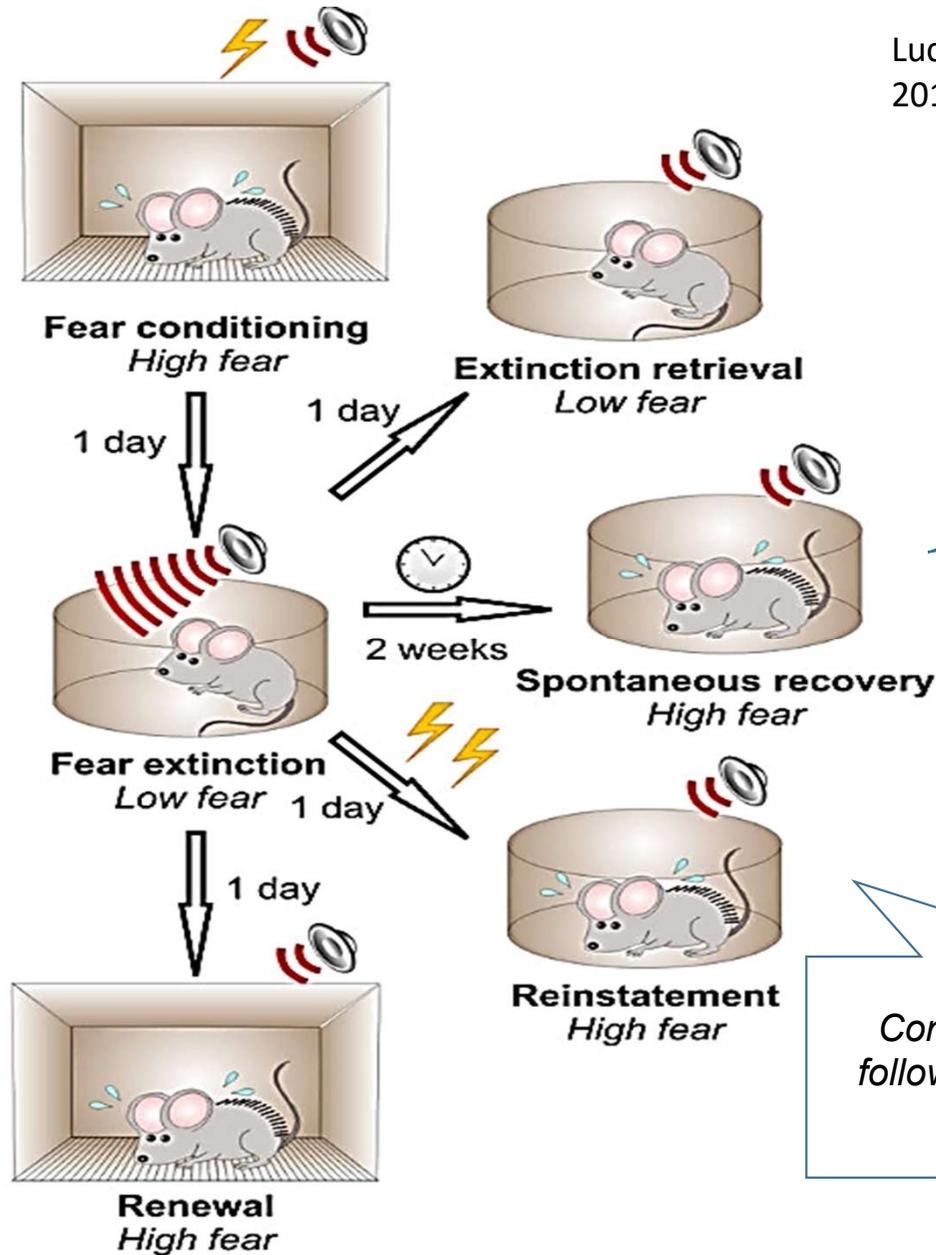
11/18

Synapses are capable of undergoing multiple rounds of bidirectional plasticity, correlating with fear acquisition/extinction

Depotentiation of conditioning induced plastic changes cannot be the only mechanism for fear extinction



Additional plastic changes inside and outside the amygdala might be involved



Extinguished fear can return at extended time intervals following extinction training in a process of spontaneous recovery

Conditioned fear can be reinstated following exposure to the unsignalled US.

