

SYMPOSIA: S55 (09:45 - 11:15, Hall H)

FEAR EXTINCTION: FROM ENGRAMS TO CIRCUITS

Chairs: Joshua Johansen and Gregory Quirk



09:50 **Gregory Quirk (Univ. Puerto Rico, PR)** Prefrontal circuits in extinction of fear and avoidance.

10:10 **Susan Sangha (Purdue Univ., USA)** Role of the prefrontal cortex in discriminating among fear, safety and extinguished fear cues.

10:30 **Joshua Johansen (RIKEN, Japan)** Regulation of fear extinction learning through distinct neuromodulatory circuits.

10:50 **Mona Maroun (Univ. Haifa, Israel)** Developmental differences in the mechanisms of extinction in the adult and post-weanling animals.

Prefrontal circuits of extinction of fear and avoidance



Gregory J. Quirk, PhD
Department of Psychiatry
Univ. Puerto Rico School of Medicine
San Juan, Puerto Rico



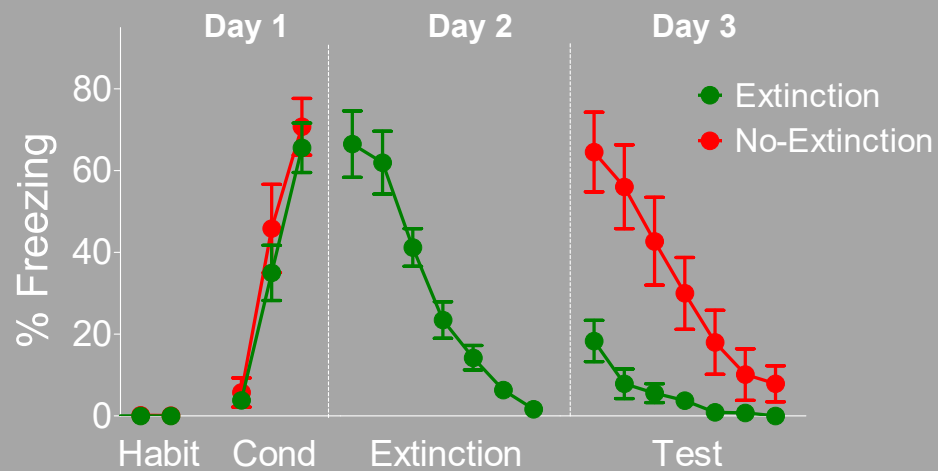
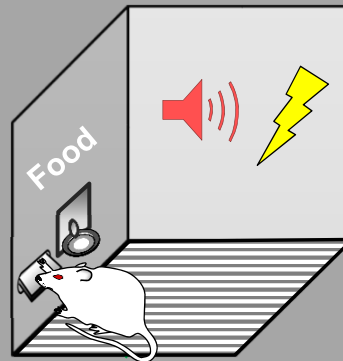
How do we respond to danger stimuli?



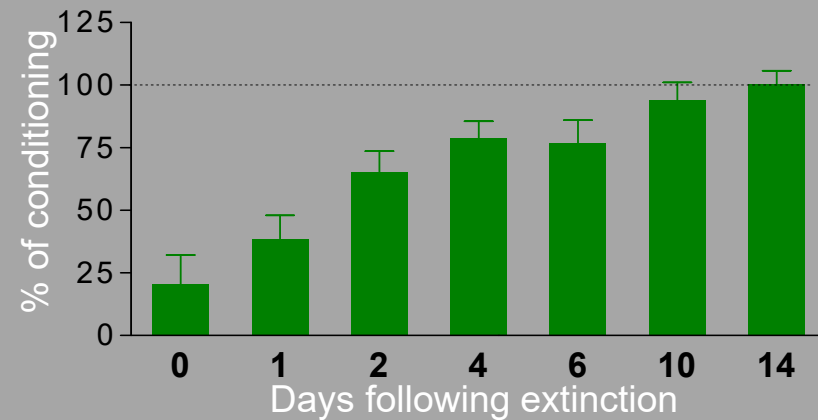
Fear responses can be...

- Passive (freezing, startle)
- Active (avoidance, fight or flight)

Auditory fear (threat) conditioning



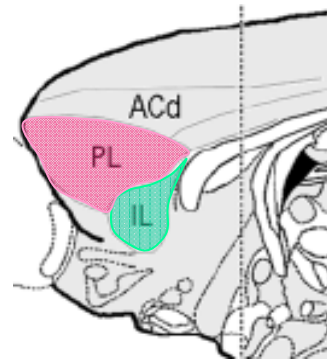
Extinction inhibits, but does not erase, fear memory



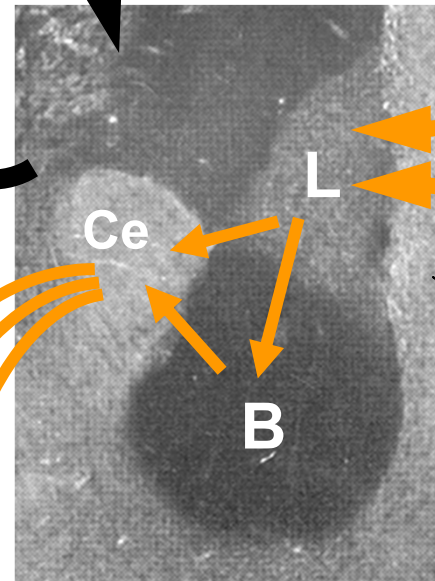
Quirk et al., 2000

What circuits regulate fear responses after extinction?

Medial Prefrontal Cortex



Prelimbic (PL)
Infralimbic (IL)

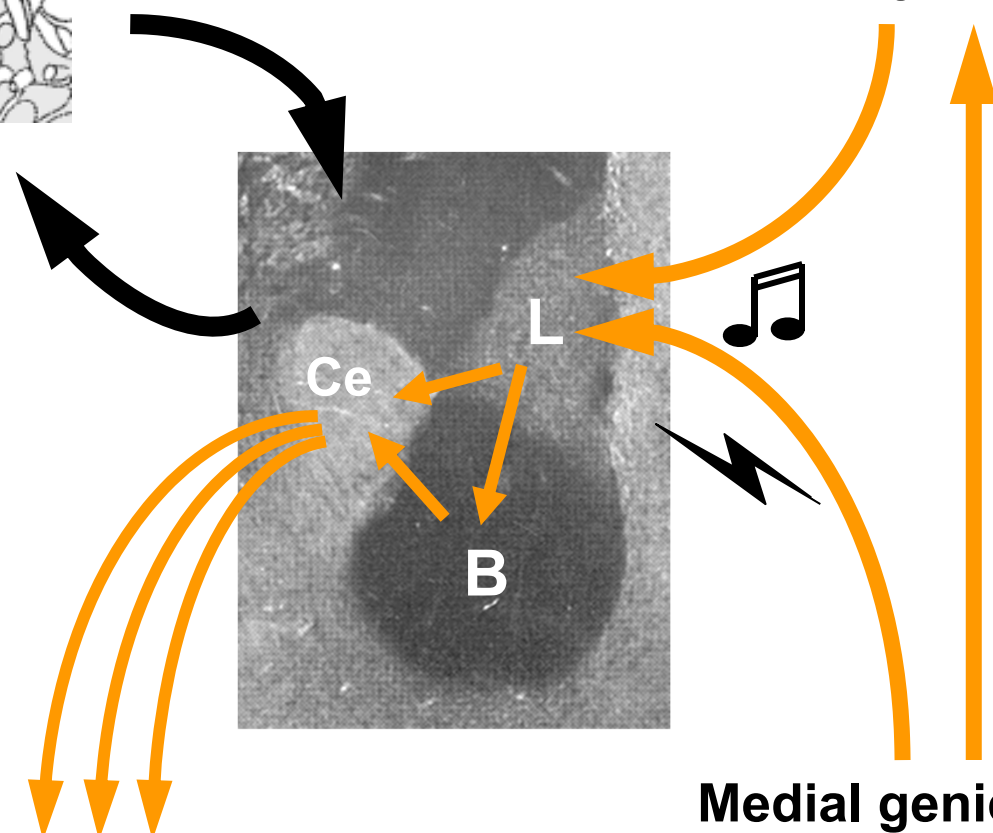


Auditory cortex



Medial geniculate
(thalamus)

