Behavioral Neuroscience: Fear thou not

Rony Paz

Rony.paz@weizmann.ac.il

Thoughts

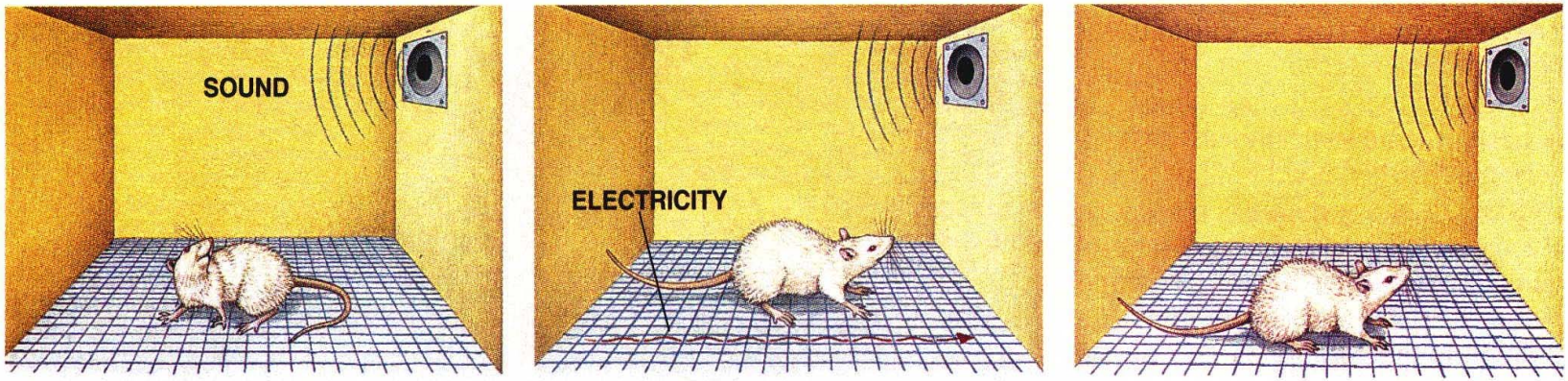
- What is a “reward”?
- Learning is best motivated by threats to survival
- Threats are much better reinforcers
- Fear is a prime motivator

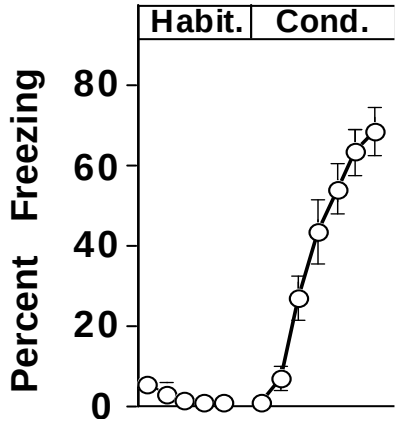
	Decreases behavior	Increases behavior
Presented	Positive punishment	Positive reinforcer
Taken away	Negative punishment	Negative reinforcer

Taking drugs?

More fun,
less withdrawal

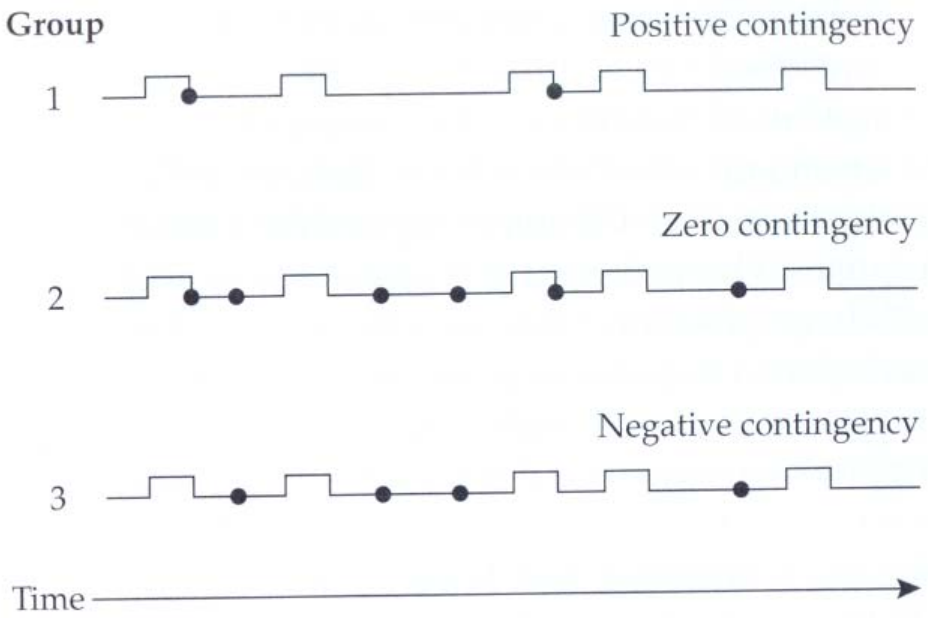
Classical fear conditioning

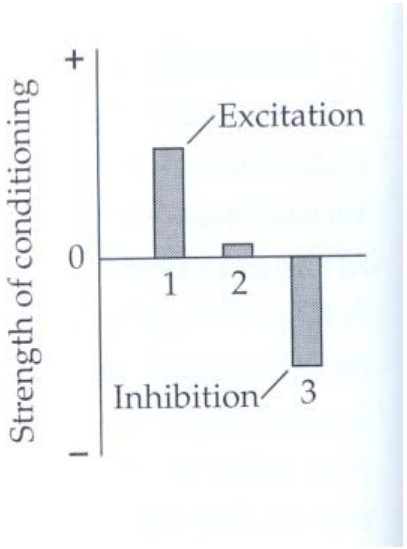




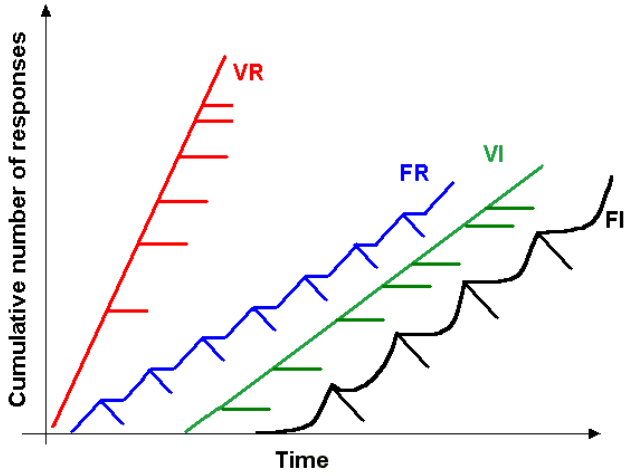
CS-US pairing
Tone = conditioned stimulus (CS)
Foot-shock = unconditioned stimulus (US)
Freezing = conditioned response (CR-UR)