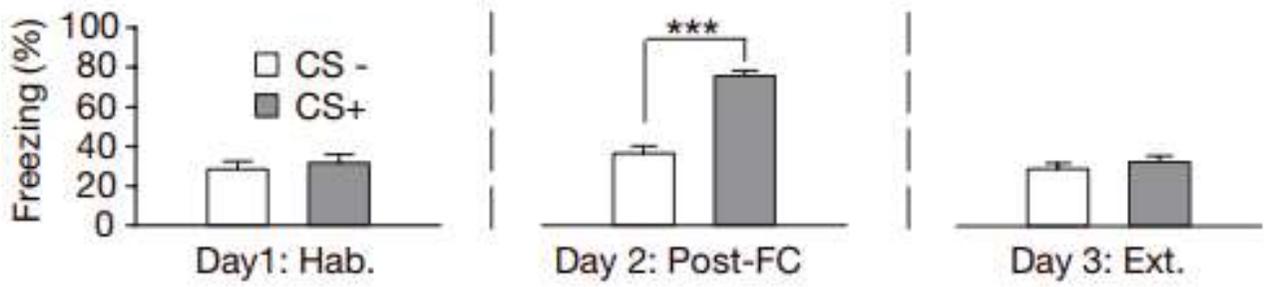
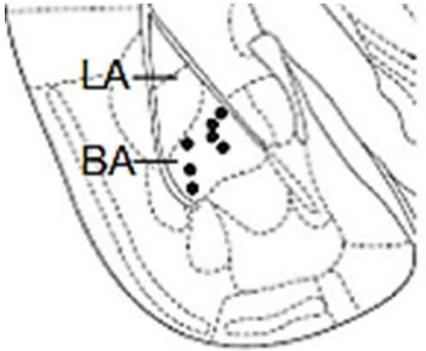
Due to context-specificity of fear extinction, the conditioned fear response can reappear when the context is changed

Neuronal substrates for fear extinction

- Fear extinction can be considered as a new form of learning in which extinction networks inhibit fear networks.
- Overlaps of brain areas involved in fear acquisition and extinction: **BASOLATERAL COMPLEX**

FC=fear conditioning with association of electrical foot shock with acoustic tone

		Day 1: Hab.	Day 1: FC	Day 2: Post-FC	Day 3: Ext.
Unpaired (CTRL)	CS -	4 CS	5 CS	CS	4 CS
	CS +	4 CS	5 CS-US	CS	12 CS
		Conditioning context		Extinction context	