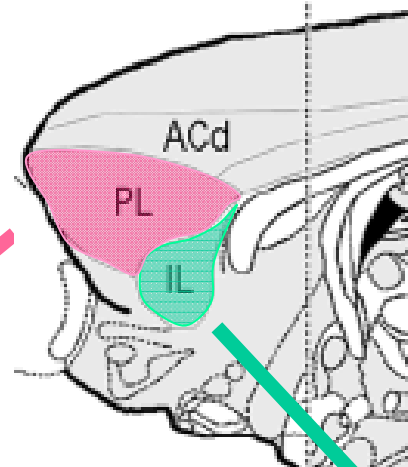
Hypothalamus (autonomic)
Central gray (freezing)
Reticular formation (startle)



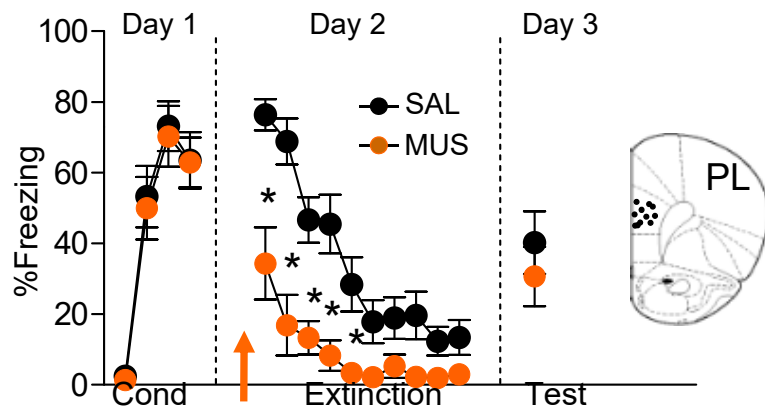
Inactivation of PL and IL have opposite effects on freezing



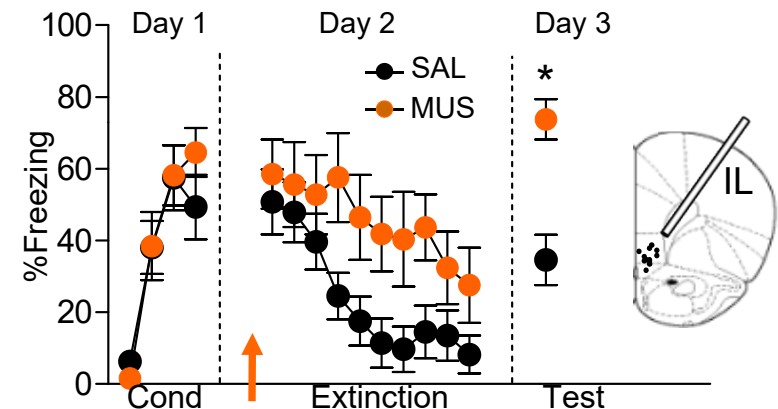
Muscimol (GABA agonist)



PL is necessary for retrieval of fear

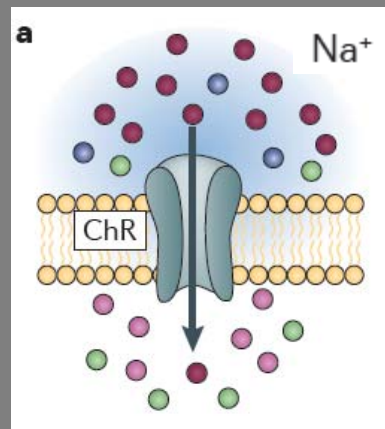
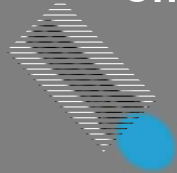


IL is necessary for extinction of fear



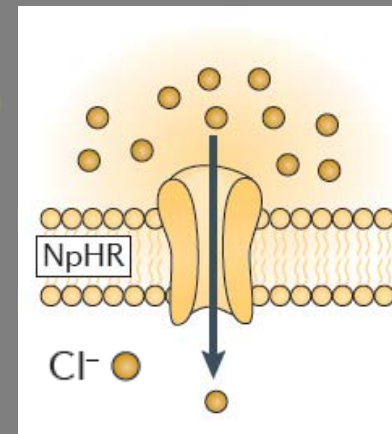
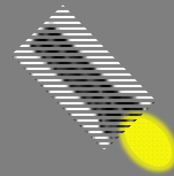
Revisiting the role of IL with optogenetics

Activating neurons: Channelrhodopsin (ChR2)



AAV CaMKIIa-ChR2-eYFP
(glutamatergic neurons)

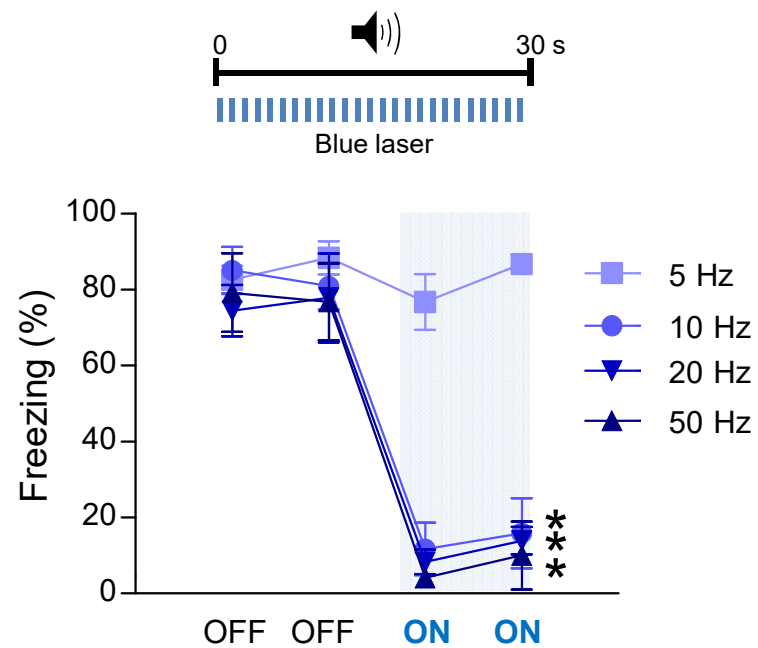
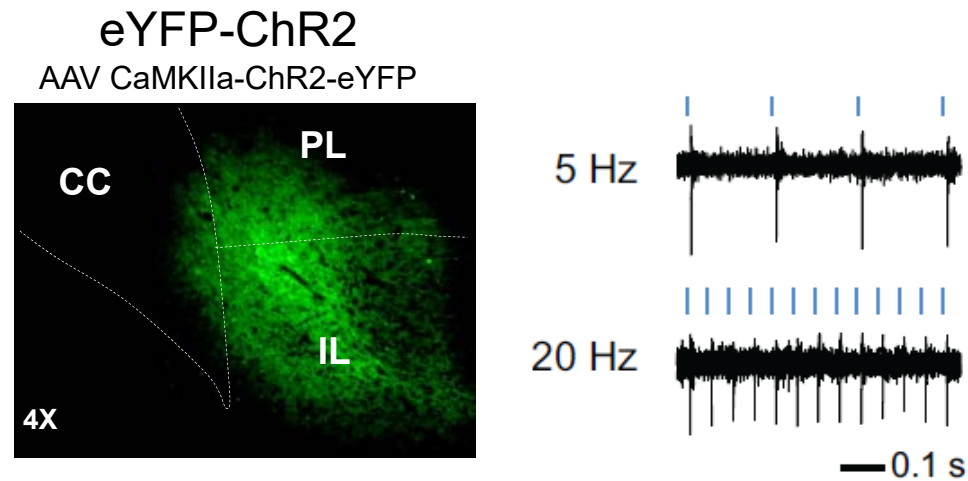
Silencing neurons: Halorhodopsin (NpHR)



AAV CaMKIIa-eNpHR3.0-eYFP
(glutamatergic neurons)

