Behavioral Neuroscience: Fear thou not

Pavlovian conditioning, an enduring model of associative learning

Thoughts

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

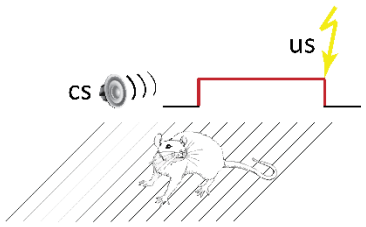
	Decreases behavior	Increases behavior
Presented	Positive punishment	Positive reinforcer
Taken away	Negative punishment	Negative reinforcer

Classical fear conditioning

A

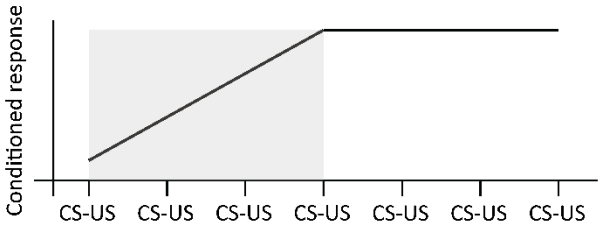
Acquisition in wake animals

Behavioral setup



Behavioral paradigm

Behavioral result

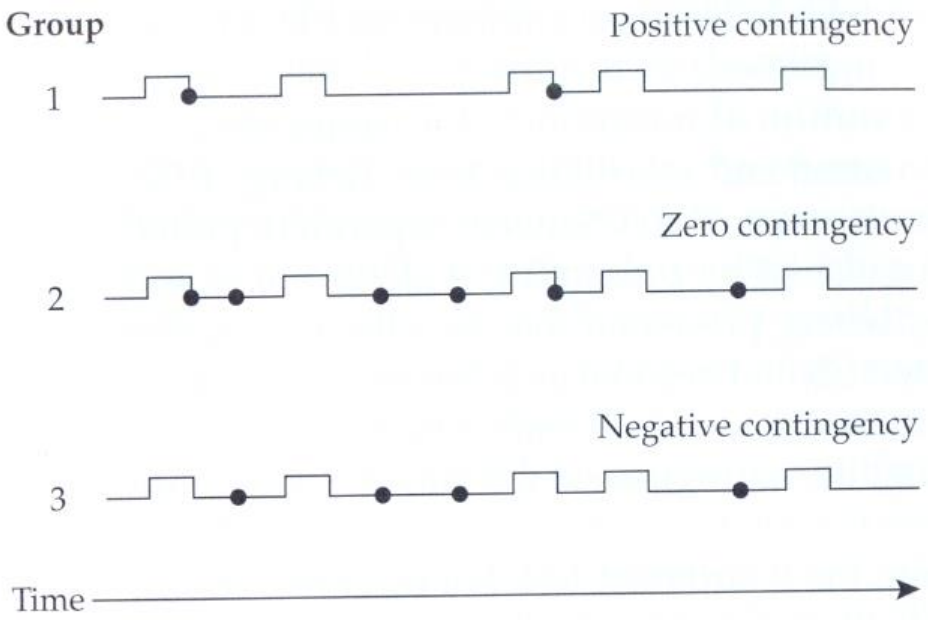


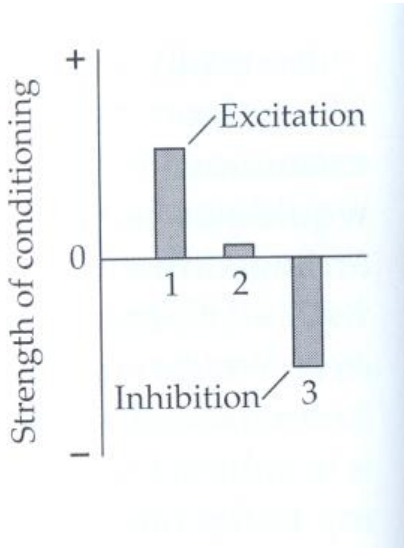
CS-US pairing
Tone = conditioned stimulus (CS)
Foot-shock = unconditioned stimulus (US)
Freezing = conditioned response (CR-UR)