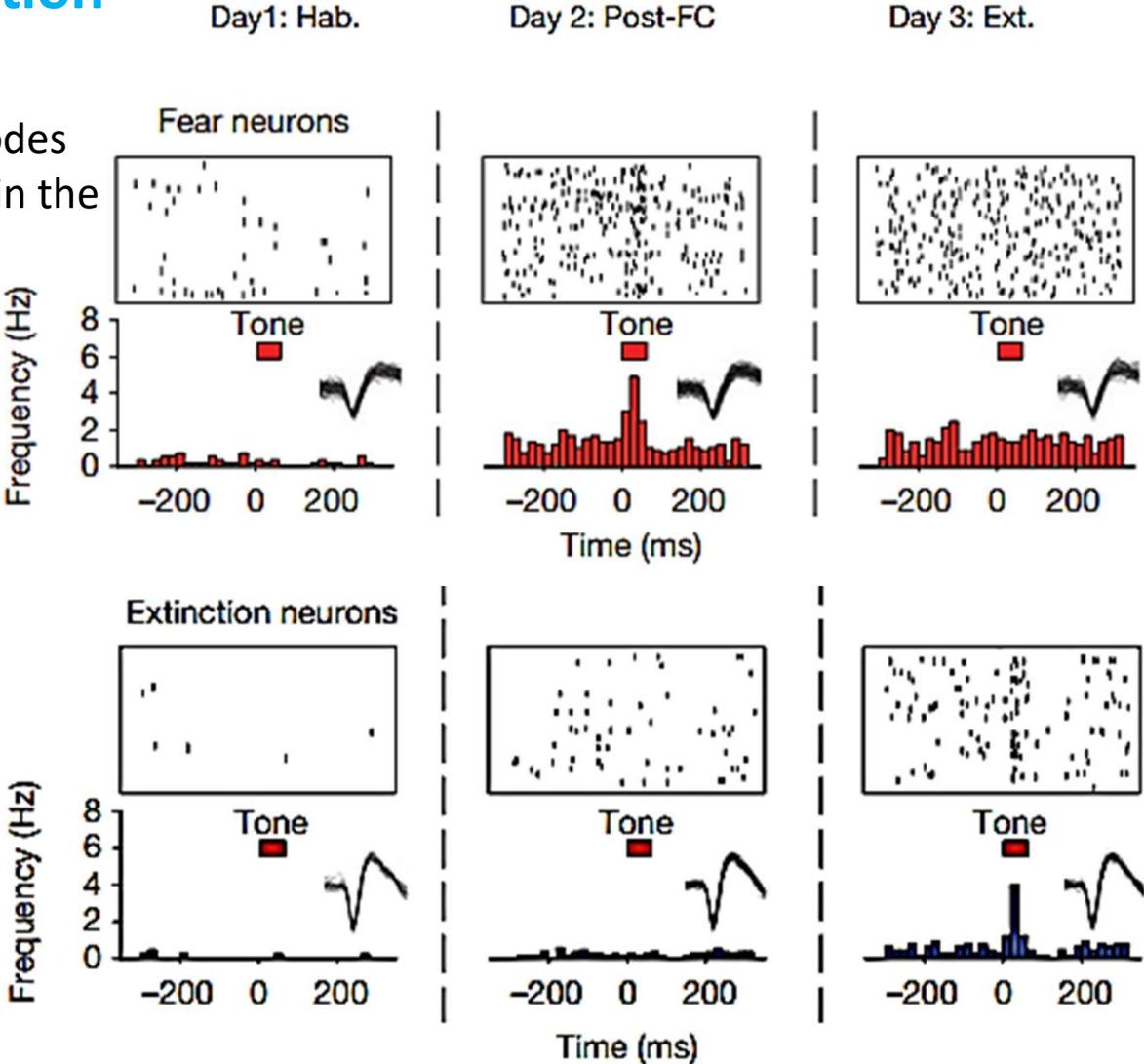
Neuronal substrates for fear extinction



Chronic recording electrodes (18 channels) implanted in the **BASOLATERAL COMPLEX**

Fear neurons are potentiated and depotentiated during fear conditioning and extinction, respectively.