Contingency: co-occurence

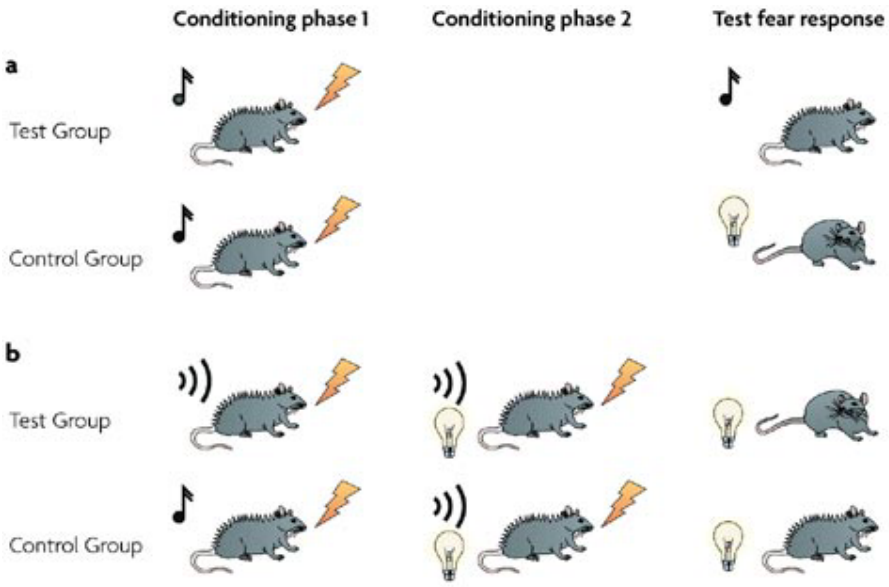




Schedules of reinforcement:
Variable/fixed interval/ratio



More than contingency: Surprise / added information

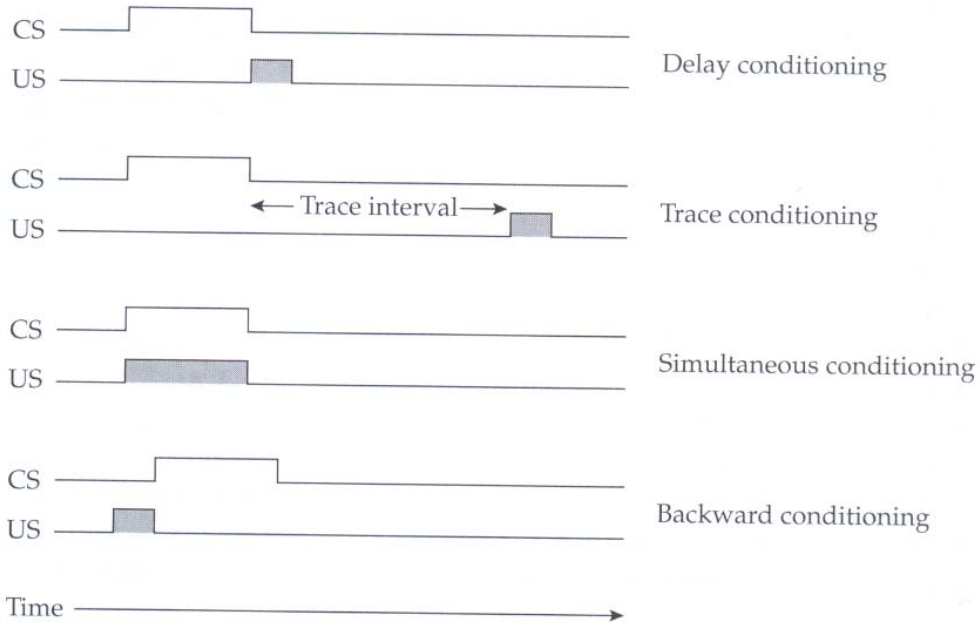


Aversive conditioning

Blocking

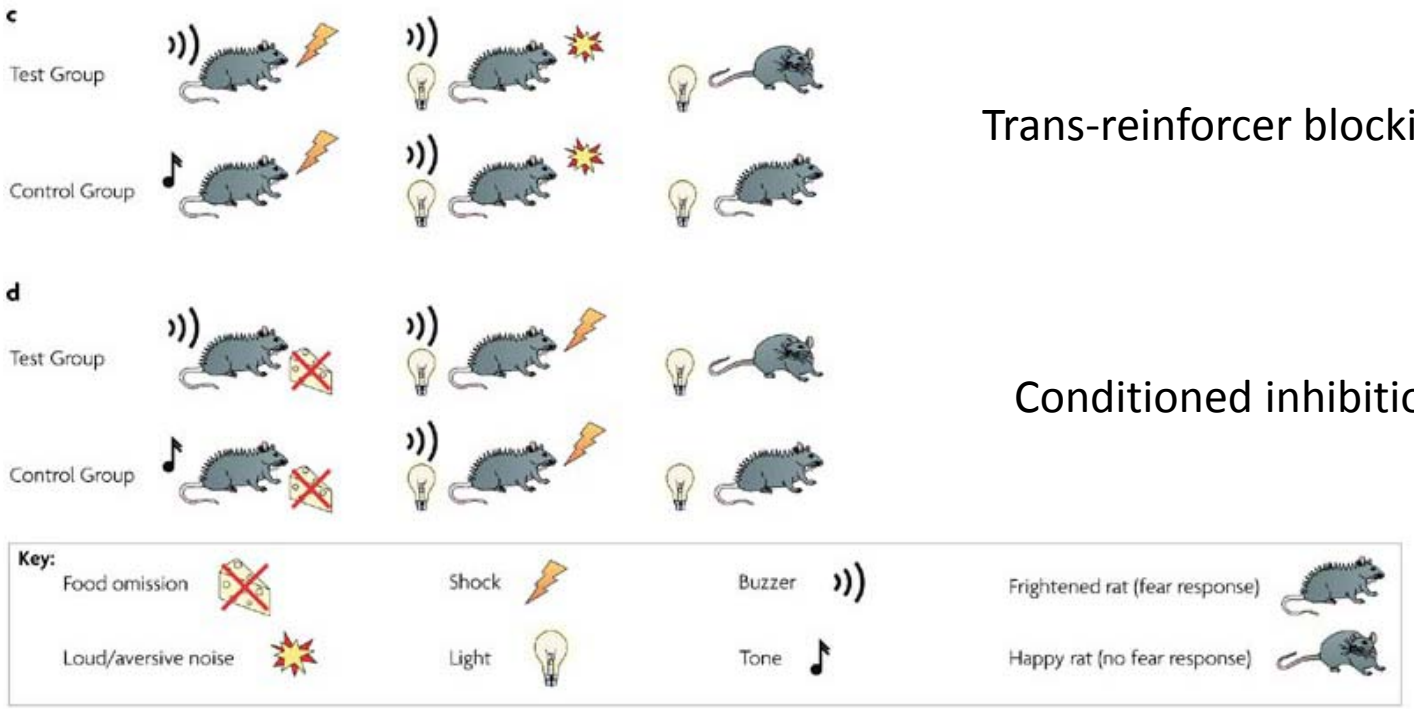
Nature Reviews | Neuroscience

Rules of thumb for conditioning strength



- Backward < simultaneous < trace < delay
- In trace: short interval > long interval
- In delay: short CS > long CS
- Salience of the CS
- Strength of the US
- Spaced trials is better than massed trials (the ratio between inter-trial-interval and the CS)

But notice it is hard to estimate backwards learning



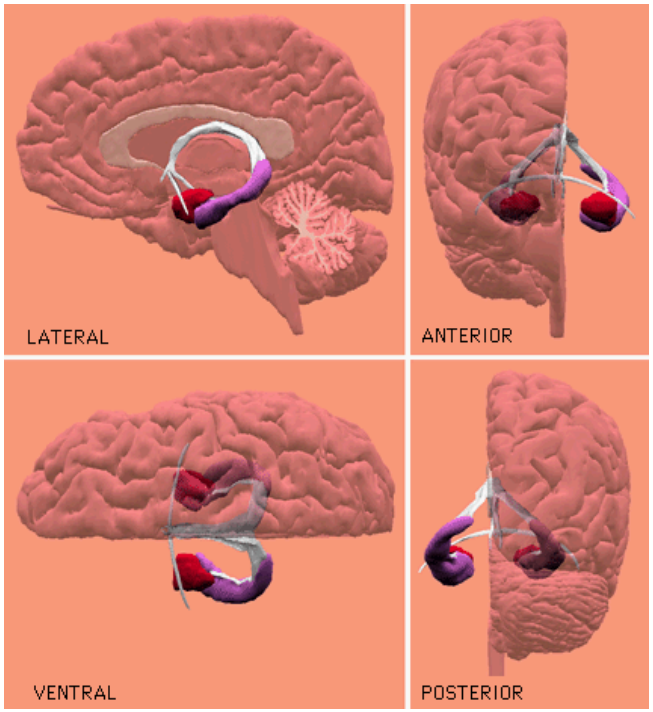
Trans-reinforcer blocking

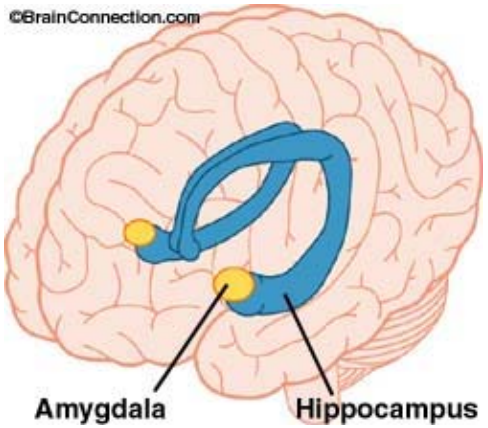
Conditioned inhibition

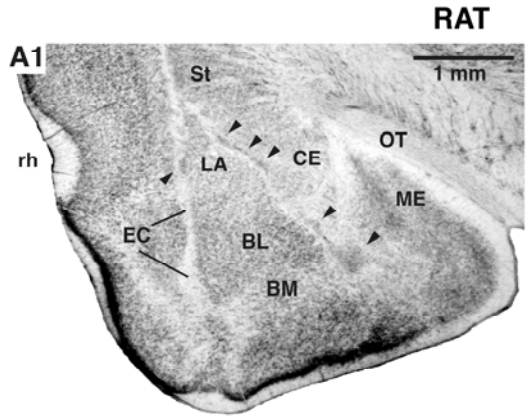
Nature Reviews | Neuroscience

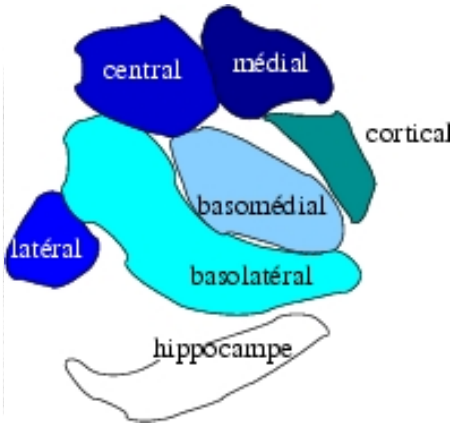
Suggests common brain mechanisms

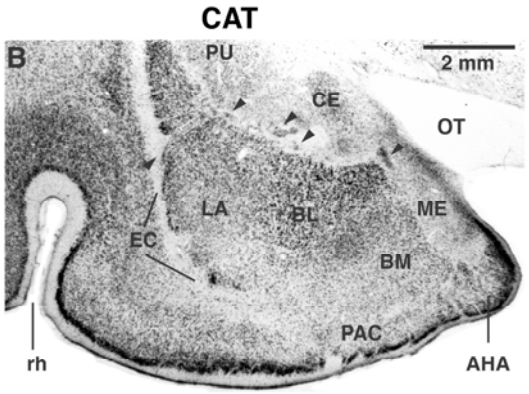
Amygdala

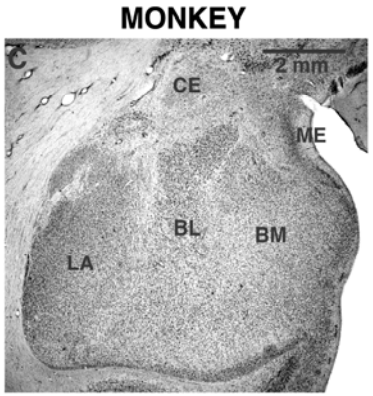

LATERAL
ANTERIOR
VENTRAL
POSTERIOR


©BrainConnection.com
Amygdala
Hippocampus


RAT
A1
St
1 mm
rh
LA
CE
OT
ME
EC
BL
BM

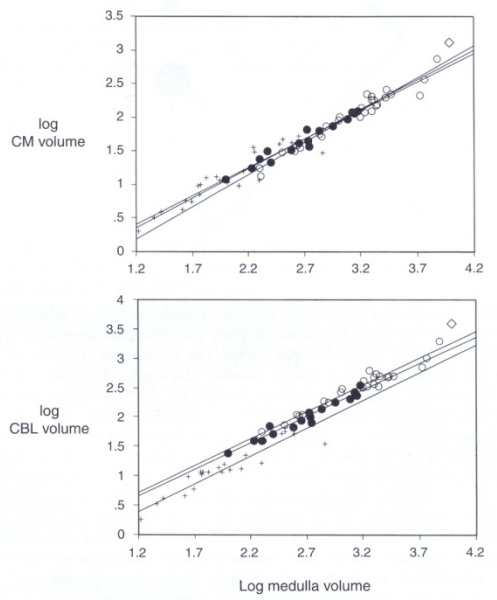

central
médial
cortical
basomédial
latéral
basolatéral
hippocampe

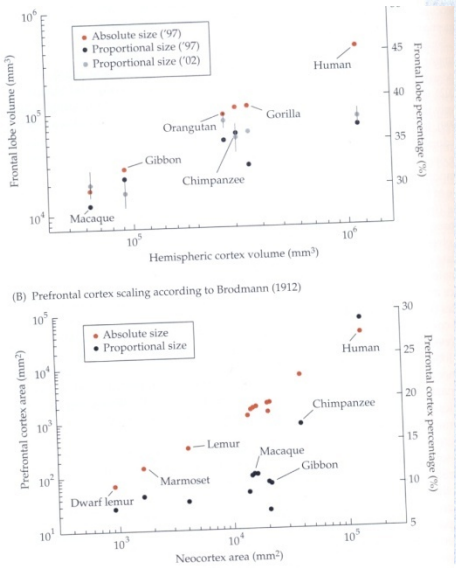

CAT
B
PU
2 mm
CE
OT
LA
BL
ME
EC
BM
PAC
rh
AHA

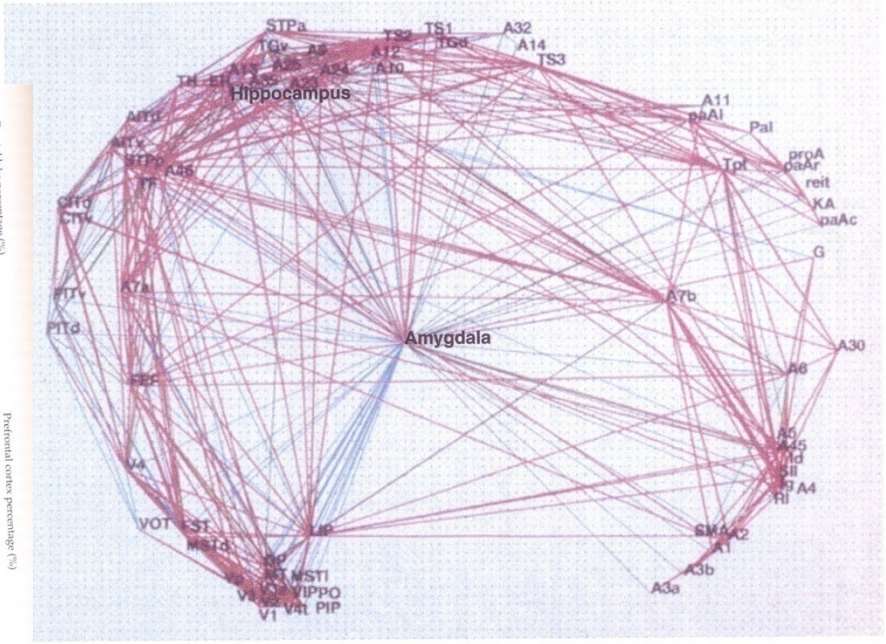

MONKEY
C
2 mm
CE
ME
BL
BM
LA

Amygdala and its basolateral complex (BLA)