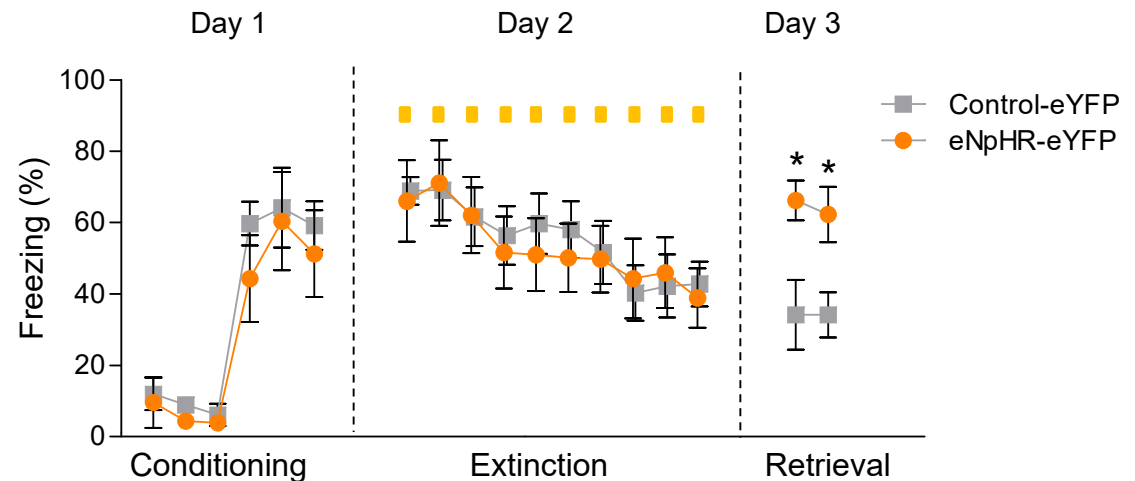
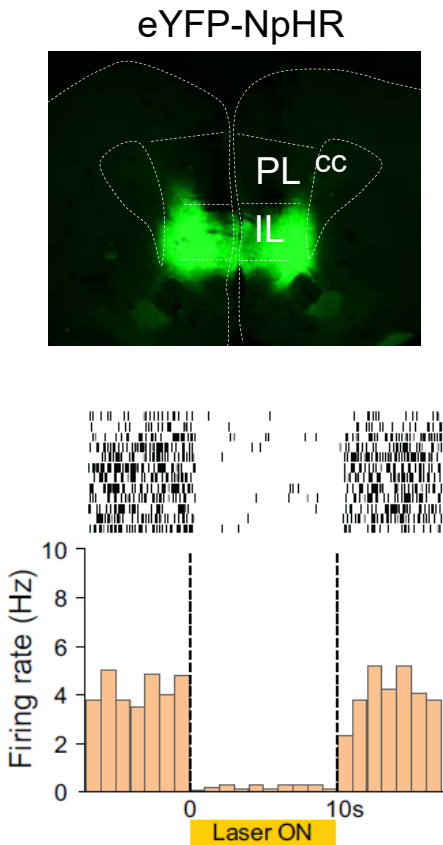
(Tye and Deisseroth, 2012)

Activation of IL neurons with ChR2 reduces freezing



Silencing IL neurons during extinction training impairs extinction memory

Halorhodopsin (NpHR) in IL (8-10 mW)

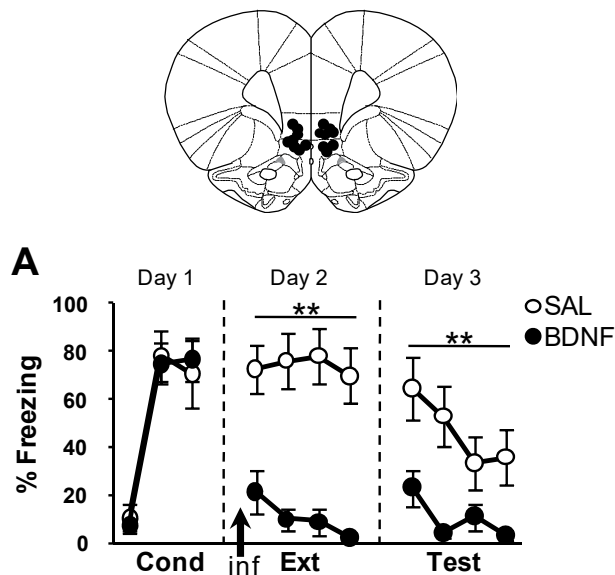


IL tone responses are necessary for later retrieval of extinction

Brain derived neurotrophic factor (BDNF) inputs to IL are necessary for fear extinction

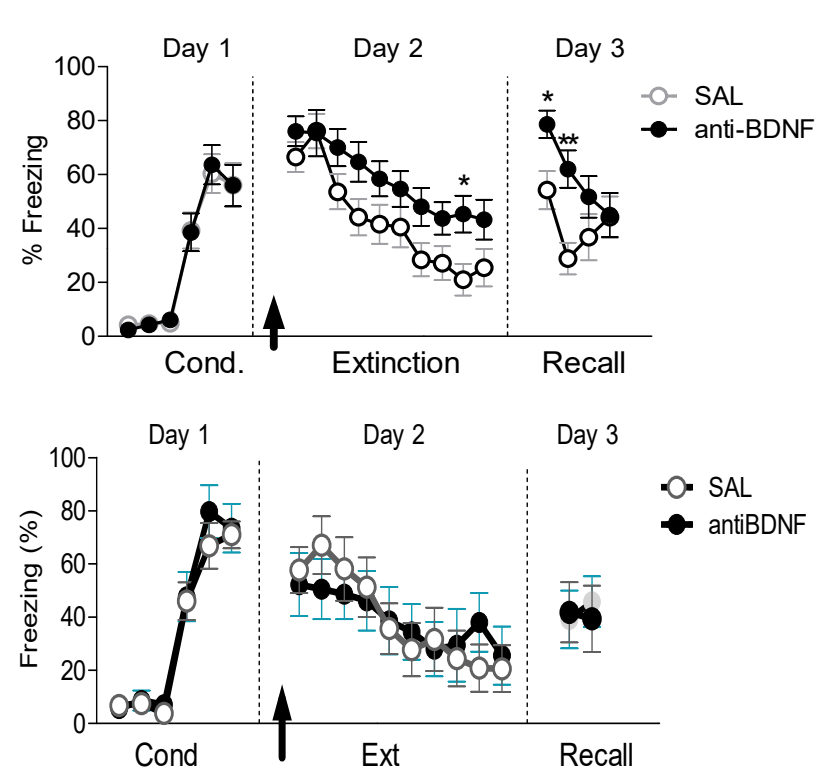


Infusing BDNF into IL facilitates extinction



Peters et al., *Science*, 2010

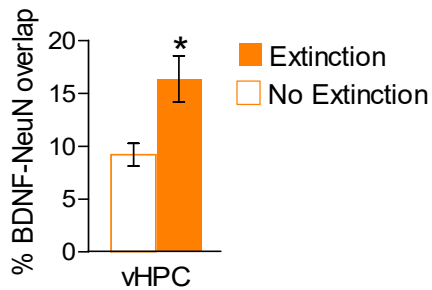
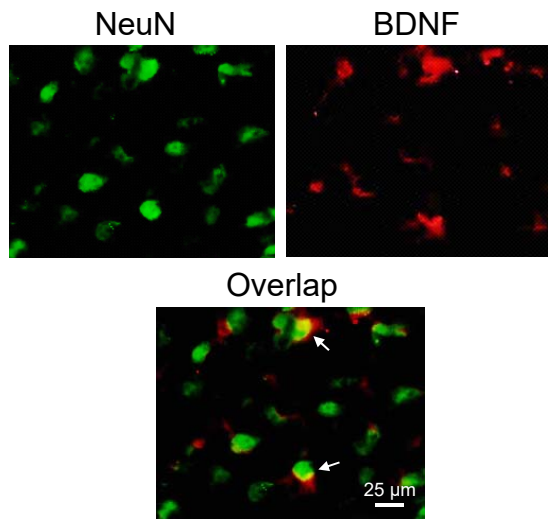
Blocking BDNF in IL with an antibody impairs extinction