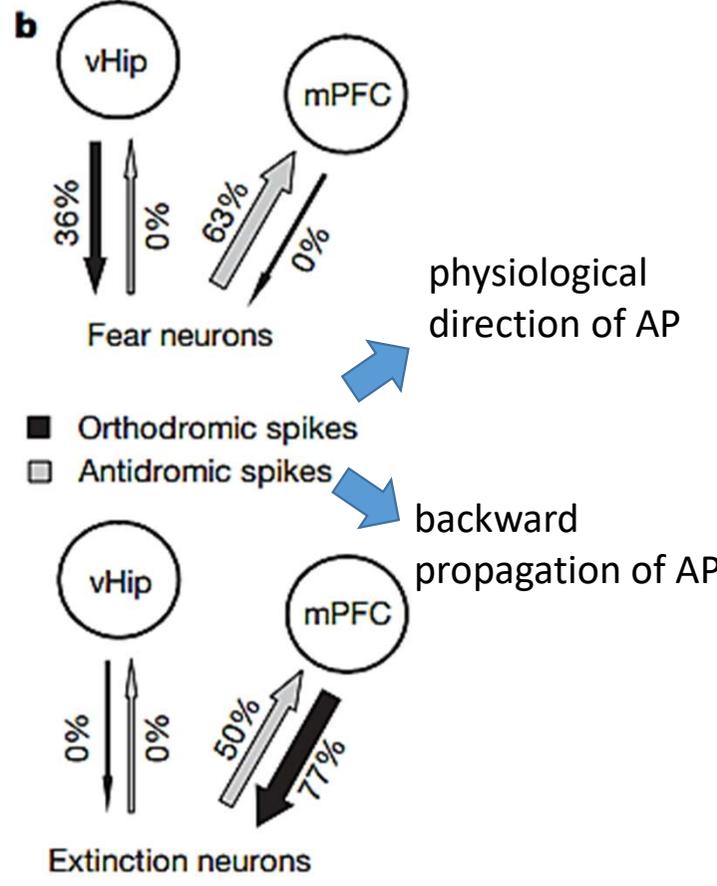
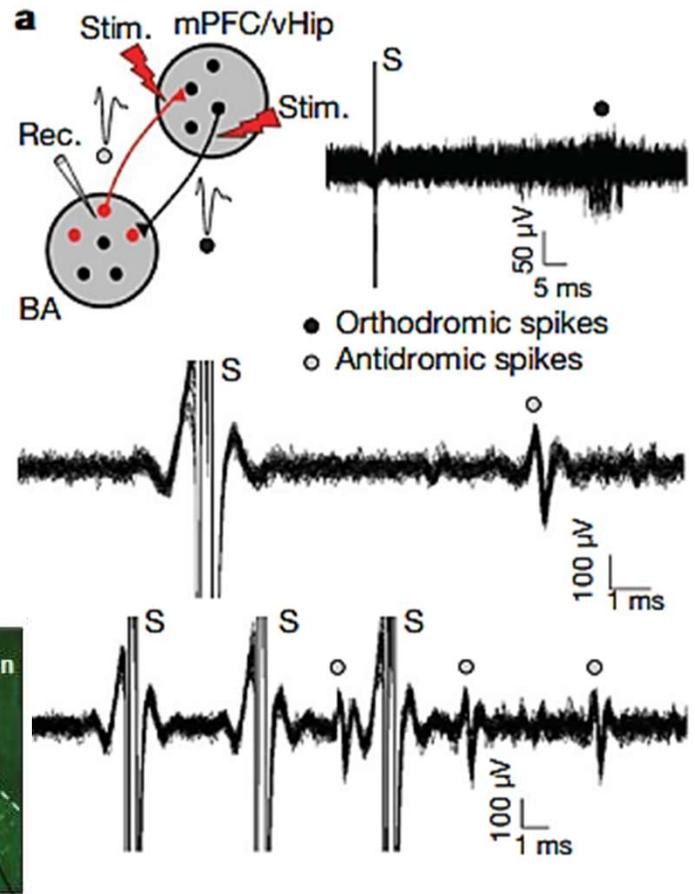
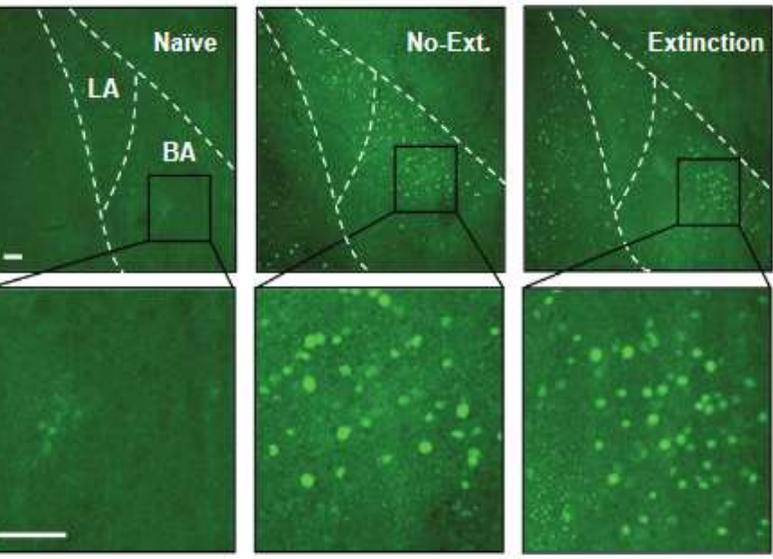
Another group of cells in the BA, **extinction neurons**, are selectively activated during extinction procedure.