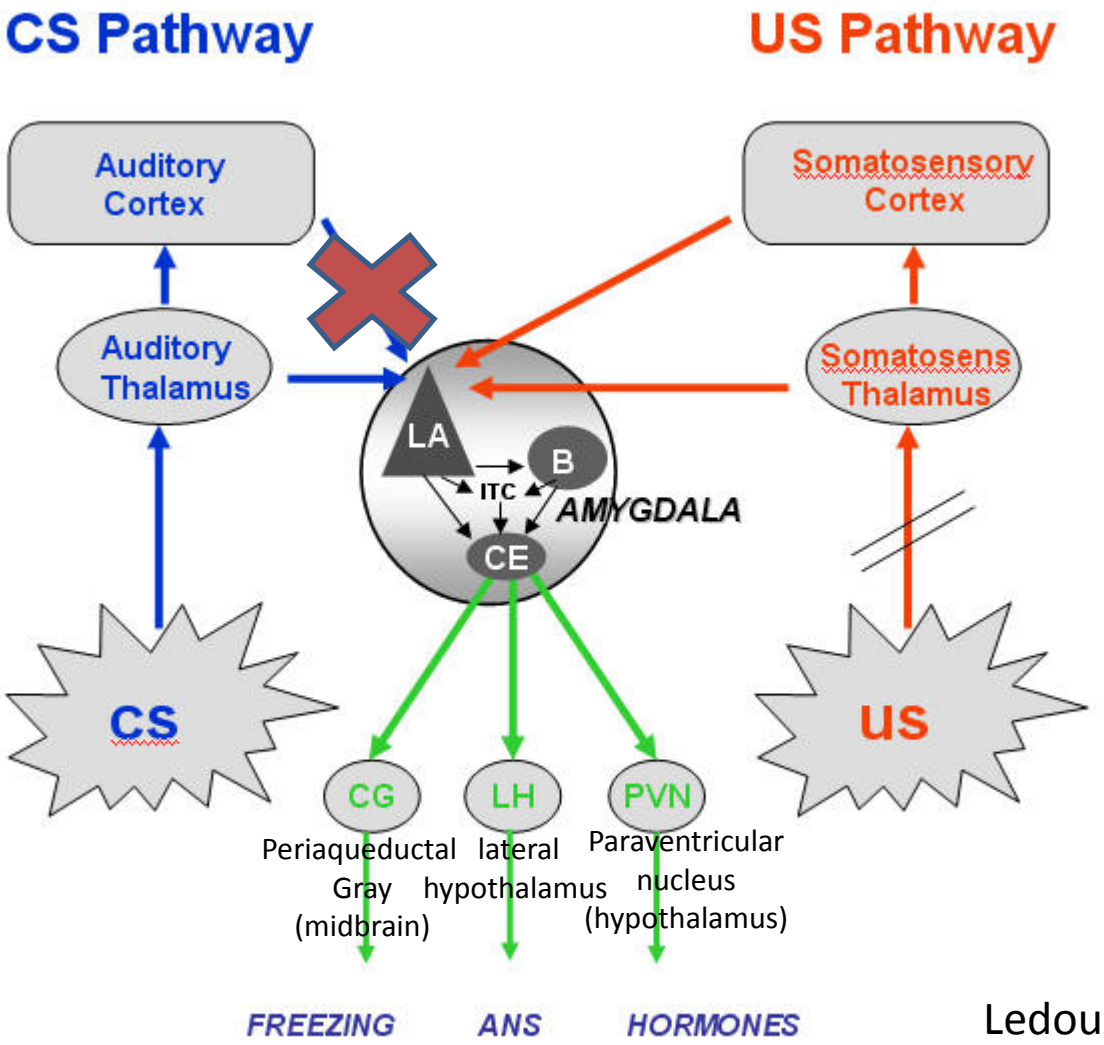
- BLA evolution parallels that of the prefrontal cortex
- BLA cell types reminiscent of cortex
- Cortical projections are much more extensive in primates
- Most cortical projections of the amygdala originate from BLA (none from CEA)





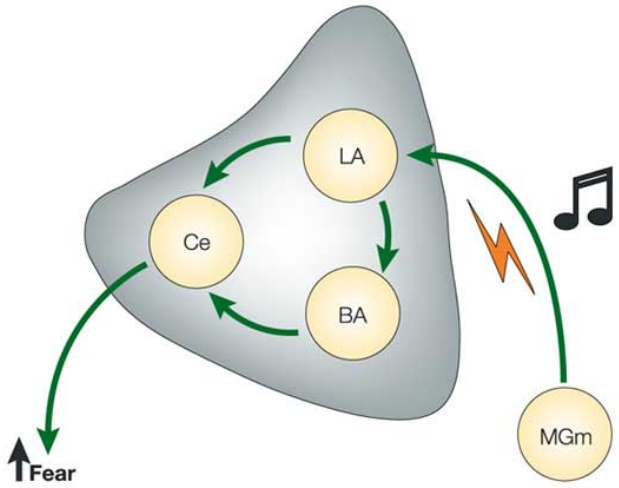


Fear circuit

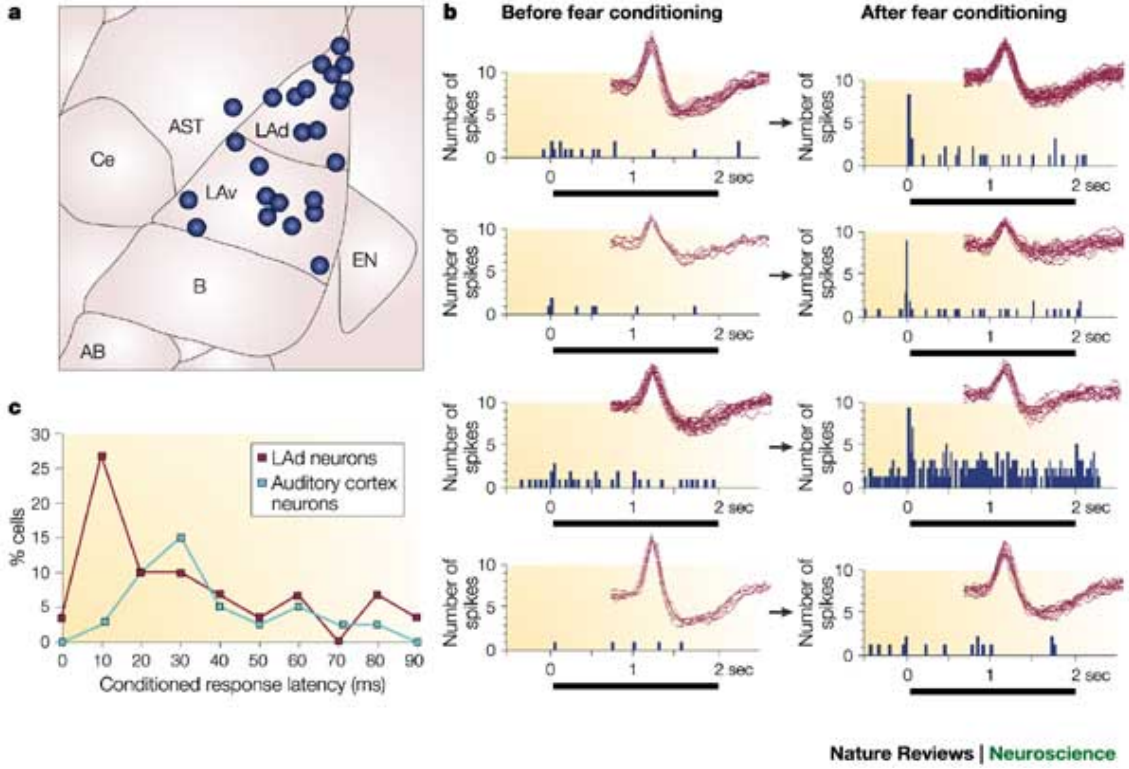


Ledoux, Mcgaugh, Davis

Neurons acquire tone responses after conditioning



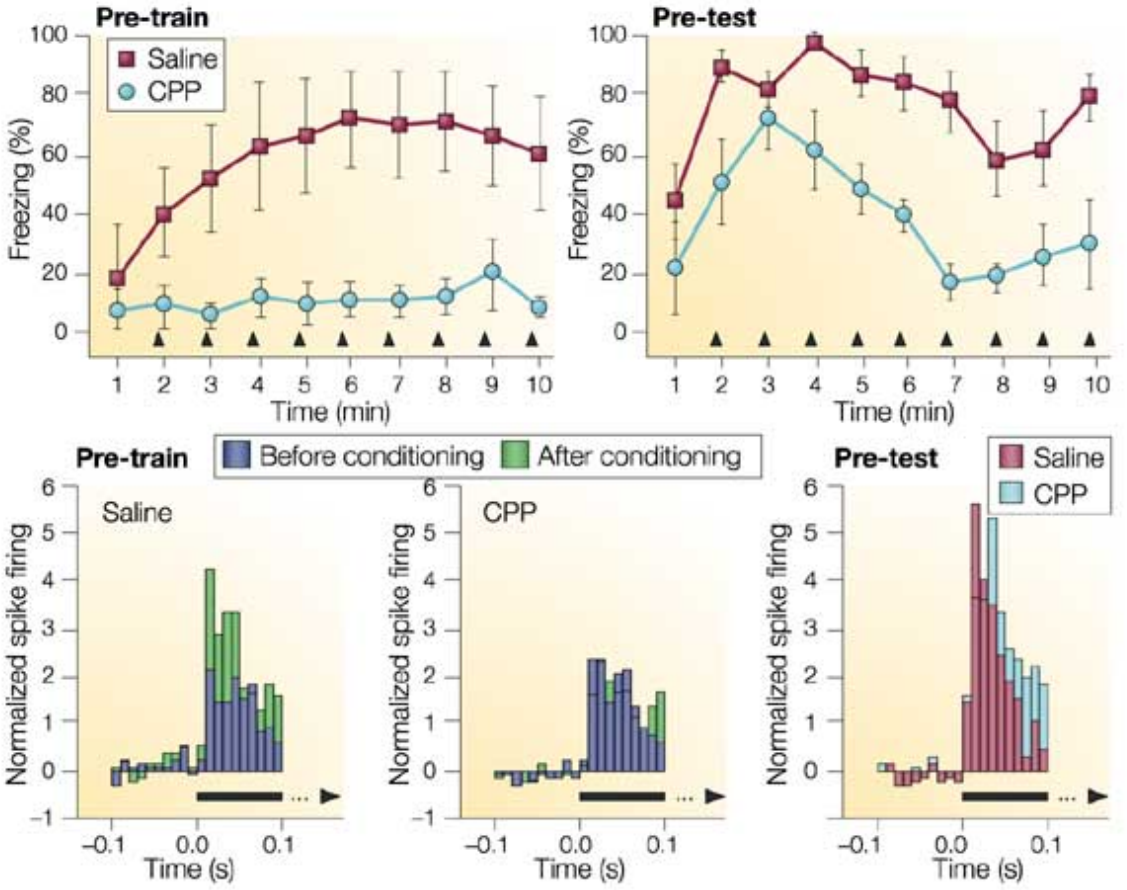
Nature Reviews | Neuroscience



Nature Reviews | Neuroscience

LTP in the LA is required

NMDA (***N***-methyl-**D**-aspartate, glutamate receptor) is involved in both the acquisition of fear memory and the induction of long-term potentiation (LTP) in the amygdala.