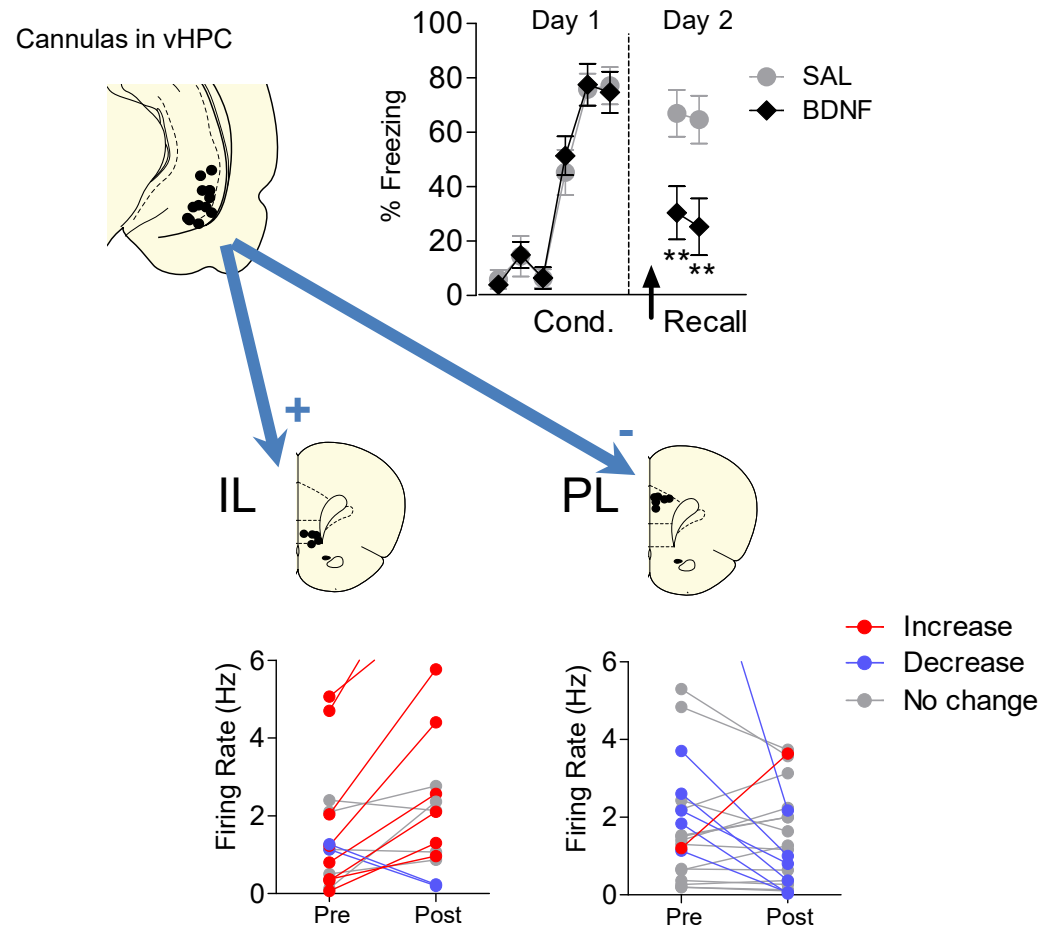
Rosas-Vidal et al., *NPP*, 2014

Ventral hippocampus is the likely source of BDNF in IL

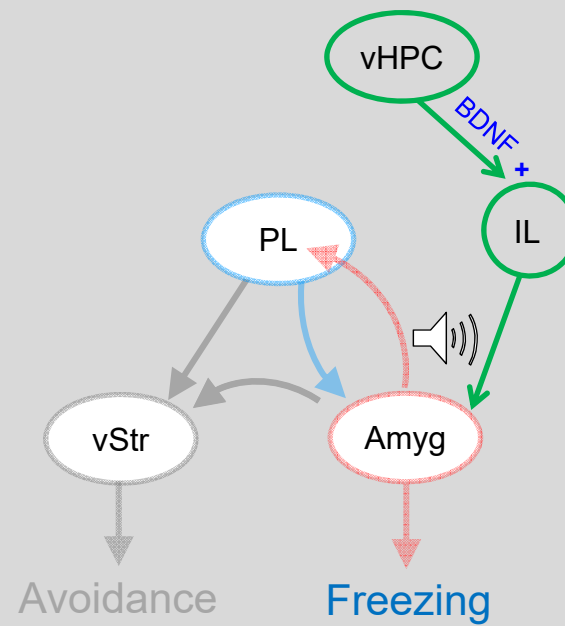
Extinction training increases BDNF expression in vHPC neurons



Infusing BDNF in vHPC facilitates extinction and activates IL



Extinction of conditioned fear



Fear responses can be...

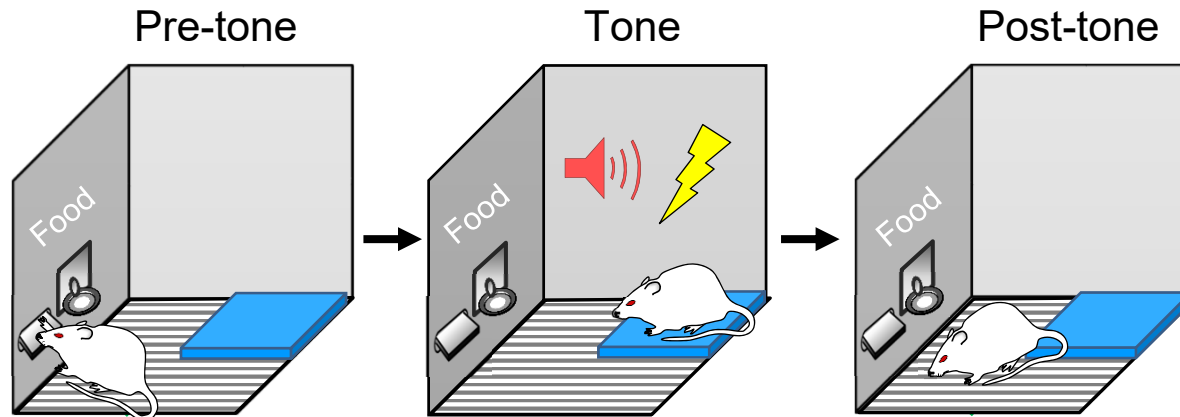
- **Passive (freezing, startle)**
- • **Active (avoidance, flight)**

Active avoidance can be seen as

Positive: a coping strategy that reduces the likelihood of danger.

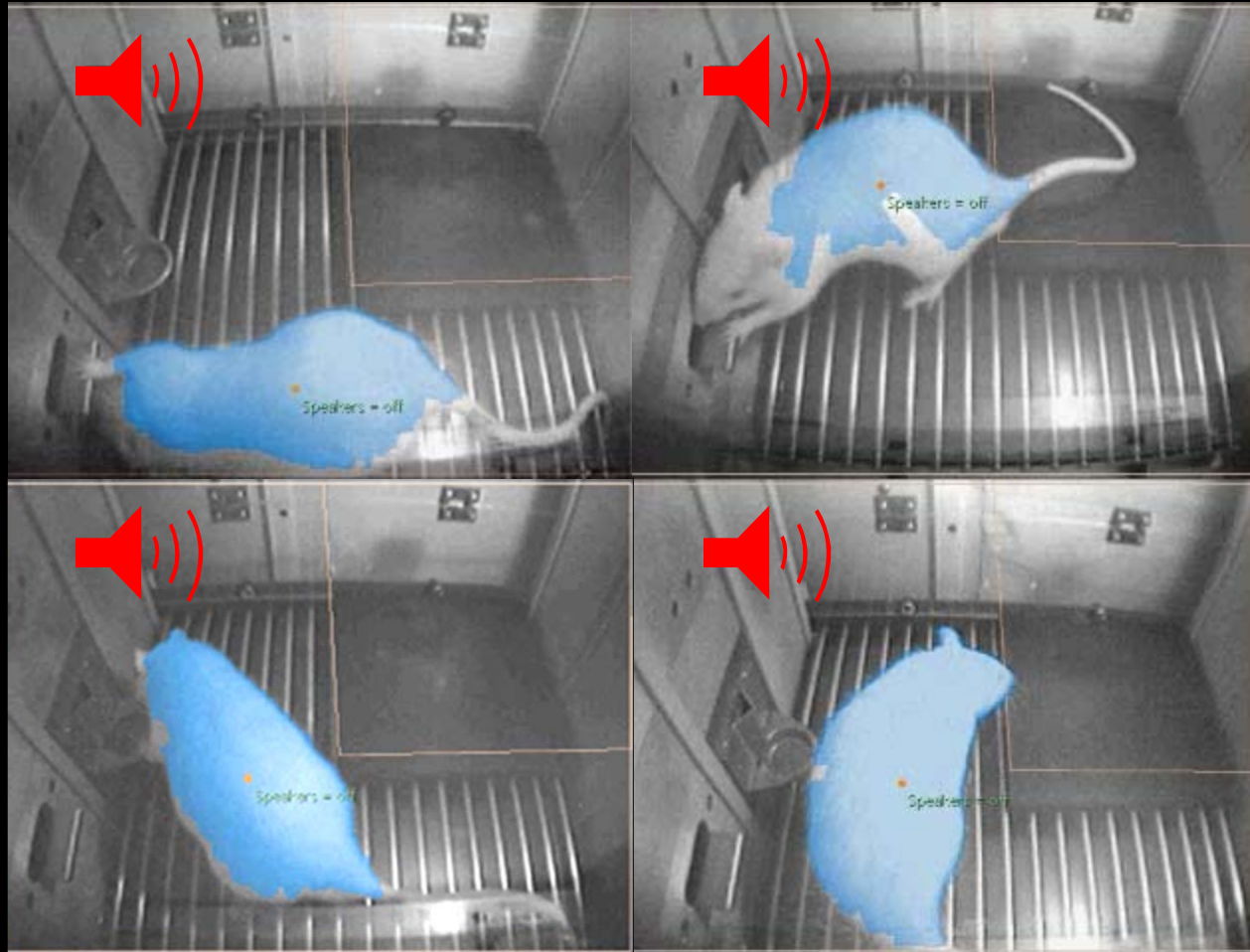
Negative: interferes with goals; is excessive in PTSD, OCD, phobias; reduces opportunities for extinction.