The CS predicts the US → CR

Samuel et al., 2018

Contingency: co-occurrence

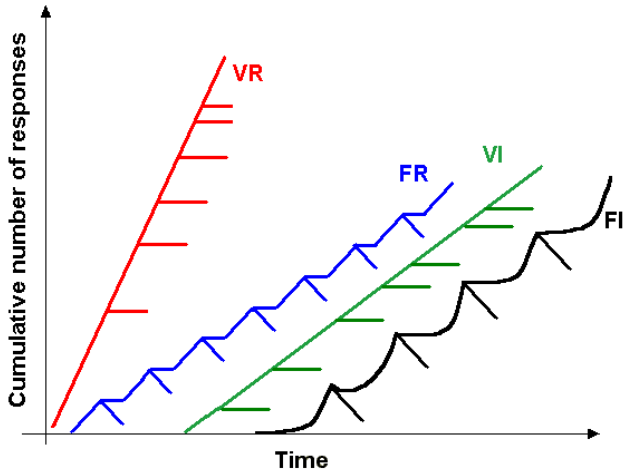




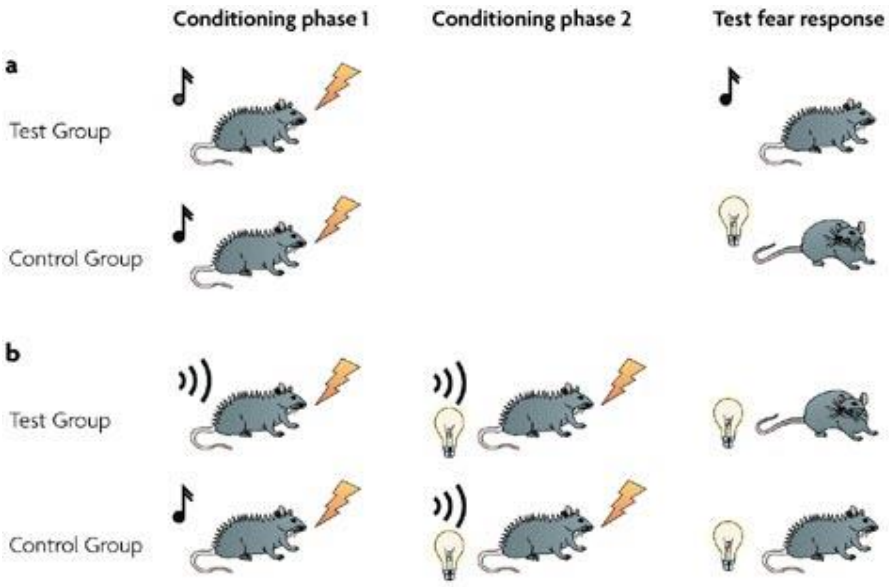
Schedules of reinforcement:
Variable/fixed interval/ratio

Variable-ratio - number of responses needed for a reward varies

Variable-interval - the subject gets the reinforcement based on varying and unpredictable amounts of time