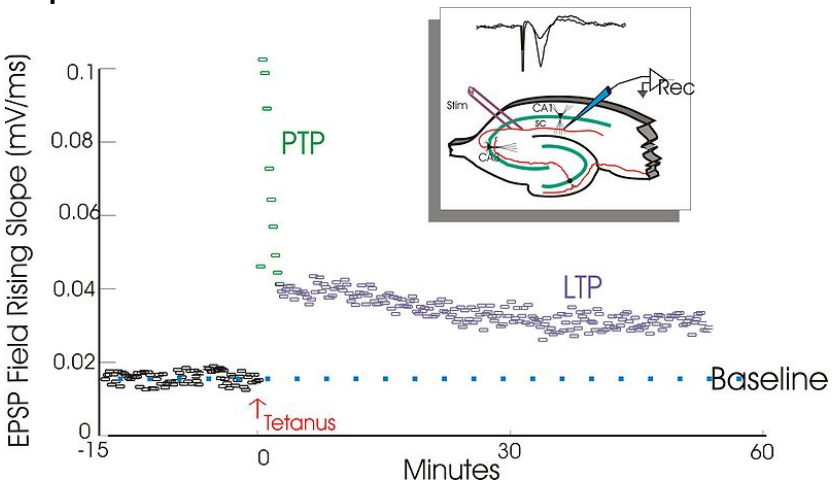


Nature Reviews | Neuroscience

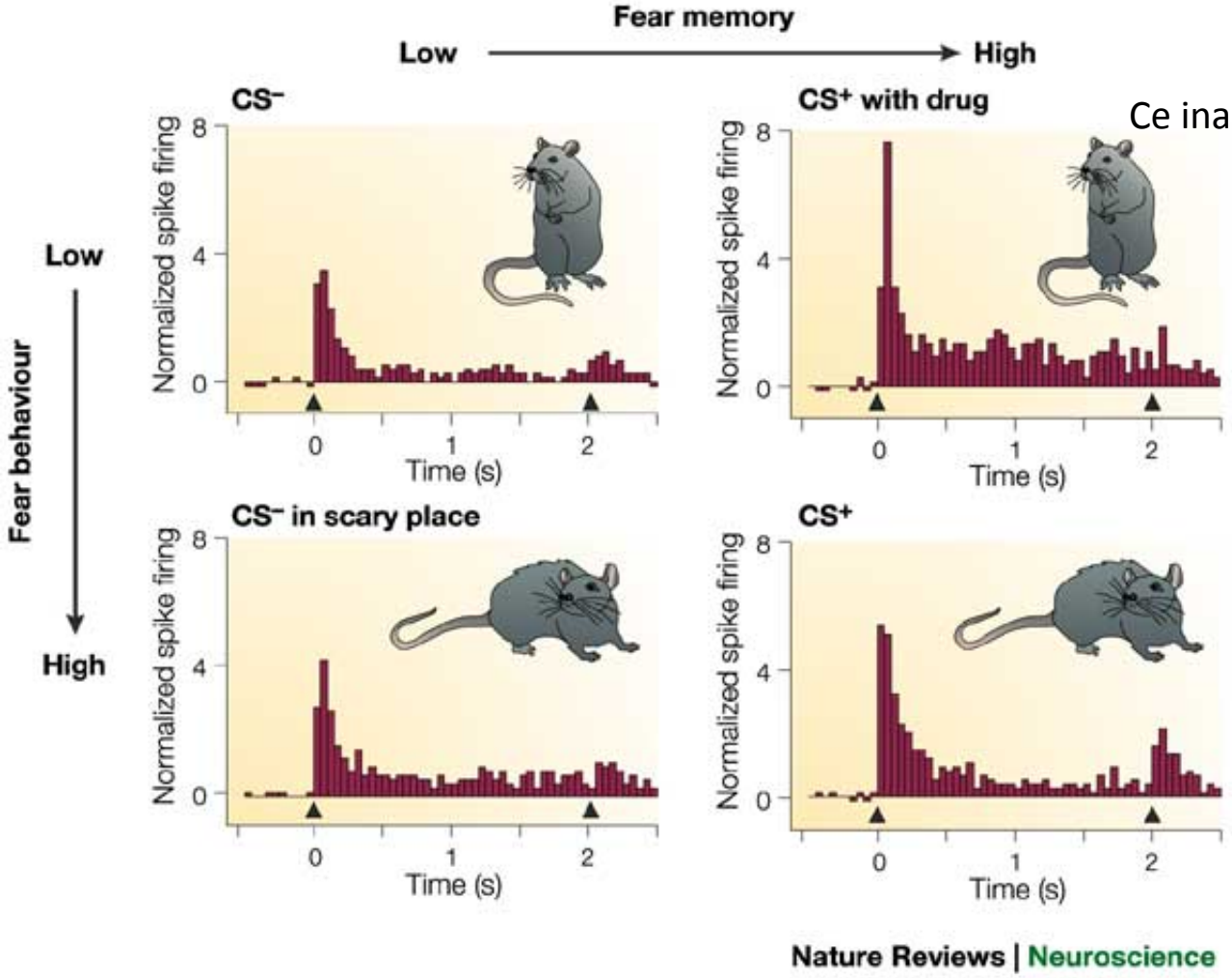
CPP (3-(2-carboxypiperazin-4-yl) propyl-1-phosphonic acid), a competitive NMDA-receptor antagonist

Long-term potentiation (LTP)

- Lomo, Bliss, Andersen, 1966, Hippocampus.
- Induced artificially by tetanic stimulation
- Long-lasting enhancement in signal transmission between two neurons that results from stimulating them synchronously.
- Increase in synaptic strength
- A cellular mechanism for learning and memory.
- Requires protein synthesis
- **Hebbian LTP** requires simultaneous pre- and postsynaptic depolarization for its induction ("fire together – wire together")
  - Specificity: to synapse
  - Associativity: associates a weak with a strong input
  - Coopertaivity: weak stimulation of many



LA encodes memory independent of fear behavior

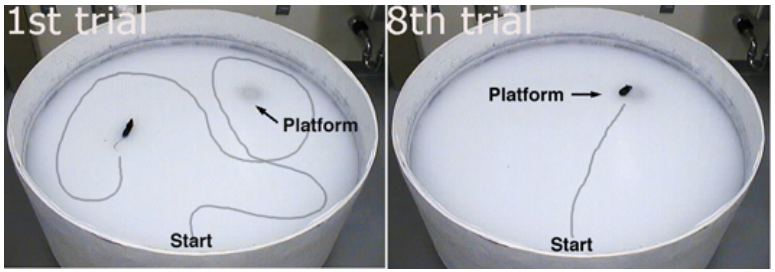


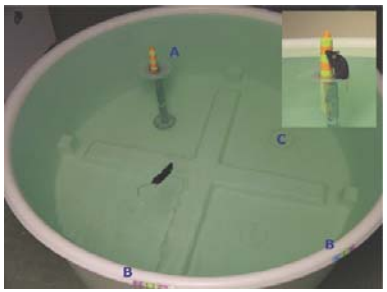
Ce inactivation

Amygdala modulation of memory

- Hippocampal dependent learning: spatial
- Striatum dependent-learning: cue-related

Morris water maze





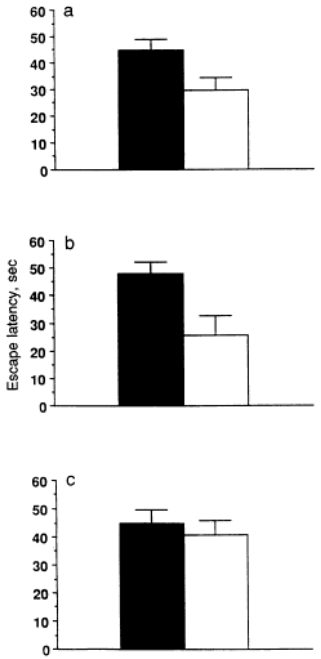


FIG. 1. Mean (±SE) escape latencies of *d*-amphetamine (10 μg) (□) and saline-treated (■) rats on the retention test trial in the spatial task. (*a*) Hippocampal injections. (*b*) Amygdala injections. (*c*) Caudate nucleus injections.

posttraining intracaudate and intrahippocampal injections of *d*-amphetamine on retention of cued and spatial learning in

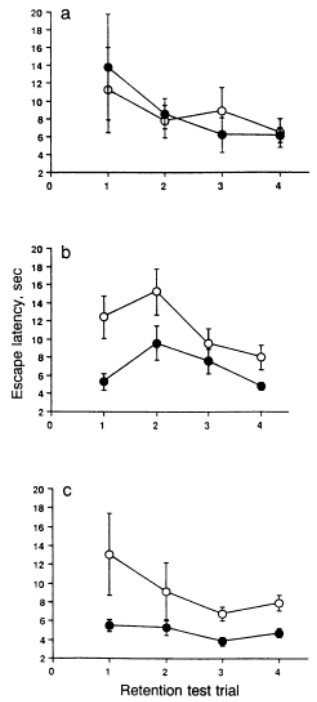


FIG. 2. Mean (±SE) escape latencies of *d*-amphetamine (10 μg) (●) and saline-treated (○) rats on the retention test trial in the cued task. (*a*) Hippocampal injections. (*b*) Amygdala injections. (*c*) Caudate nucleus injections.

Injection of d-amphetamine into the Amygdala affects both if right after training, but not if pre-testing

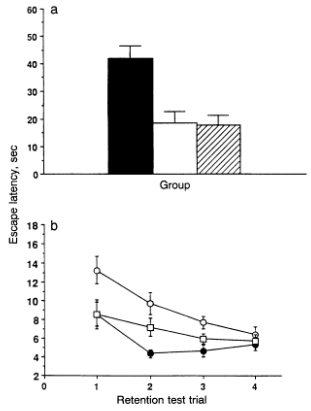


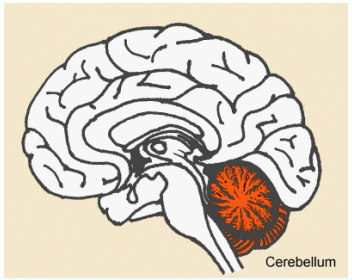
FIG. 3. Mean (±SE) escape latencies of rats receiving intraamygdala posttraining *d*-amphetamine or saline and rats receiving preretention test lidocaine or saline on the retention test trial(s) in the spatial task (*a*) and cued task (*b*). Posttraining/preretention: ■ (*a*) and ○ (*b*), saline/saline; □ (*a*) and ● (*b*), *d*-amphetamine/saline; ▨ (*a*) and □ (*b*), *d*-amphetamine/lidocaine.

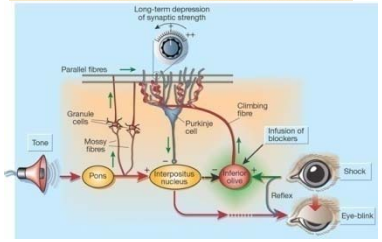
Packard, Mcgaugh

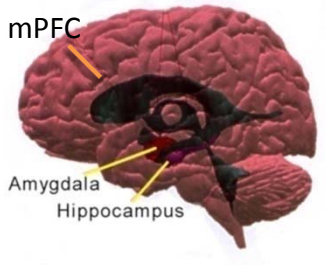
So, does it encode the memory or just modulates it?