Neuronal substrates for fear extinction

Although c-fos expression studies show that **fear and extinction neurons** are not segregated in different regions of BA, they form part of discrete neuronal circuits.

c-fos expression



Orthodromic spikes vs **Antidromic spikes**
 high failure rates vs ability to follow 200 Hz frequency stimulation
 variable latency (>0.3 ms jitter) vs stable latency (<0.3 ms jitter)

Herry et al, 2008, Nature, doi:10.1038/nature07166

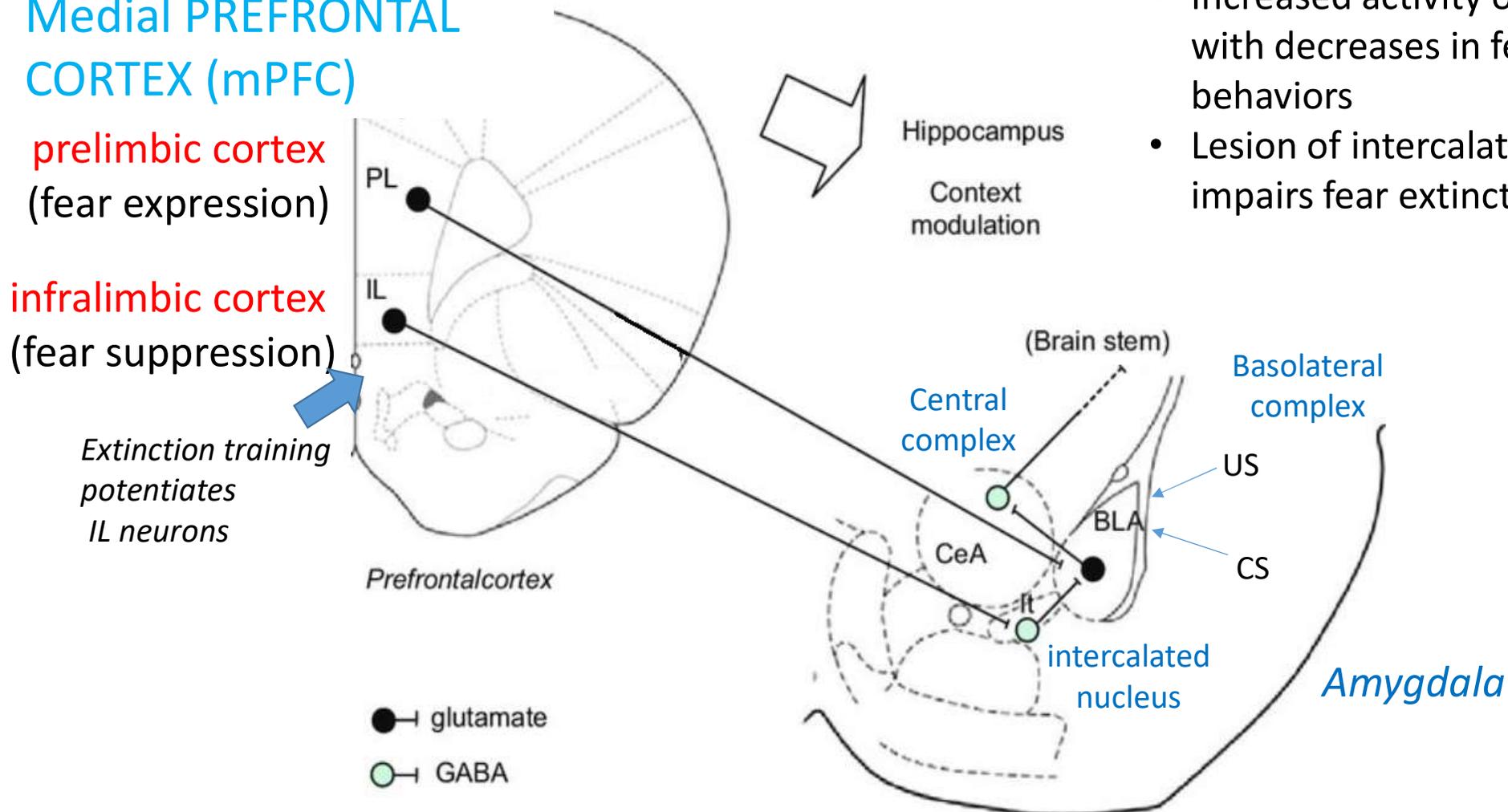
The medial PreFrontal Cortex (mPFC) exerts a top-down control of limbic regions

Medial PREFRONTAL CORTEX (mPFC)

prelimbic cortex (fear expression)

infralimbic cortex (fear suppression)