More than contingency: Surprise / added information



Aversive conditioning

Tone + Shock = CR
Tone + Light = No CR
Tone = predictor

Blocking

No CR to light → the outcome is already well predicted

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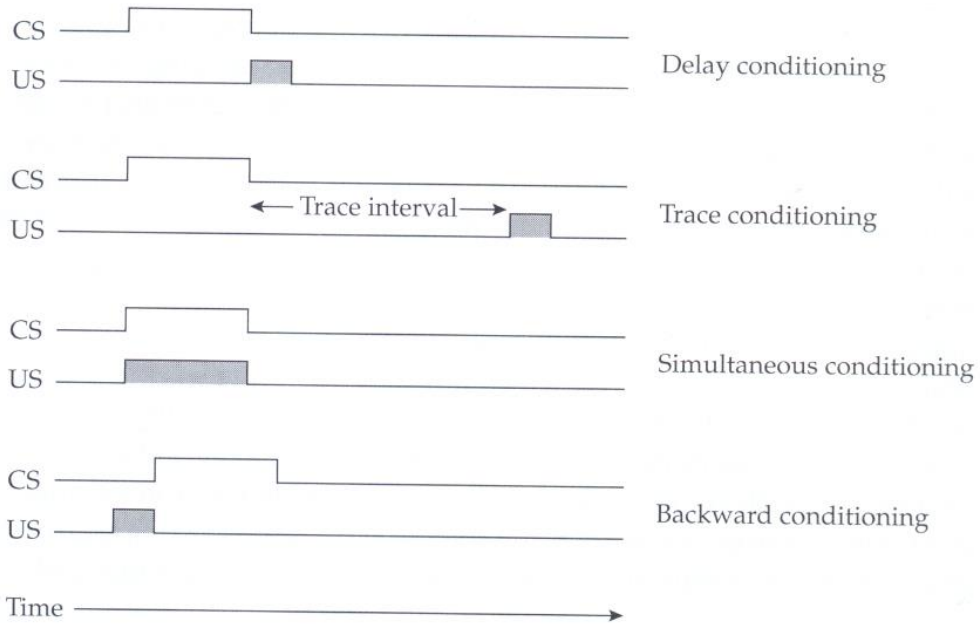
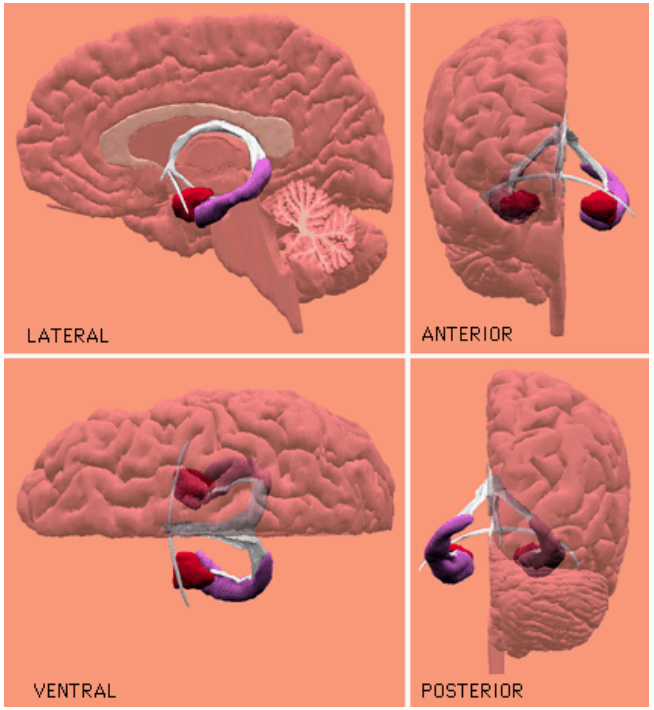
Rules of thumb for conditioning strength



- 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

Amygdala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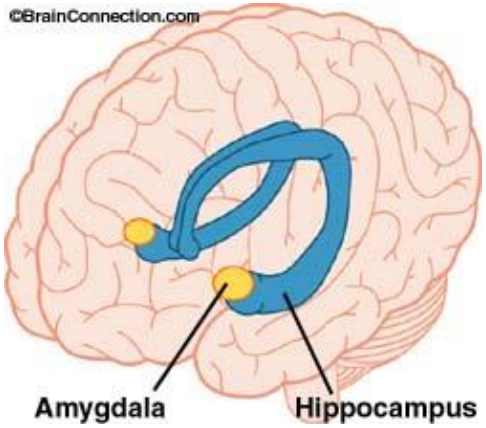
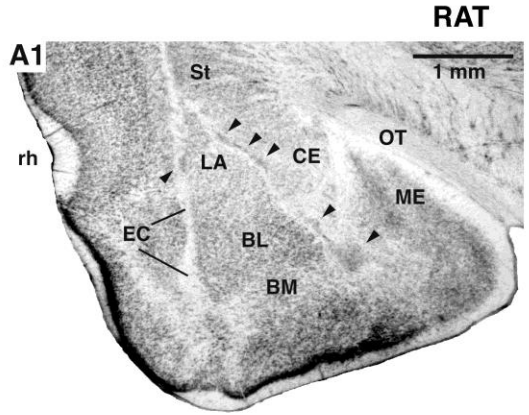
ANTERIOR
VENTRAL
POSTERIOR