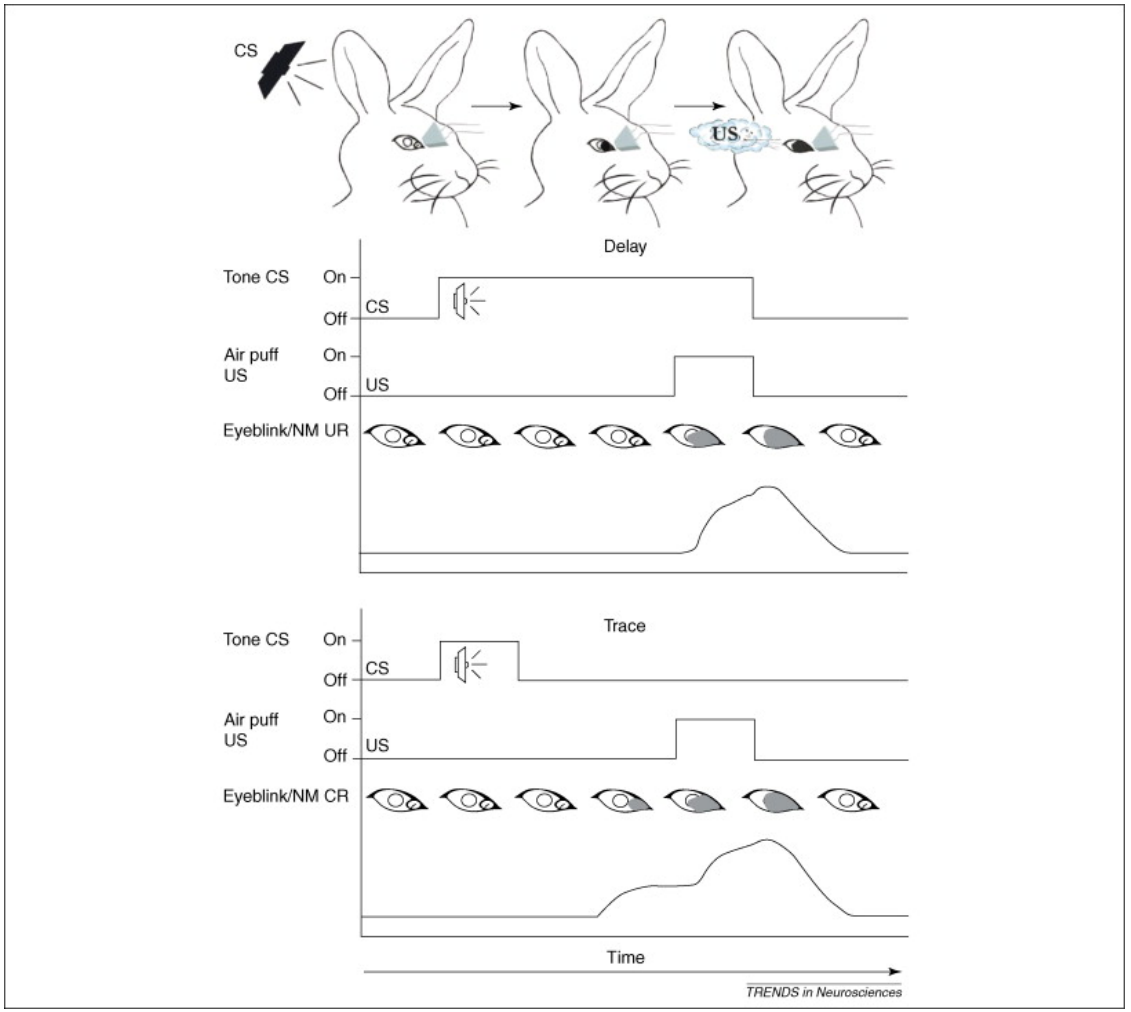
- **It depends.**

Eyelid (blink) reflex conditioning



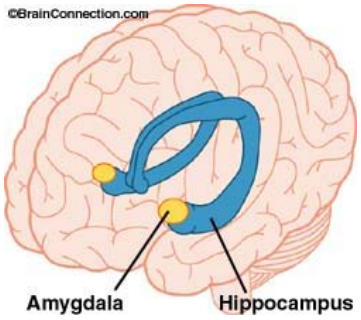


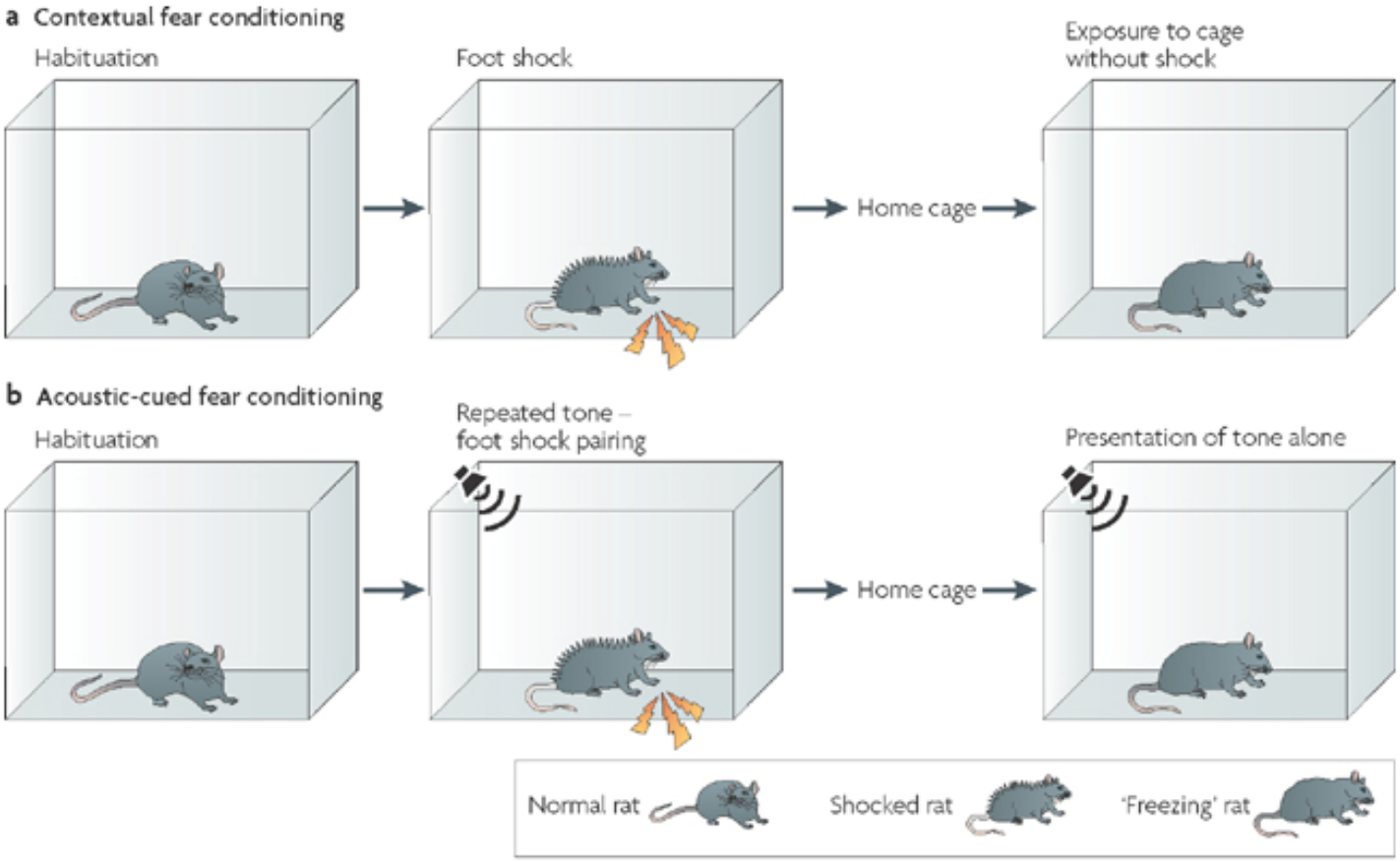




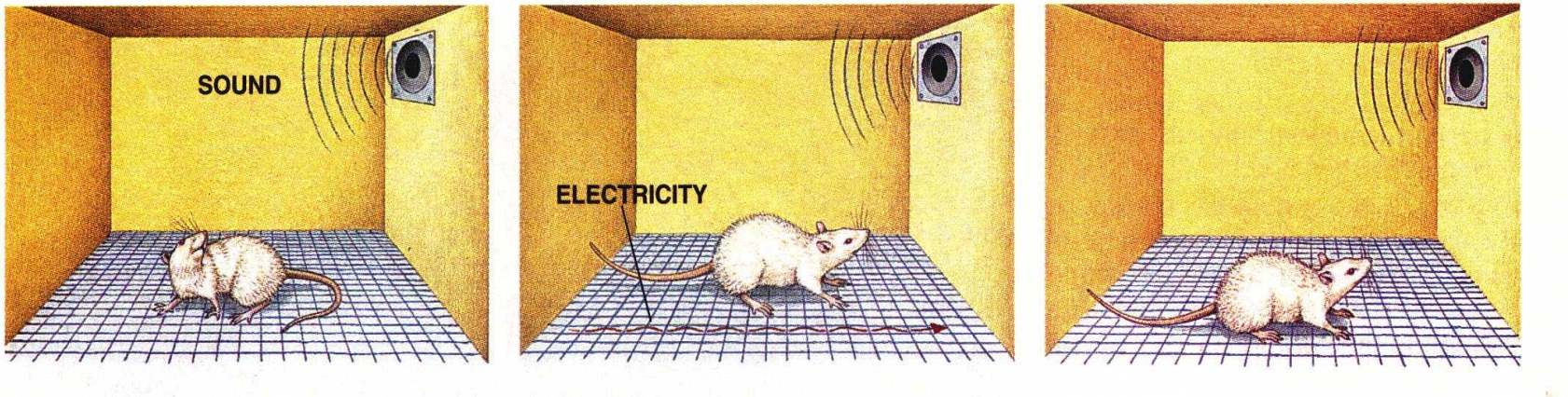
- Why is trace hippocampal-dependent?
- Maintaining the CS? Timing the trace? Harder?
- Eyelid requires ~0.3sec, and hippocampus is required when 0.5-1sec.
- In tone-shock, trace can be 3sec, and hippocampus is required for ~20sec
- This suggest context-conditioning