Extinction training potentiates IL neurons



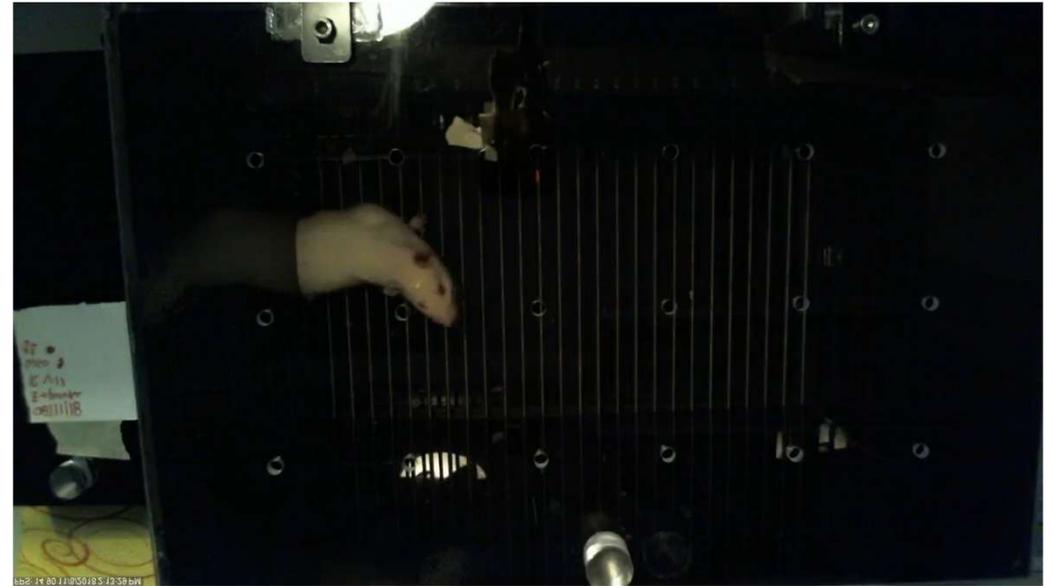
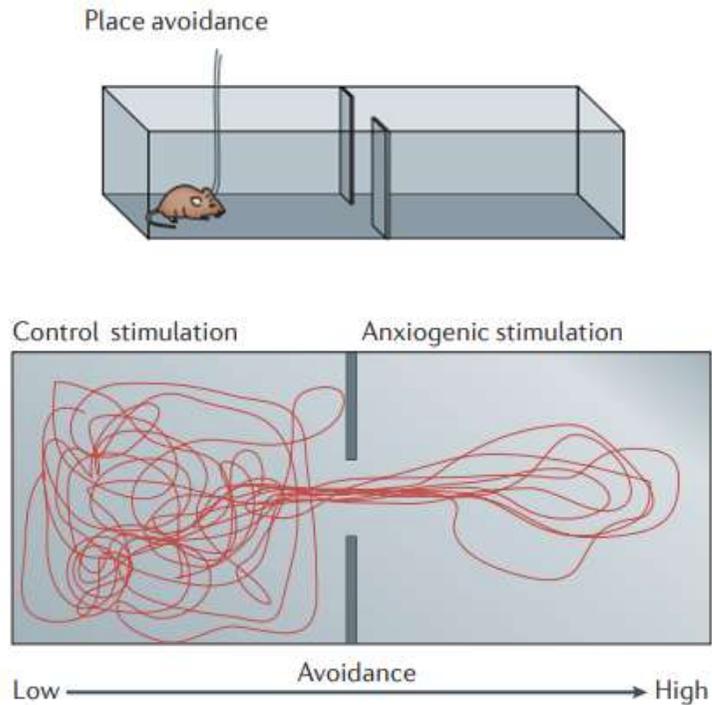
- Increased activity of IL correlates with decreases in fear related behaviors
- Lesion of intercalated nucleus impairs fear extinction