Modification of fear conditioning task: Platform-mediated avoidance

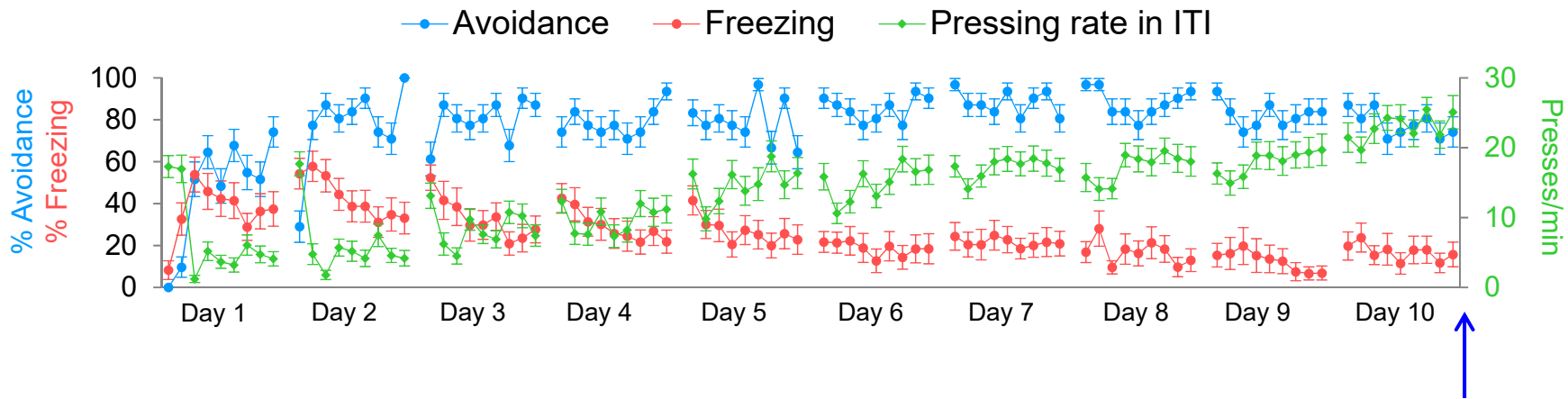
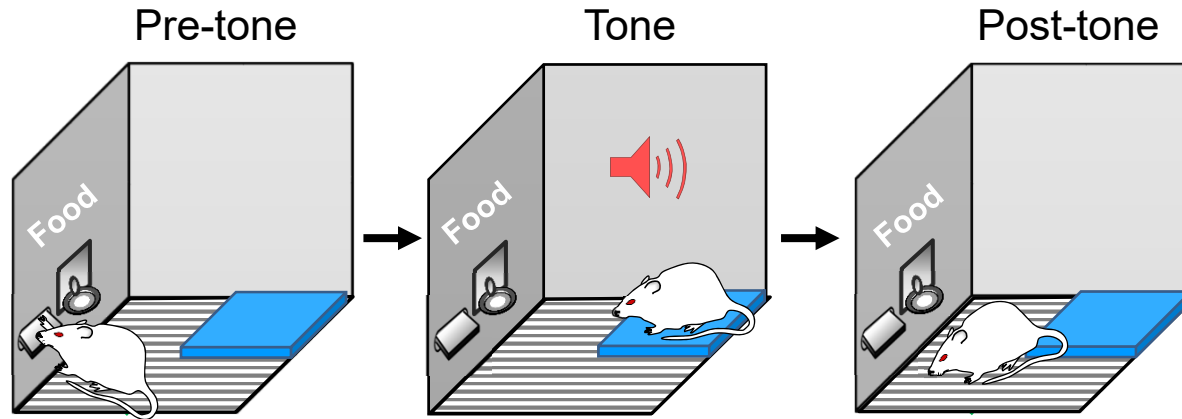


- Avoidance has a cost because it competes with access to food (similar to clinical avoidance).
- Unlike conditioned freezing, avoidance represents a “decision” based on multiple factors.

Platform-mediated avoidance

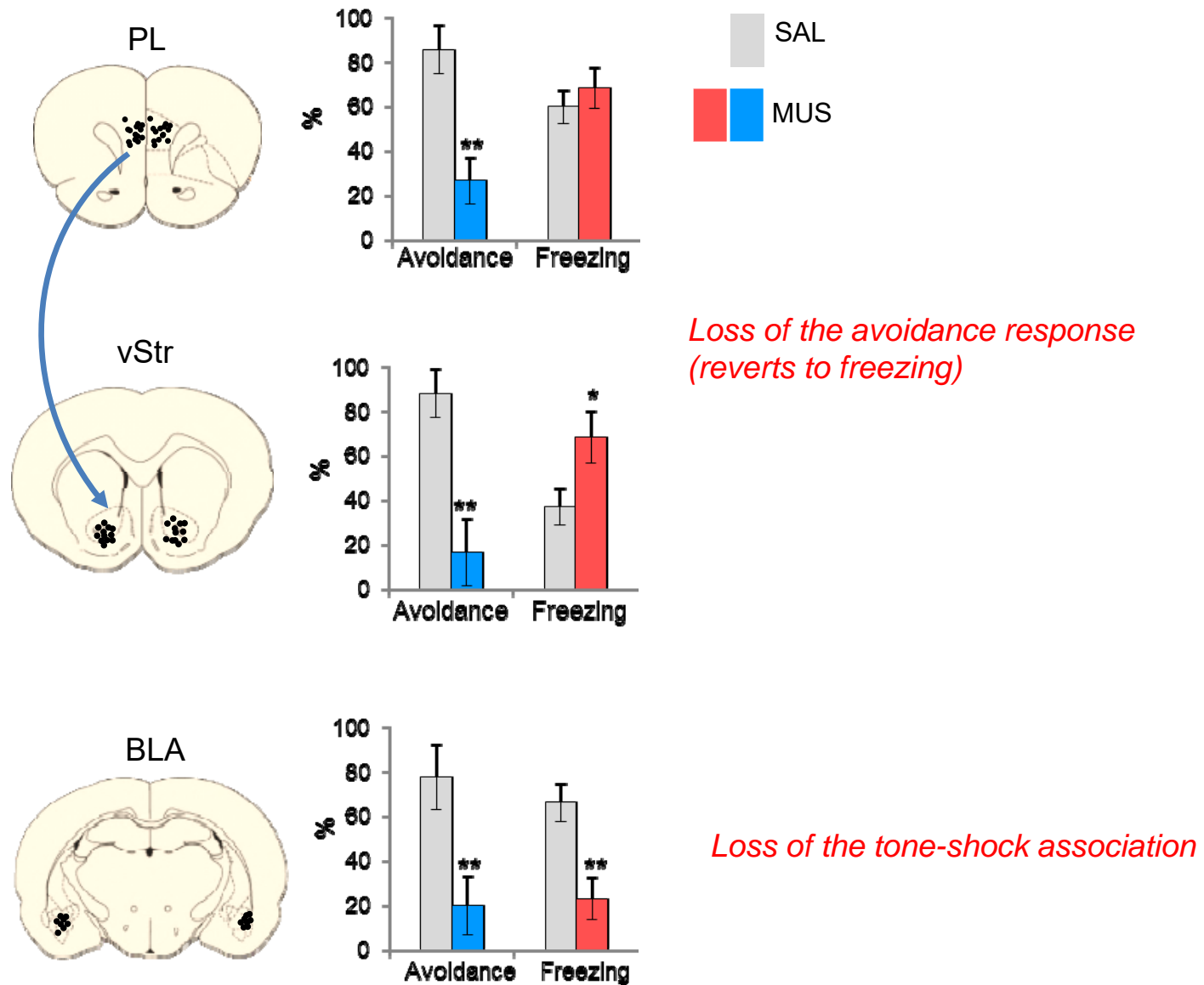


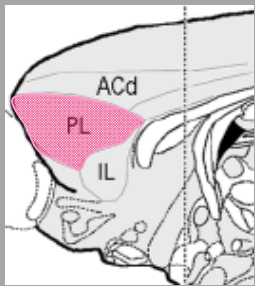
As avoidance is learned, freezing decreases



Which structures are necessary for avoidance?