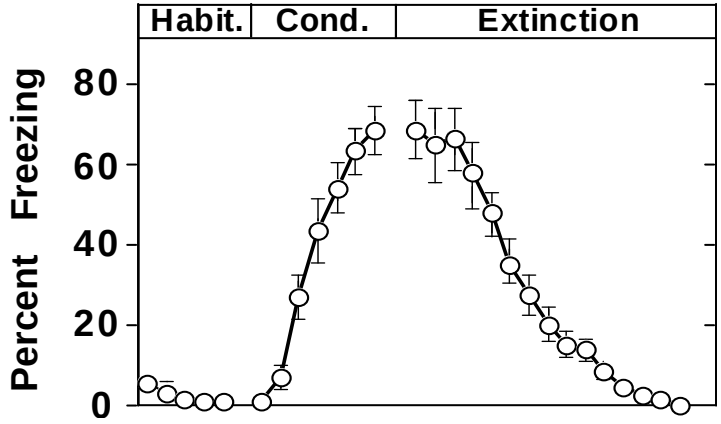
Contextual fear



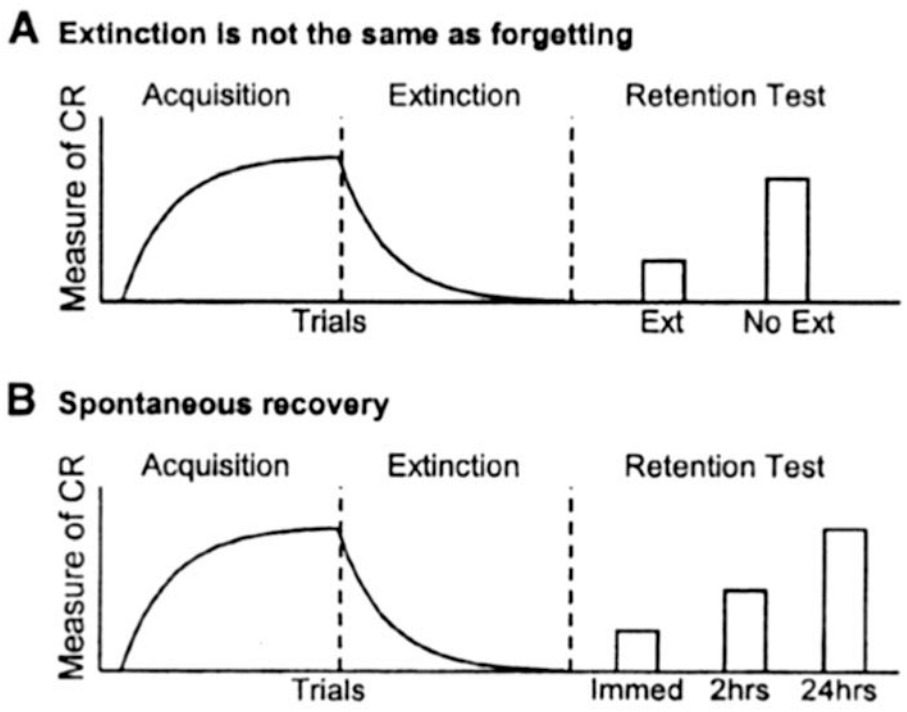


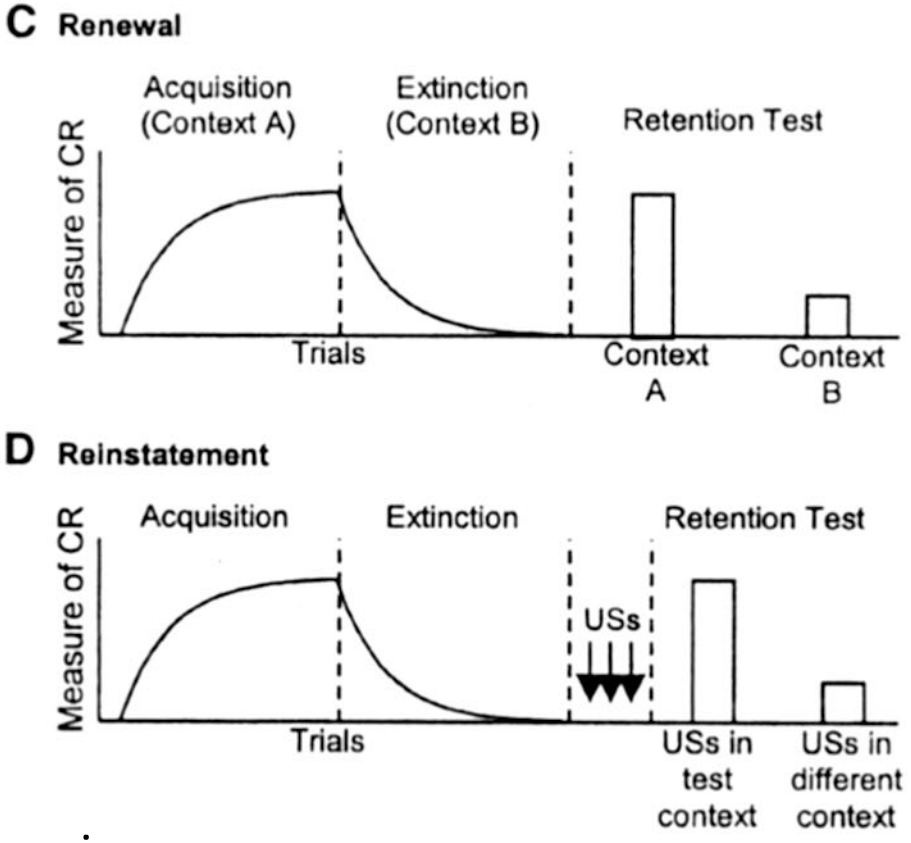
Extinction of fear-conditioning





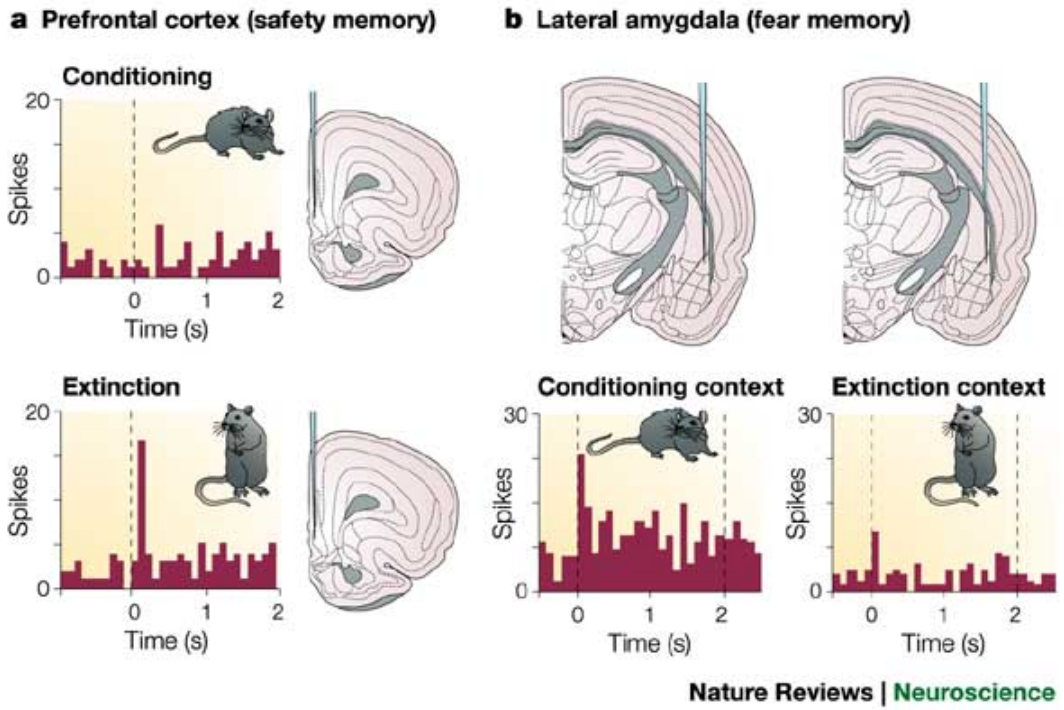
Extinction: a new learning

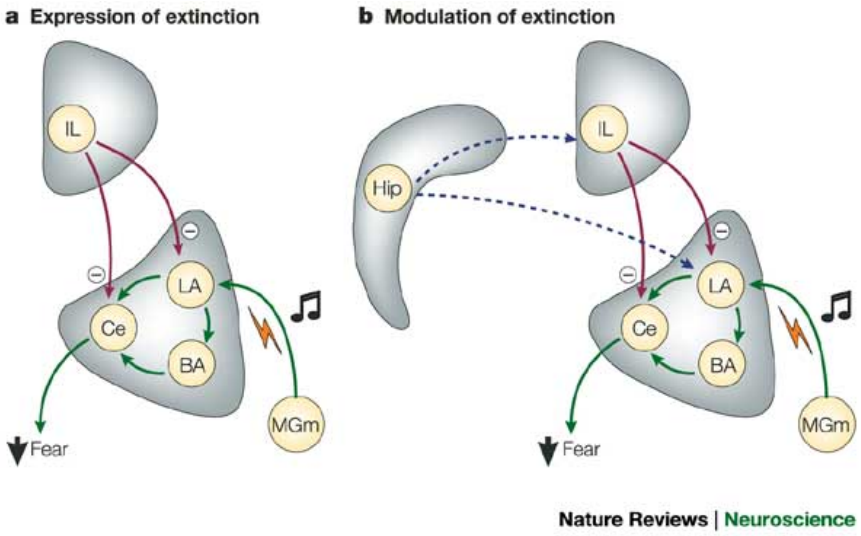


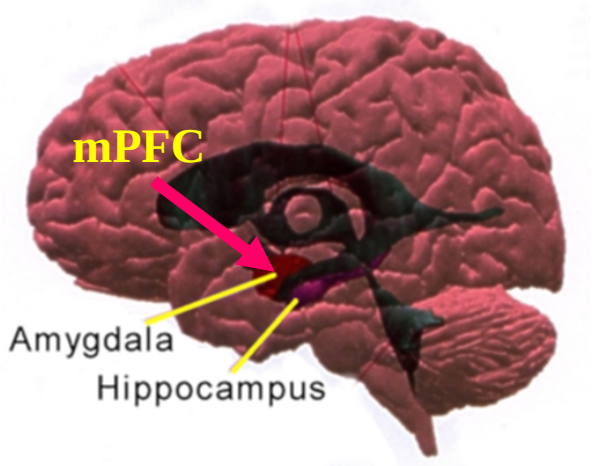


Faster re-learning

Extinction: brain mechanisms

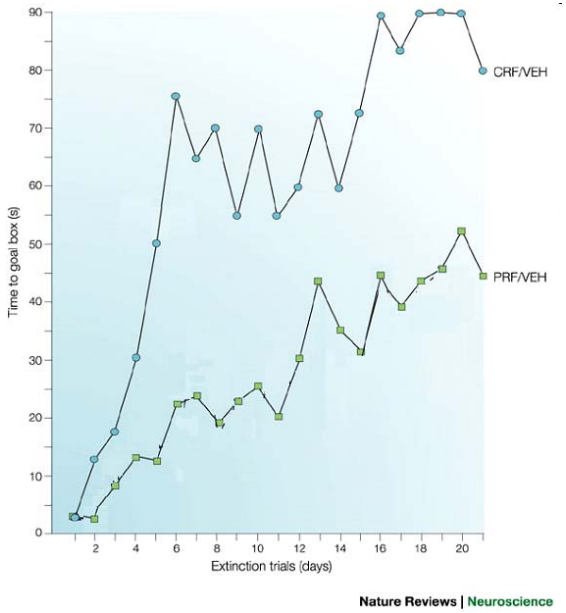






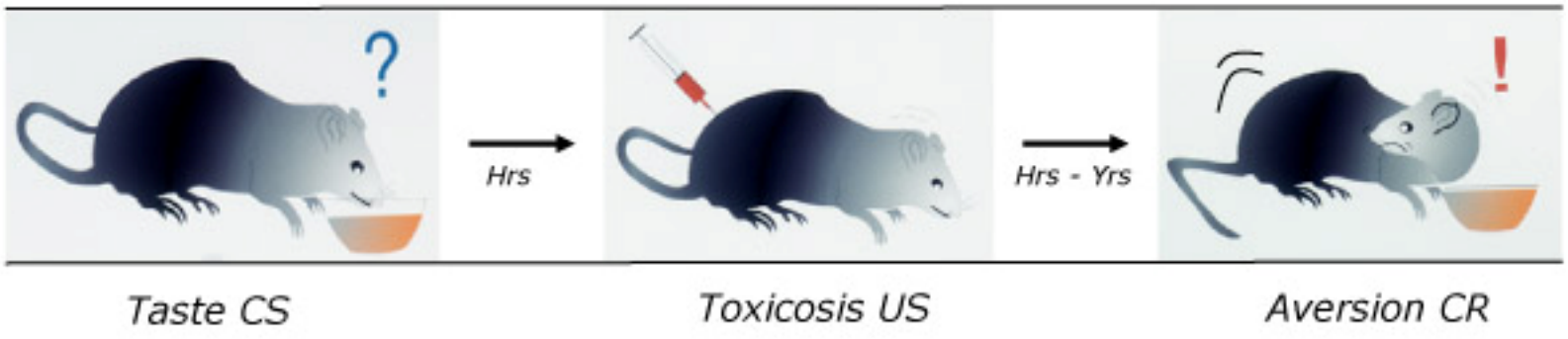
Partial reinforcement extinction effect

- Partial reinforcement
  - Fixed/variable ratio
  - Fixed/variable schedule
- Results in longer extinction learning
- Why?
  - Frustration theory (Amsel): The omission of the US induces frustration. Therefore, during extinction, the frustration predicts the US.
  - Sequential theory (Capaldi): conditioning to strings of NNNRNNNR
- Bad for behavior flexibility
- Good for education