©BrainConnection.com
Amygdala
Hippocampus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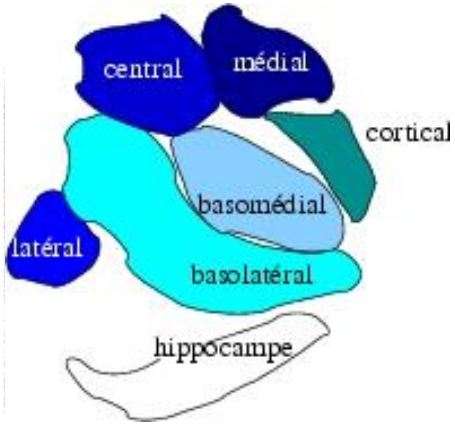
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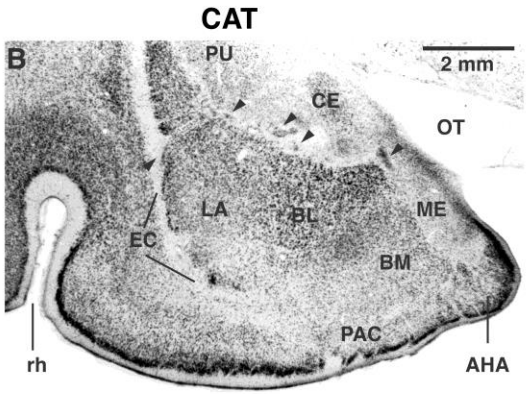
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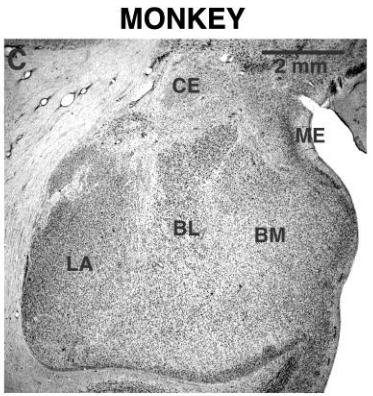
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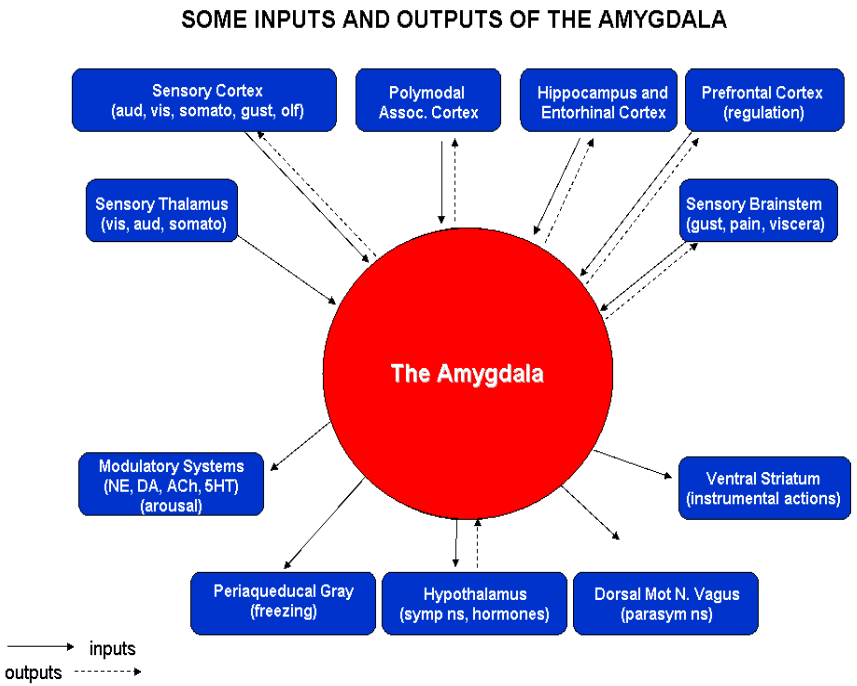
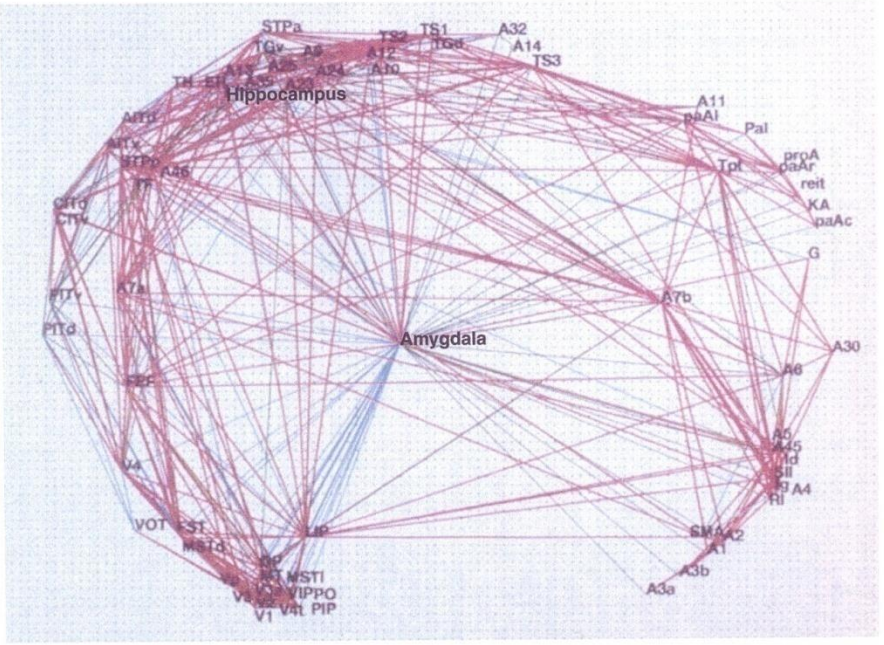