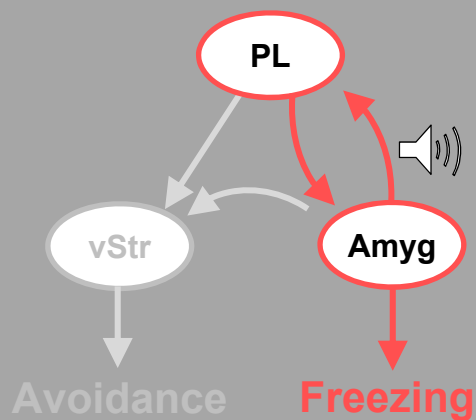
Effect of muscimol inactivation on avoidance vs. freezing



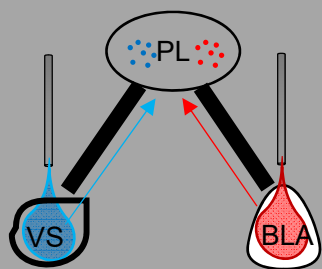
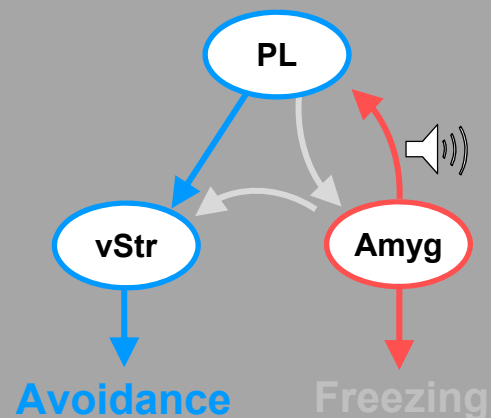


Circuits of fear conditioning vs. avoidance

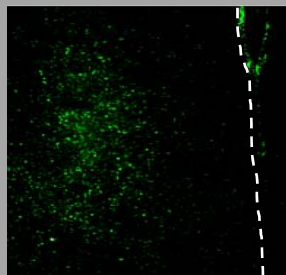
Fear conditioning



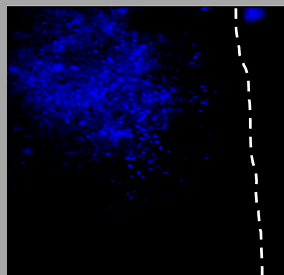
Platform avoidance



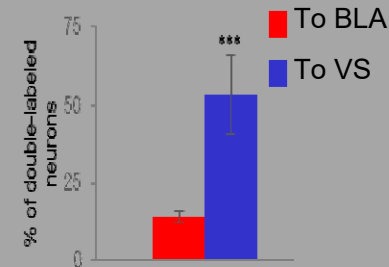
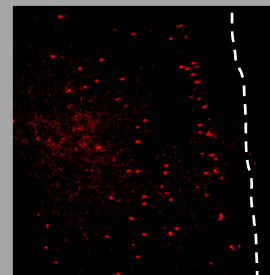
c-Fos immuno-labeled cells



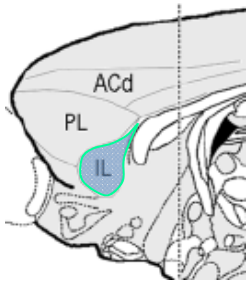
VS-projecting cells (Fast Blue)



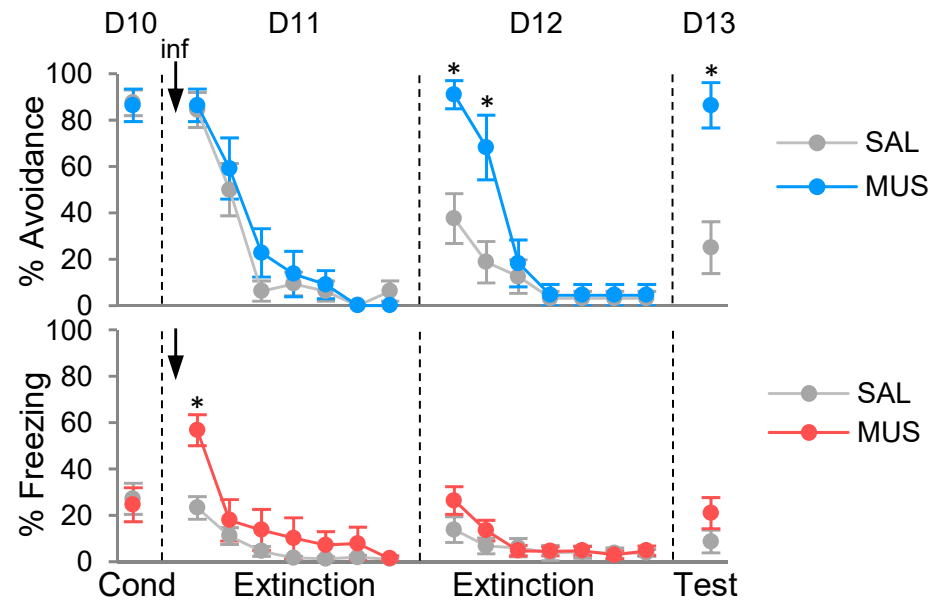
BLA-projecting cells (CTB)



What about extinction of avoidance?