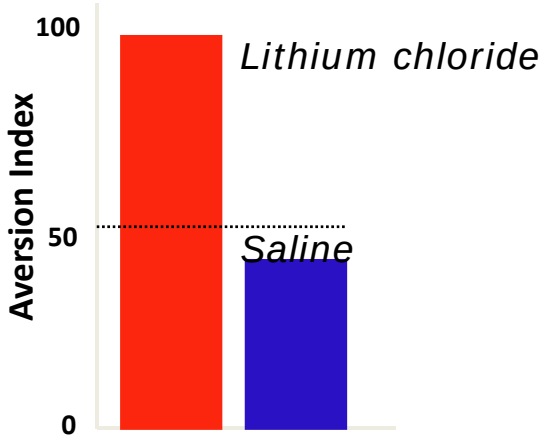


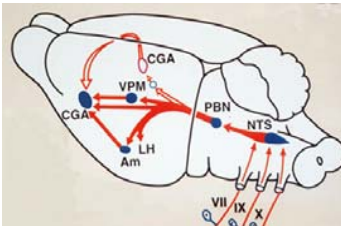
Garcia J

Conditioned Taste Aversion



- One-trial learning
- Long-delay learning (few hours)
  - A [lack of] interference effect?
  - Still a problem for neuroscientists
- Hedonic shift: changes the CS, not its predictions

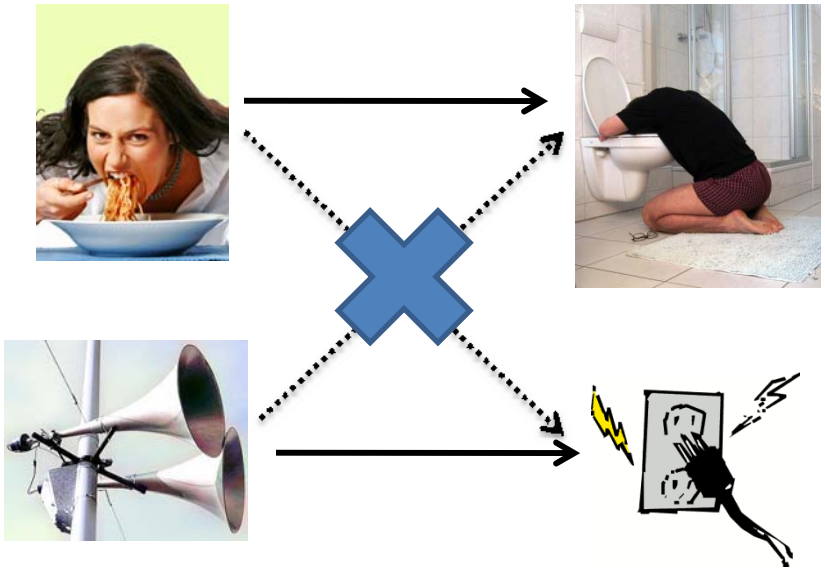




CTA

- Compound potentiation: odor + taste increase response to odor

- Preparedness:



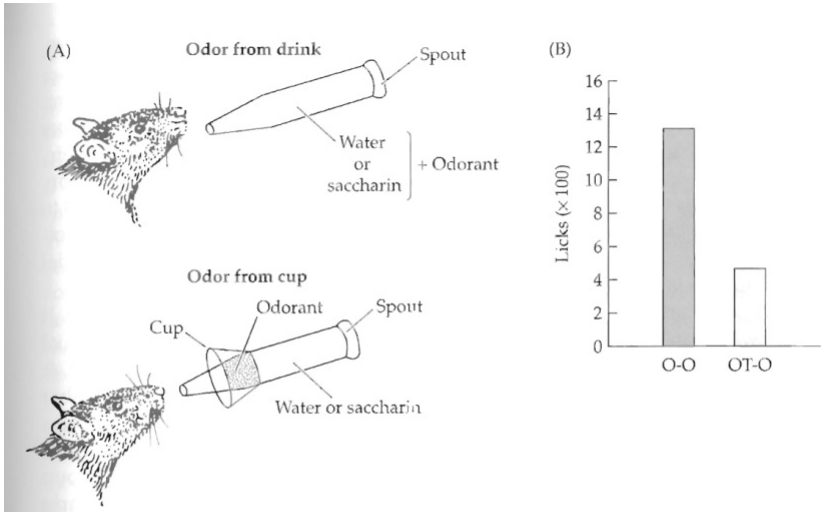
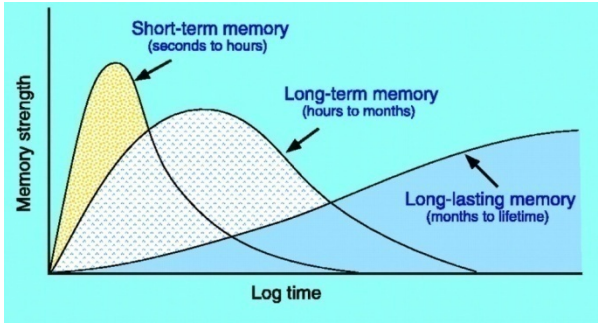
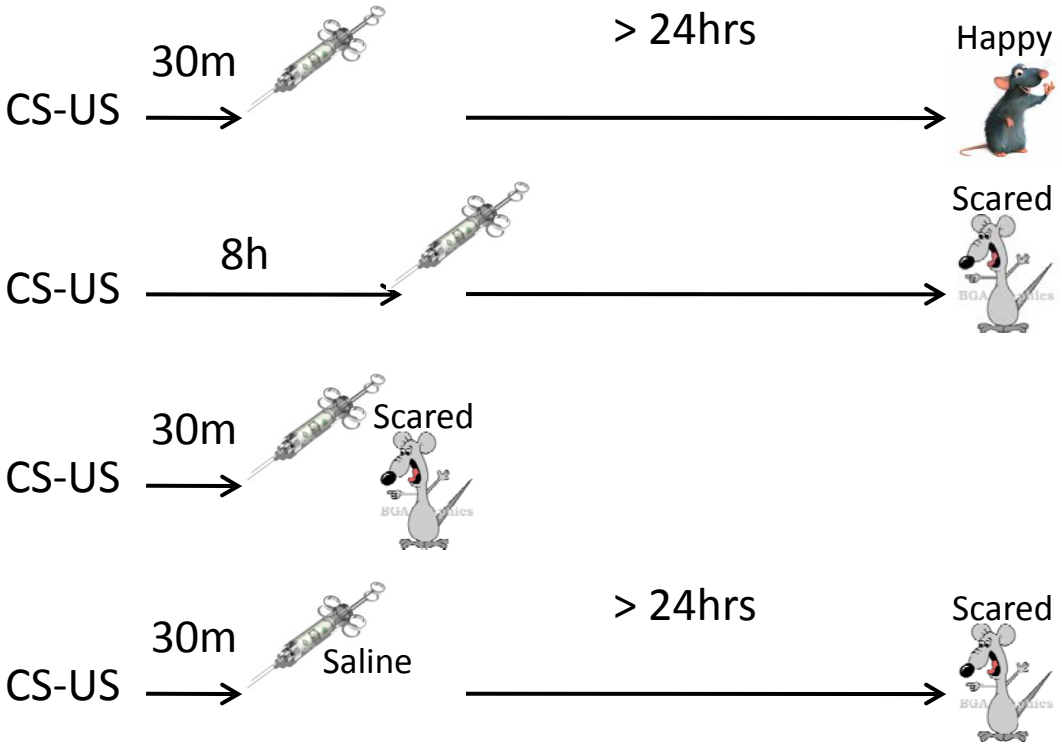


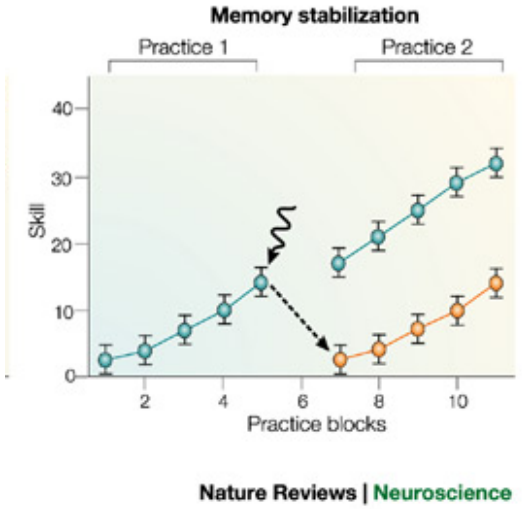
Figure 6.5 Potentiation of odor conditioning by taste. (A) A rat is given a taste in drinking water that also contains an odor. (In many experiments, the odor comes from a cup near the spout instead of being mixed in the drink.) (B) When odor is paired with illness on its own and then tested (O-O), it does not suppress consumption much. But if it has been combined with a taste on the conditioning trial (OT-O), strong odor conditioning is obtained. (A, after Inui, Shimura, & Yamamoto, 2006; B, after Palmerino et al., 1980.)