Anxiety related behaviors

FEAR: response to discrete and acutely threatening stimuli

ANXIETY: response to vague, potential threats

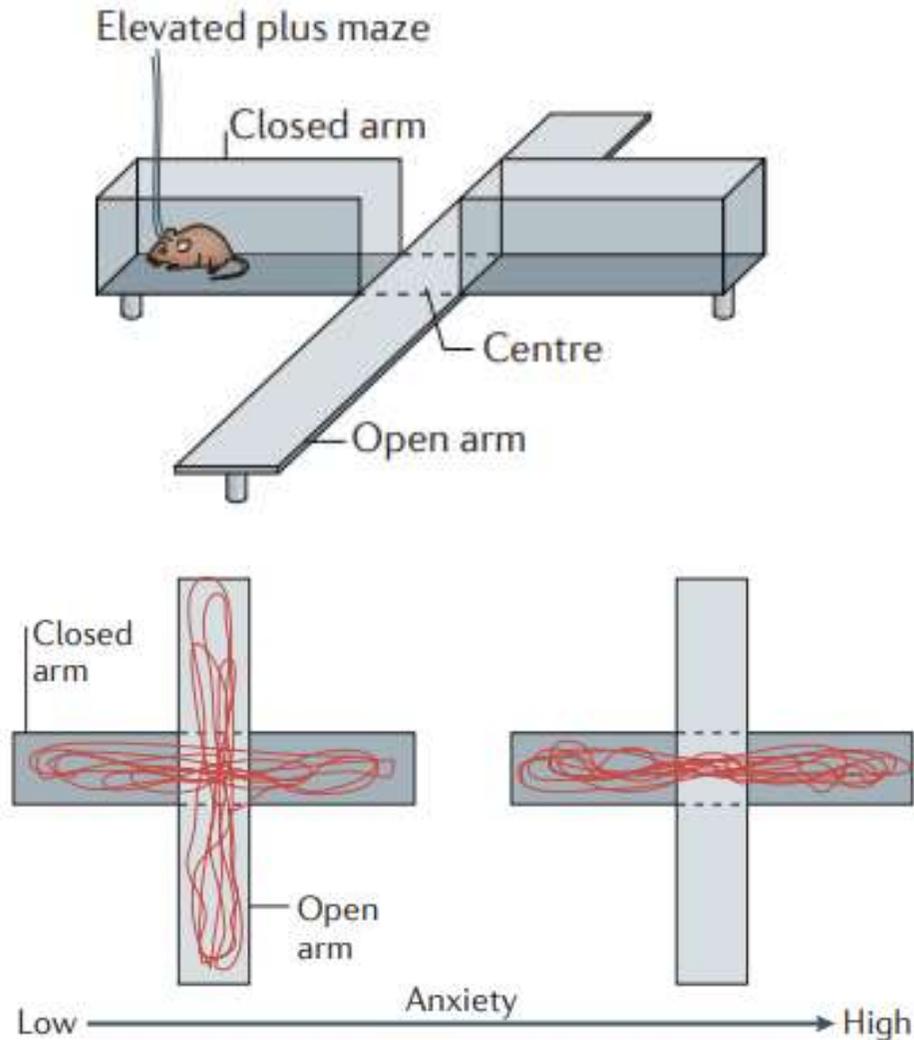
Almost
overlapping
neuronal circuits



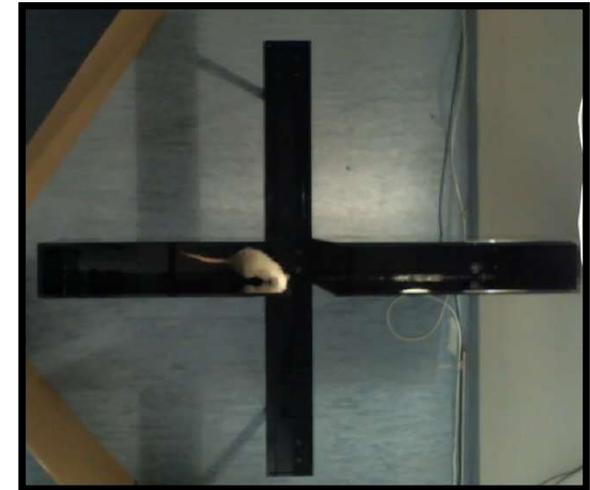
Tovote et al, 2015, Nat Neurosci, 16(6):317-31.
doi: 10.1038/nrn3945.