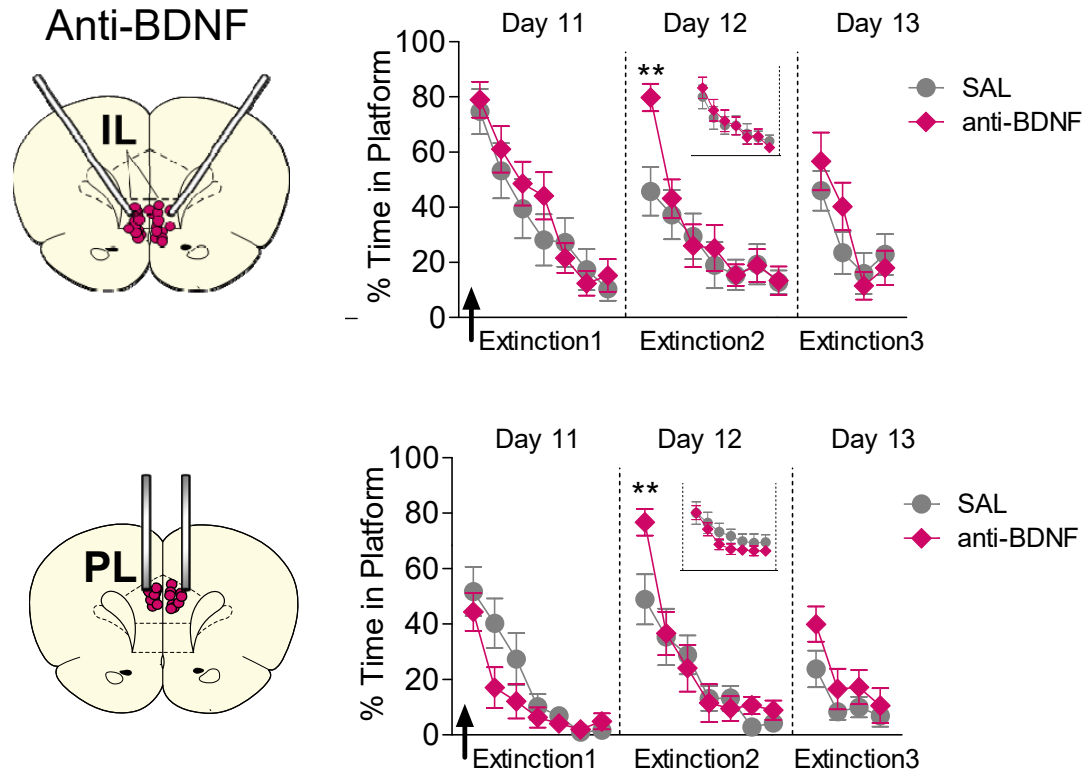


IL is necessary for avoidance extinction

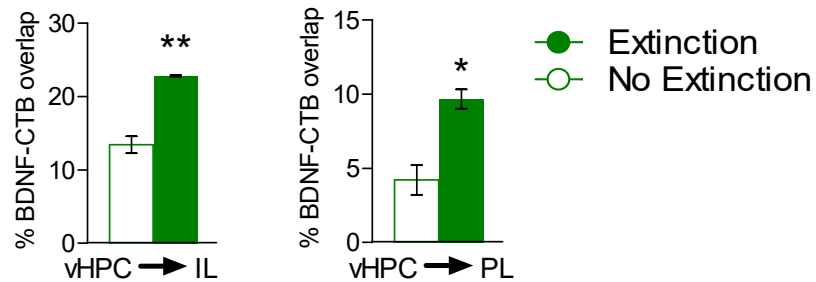
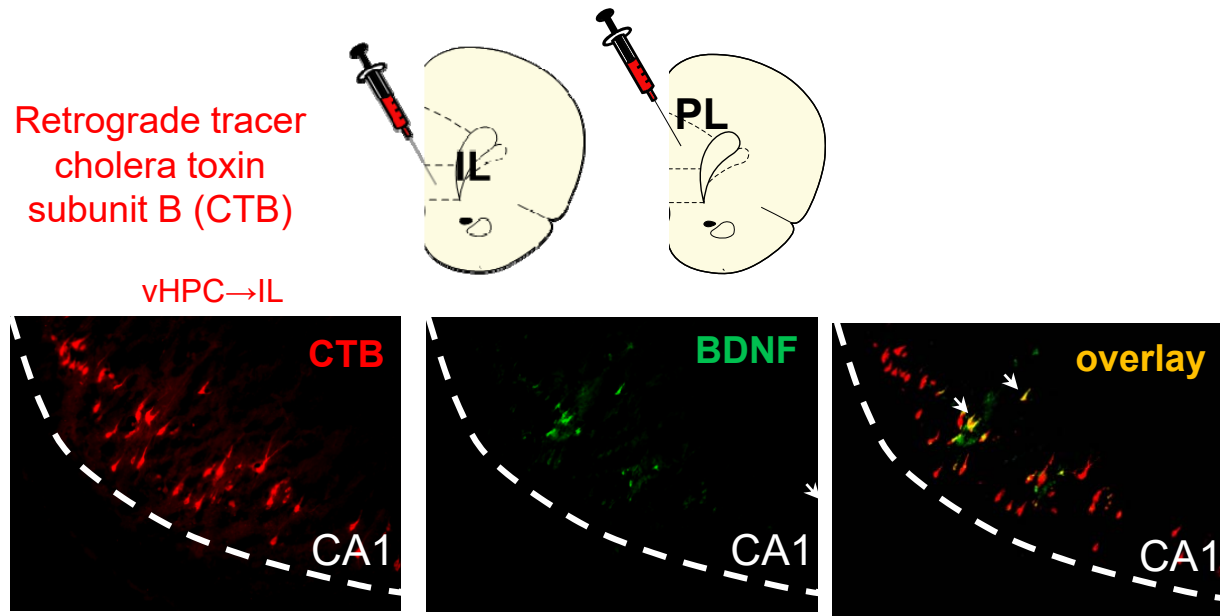


- *Persistent avoidance is not associated with increased fear*

Avoidance extinction requires BDNF in both IL and PL

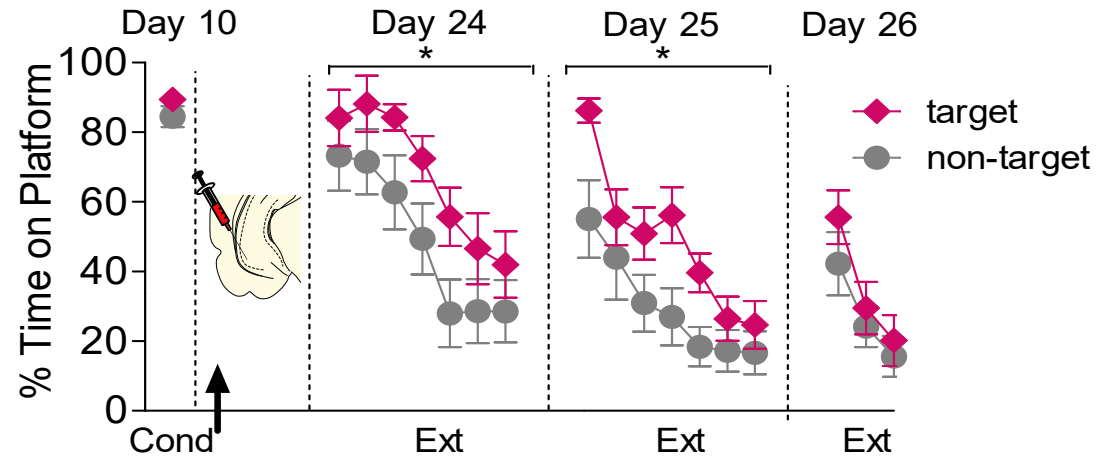
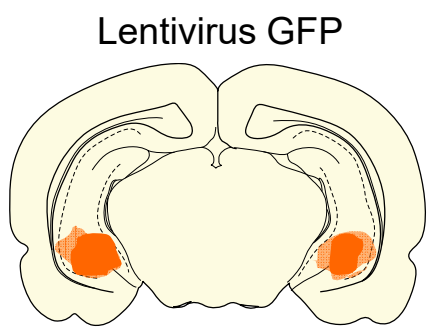
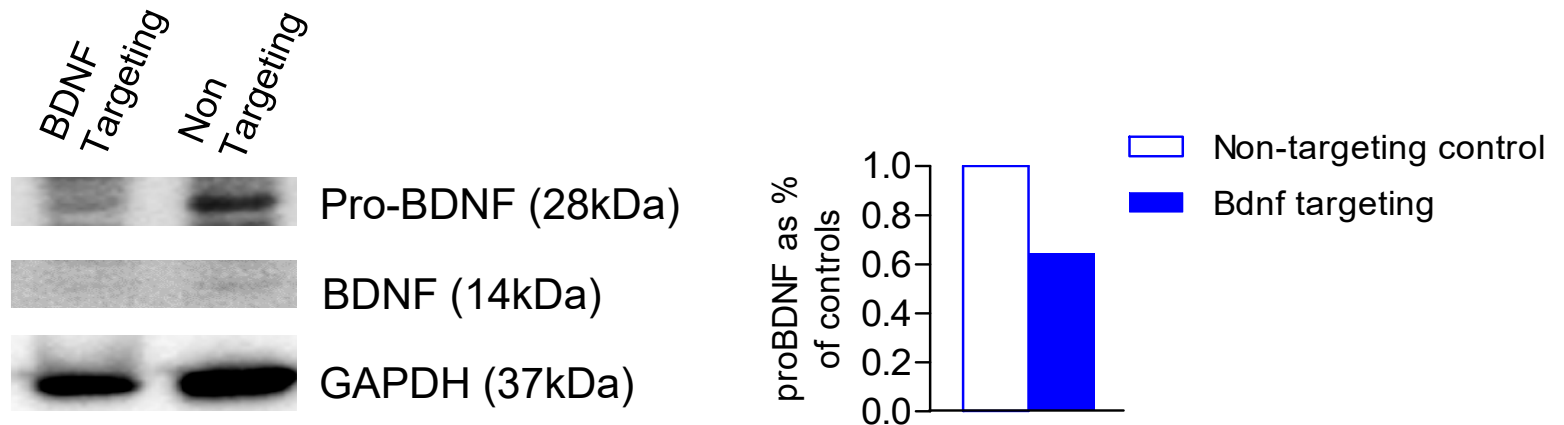