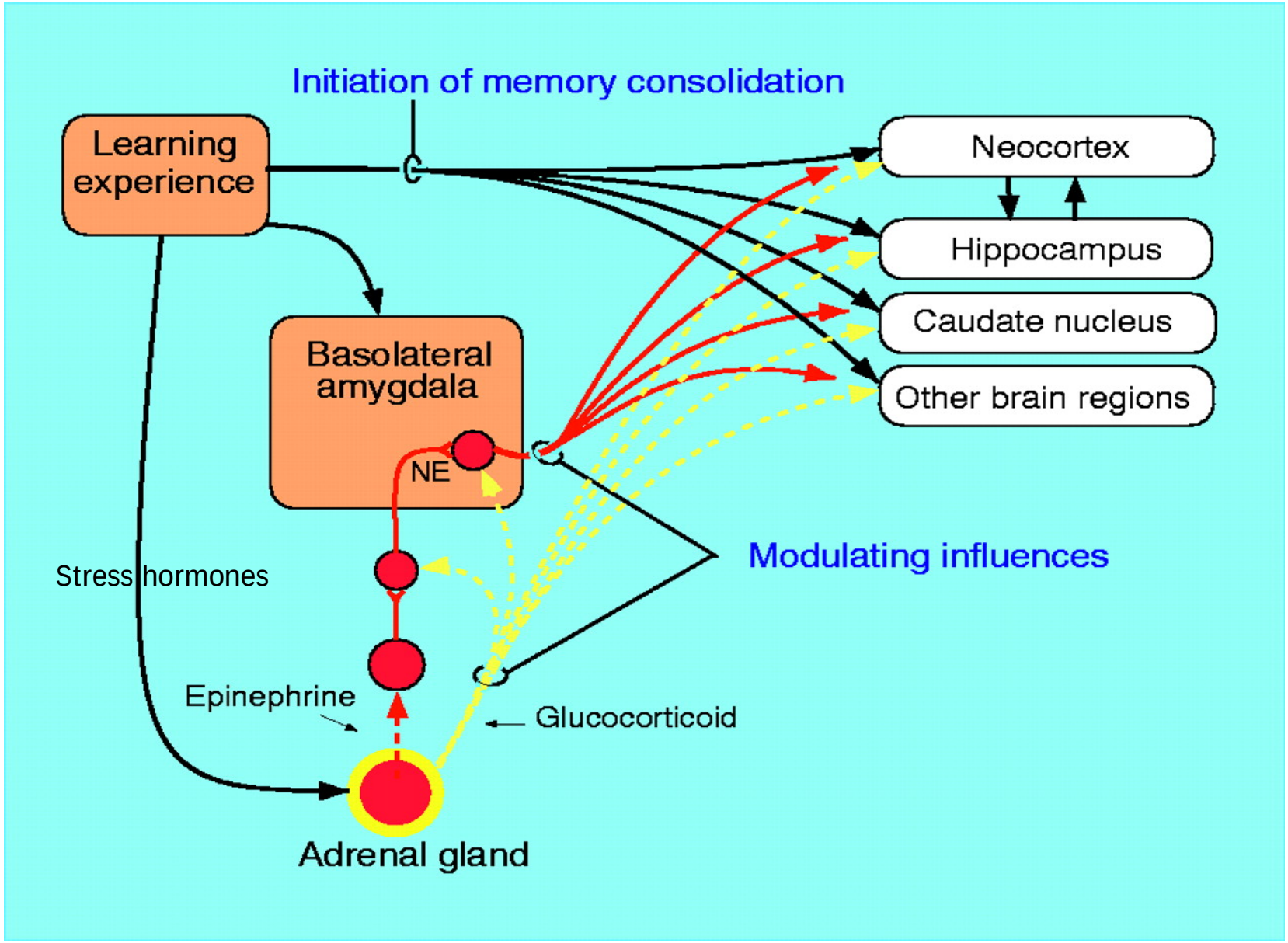
Consolidation

- Anisomycin, a protein synthesis inhibitor, into the Basolateral complex of the amygdala (BLA)
  - No effect on short-term-memory
  - No effect after XX time (rule of thumb is 6hrs)
  - But harms long-term memory below that.





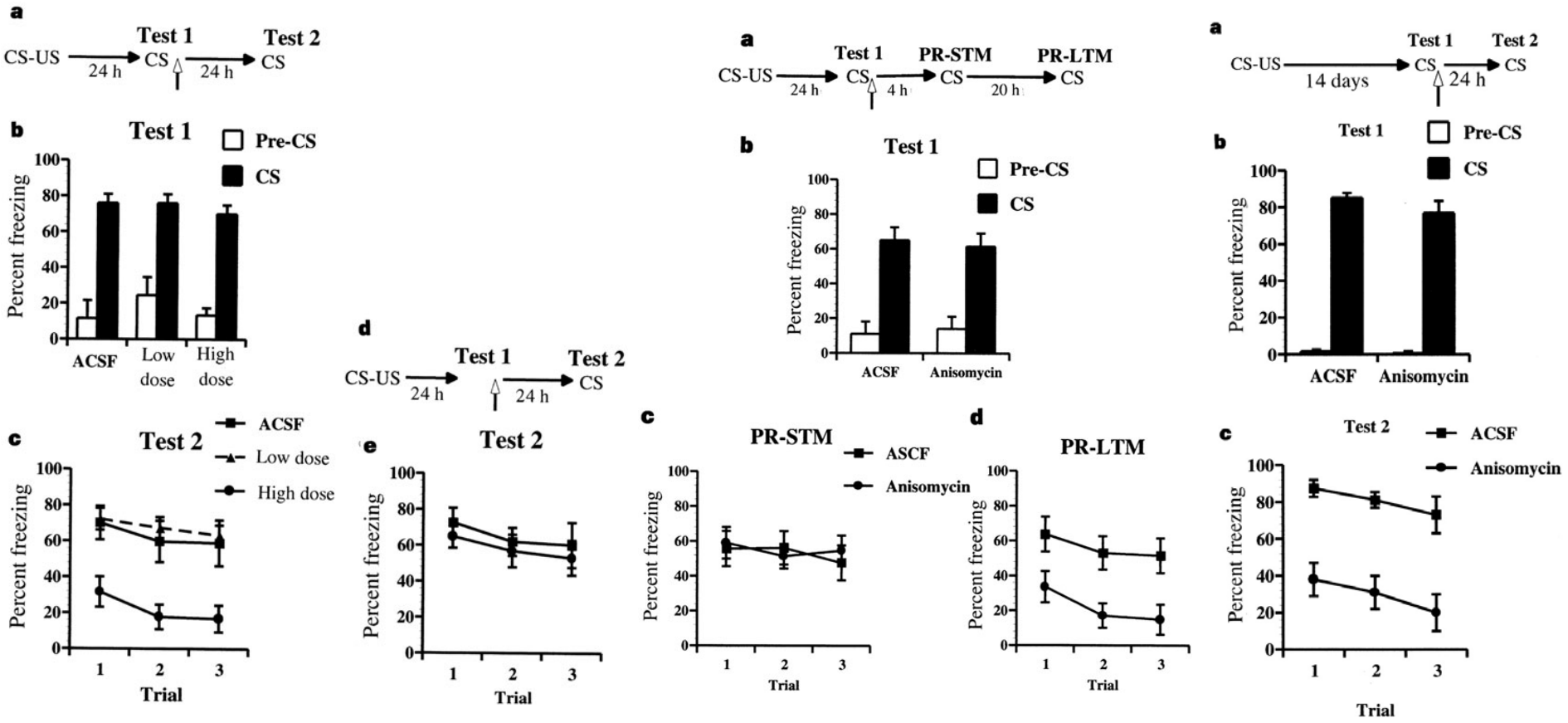




Mcgaugh JL, science, 2000

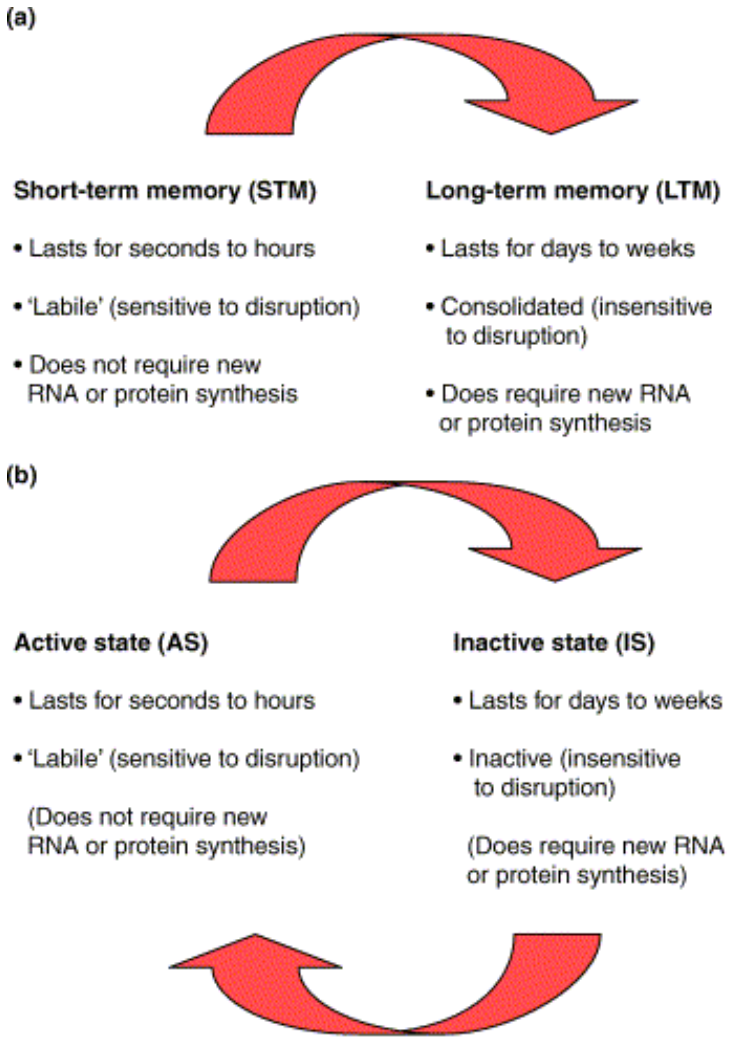
Reconsolidation

No effect on STM



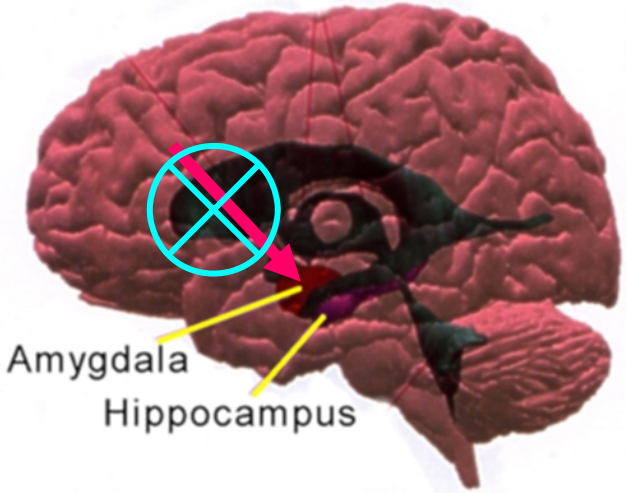
Nader, Ledoux, Nature 2000

An updated view of memories



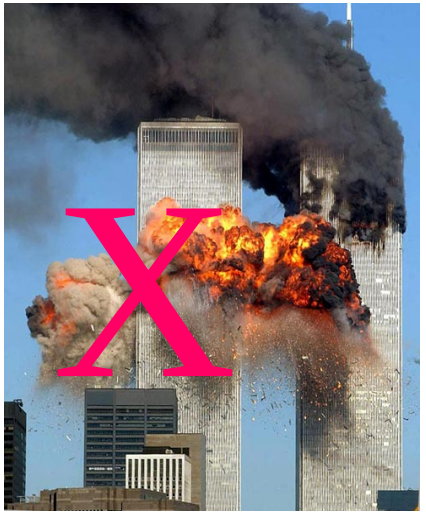
PTSD (post-traumatic-stress-disorder)

- Extinction failure



Reconsolidation and extinction: What Freud always knew

.....



Context Generalization / specificity

Stay safe, be fearless