Courtesy of AF Biagioni, Lab. Ballerini

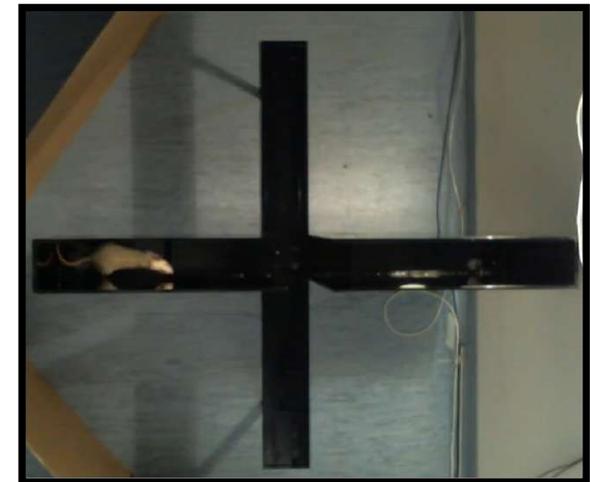
Anxiety related behaviors



No anxious animal



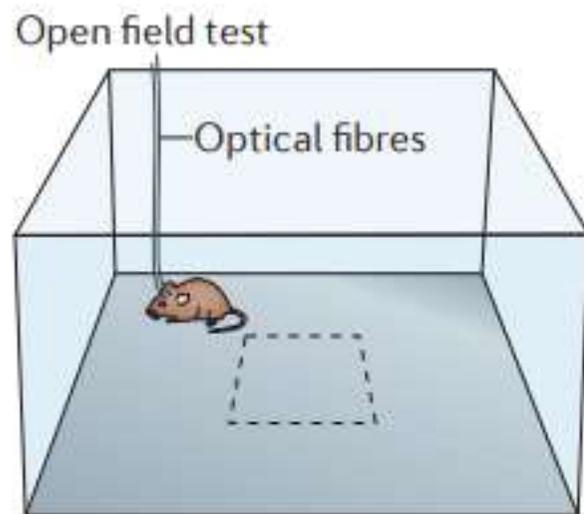
Anxious animal



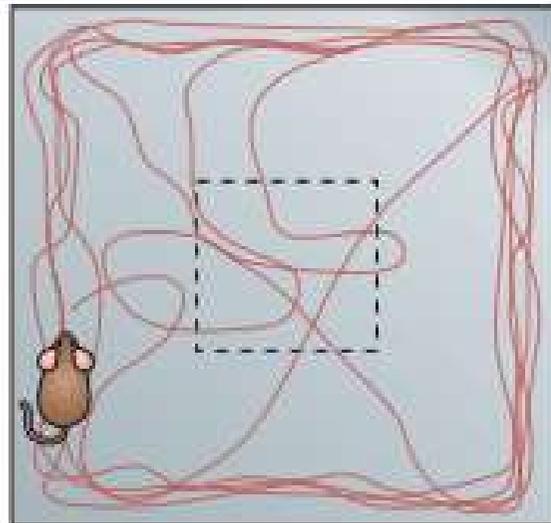
Tovote et al, 2015, Nat Neurosci, 16(6):317-31.
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Courtesy of AF Biagioni, Lab. Ballerini

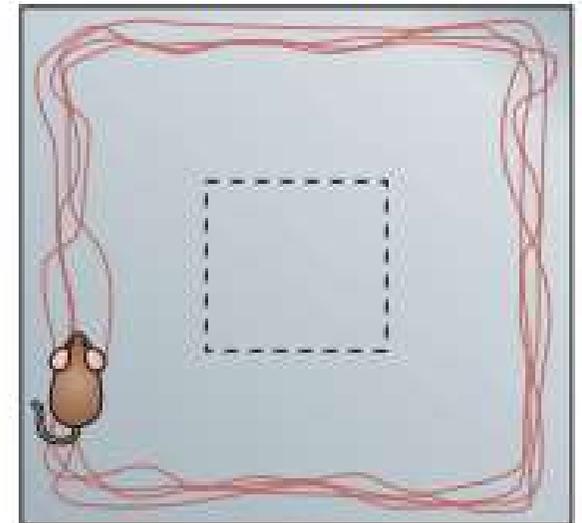
Anxiety related behaviors



Control stimulation



Anxiogenic stimulation



Conclusions

- ✓ Associative learning can be erased
 - Depotentialization of amygdalar fear circuits
 - Potentiation of parallel/competing circuits (fear extinction as new form of learning)

- ✓ In associative learning a triad of brain structures are involved
 - Amygdala, medial prefrontal cortex, hippocampus
 - They interact in fear learning/extinction