Extinction of avoidance increases BDNF expression in vHPC neurons projecting to IL and PL



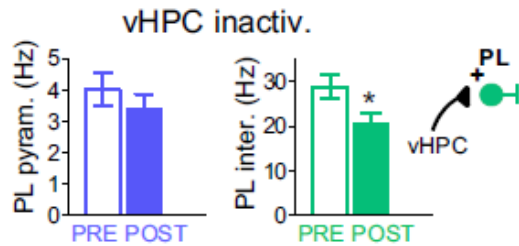
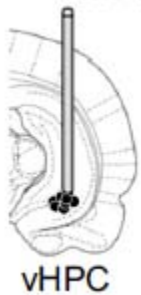
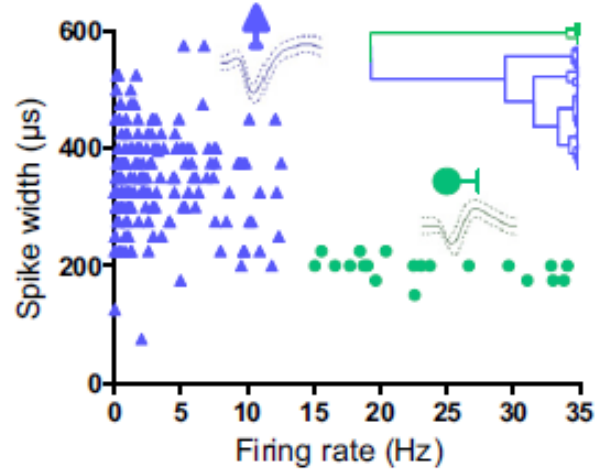
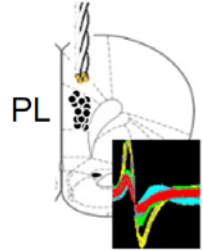
Are BDNF projections from vHPC necessary for avoidance extinction?

Reducing BDNF production in vHPC neurons (CRISPR-Cas9) impairs extinction of avoidance

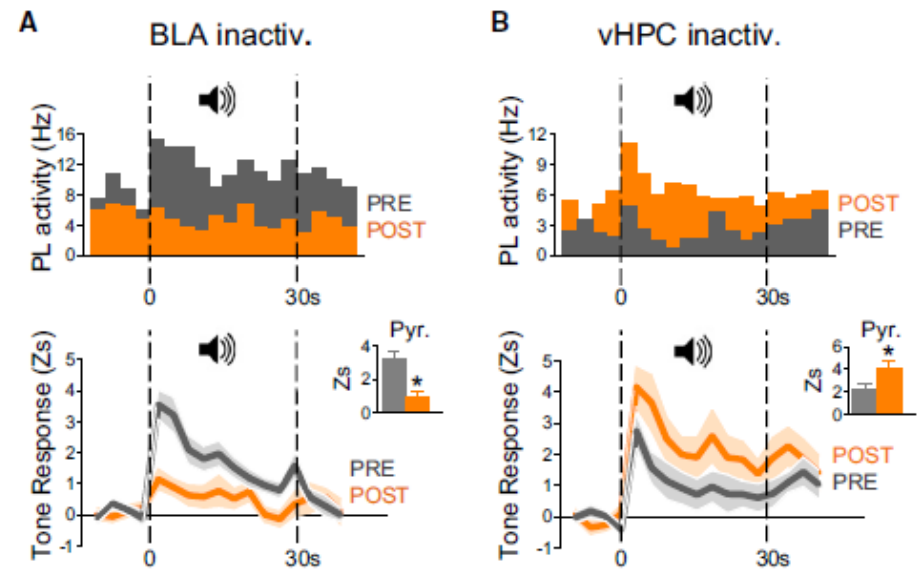


vHPC inputs to PL activate inhibitory interneurons

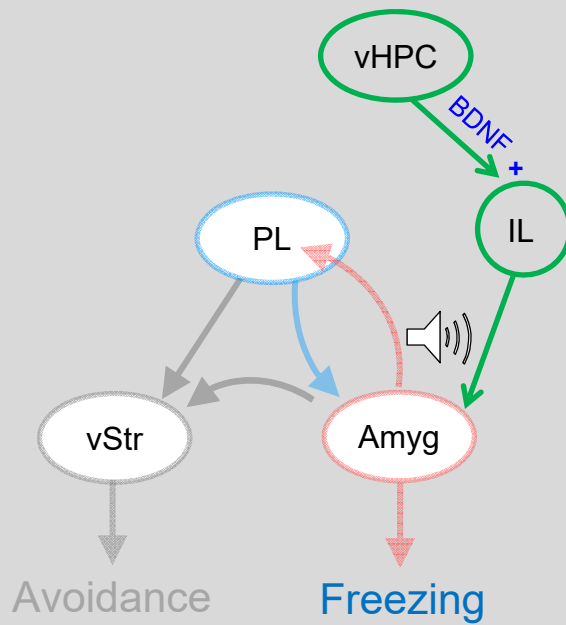
Unit-Recording



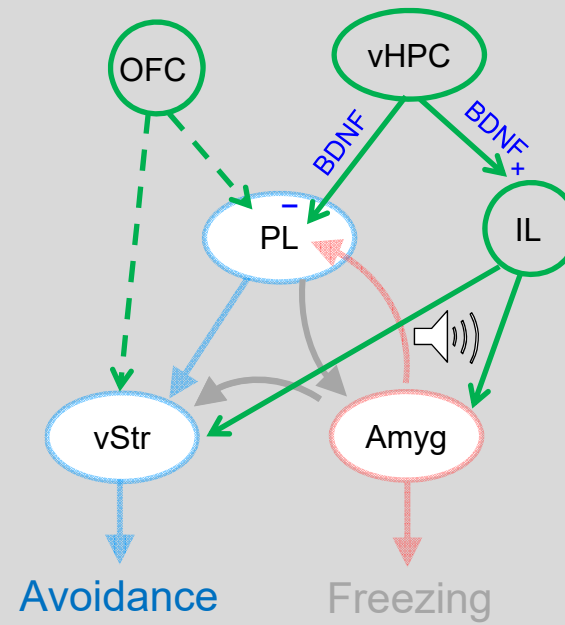
PL tone responses



Extinction of conditioned fear



Extinction of active avoidance



Laboratory of Fear Learning, Univ. of Puerto Rico

Grad Students

Christian Bravo-Rivera
Hector Bravo-Rivera
Kelvin Quinones
Luis Rosas-Vidal
Jose Rodriguez-Romaguera

Postdocs, Postbacs

Fabricio H. Do Monte
Maria Diehl
Angelica Minier

Technicians

Zarkalys Quintero
Carlos Rodriguez

Former Tainees

Francisco Amador
David Anglada
Melissa Castro
Kevin Corcoran
Kelimer Lebron
Gabriela Manzano
Mohammed Milad
Devin Mueller
Lening Olivera
Jamie Peters

Nancy Padilla-Coreano
Ciorana Roman
Edwin Santini
Demetrio Sierra Mercado
Francisco Sotres-Bayon
Ivan Vidal-Gonzalez
Anthony Burgos-Robles



Collaborators

Jennifer Baretto (UPR)
Benjamin Greenberg (Brown Univ)
Suzanne Haber (Univ Rochester)
Satish Nair (Univ Missouri)
Karen Martinez (UPR)





Search



E-alert



Submit



Login

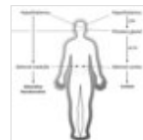
Integrating neuroscience and learning: now's the time...

Our ability to increase human potential is linked to our ability to learn at all life stages.

Review Article | 29 June 2016 | [OPEN](#)

Learning and memory under stress: implications for the classroom

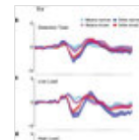
Susanne Vogel & Lars Schwabe



Article | 08 June 2016 | [OPEN](#)

Surprise responses in the human brain demonstrate statistical learning under high concurrent cognitive demand

Marta Isabel Garrido, Chee Leong James Teng [...] Jason Brett Mattingley



Editorial | 08 June 2016 | [OPEN](#)

Towards consilience in science of learning: data as currency for collaboration

Soo-Siang Lim

Part of the Nature Partner Journal series



Published in partnership with



Published in partnership with