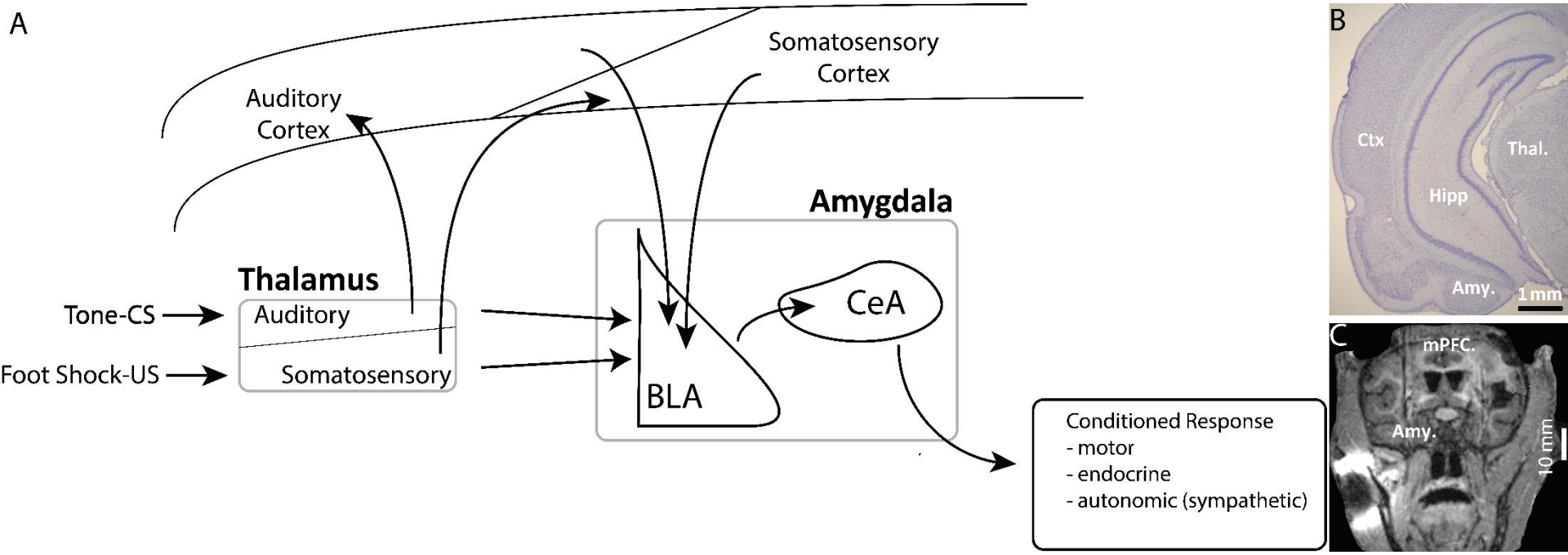
Amygdala and its basolateral complex (BLA)

- BLA evolution parallels that of the prefrontal cortex
- BLA cell types reminiscent of cortex
- Cortical projections are much more extensive in primates



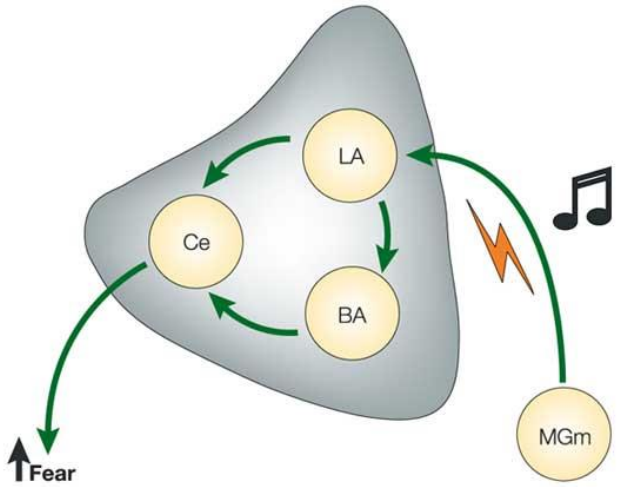


Fear circuit



Samuel et al., 2018

Neurons acquire tone responses after conditioning



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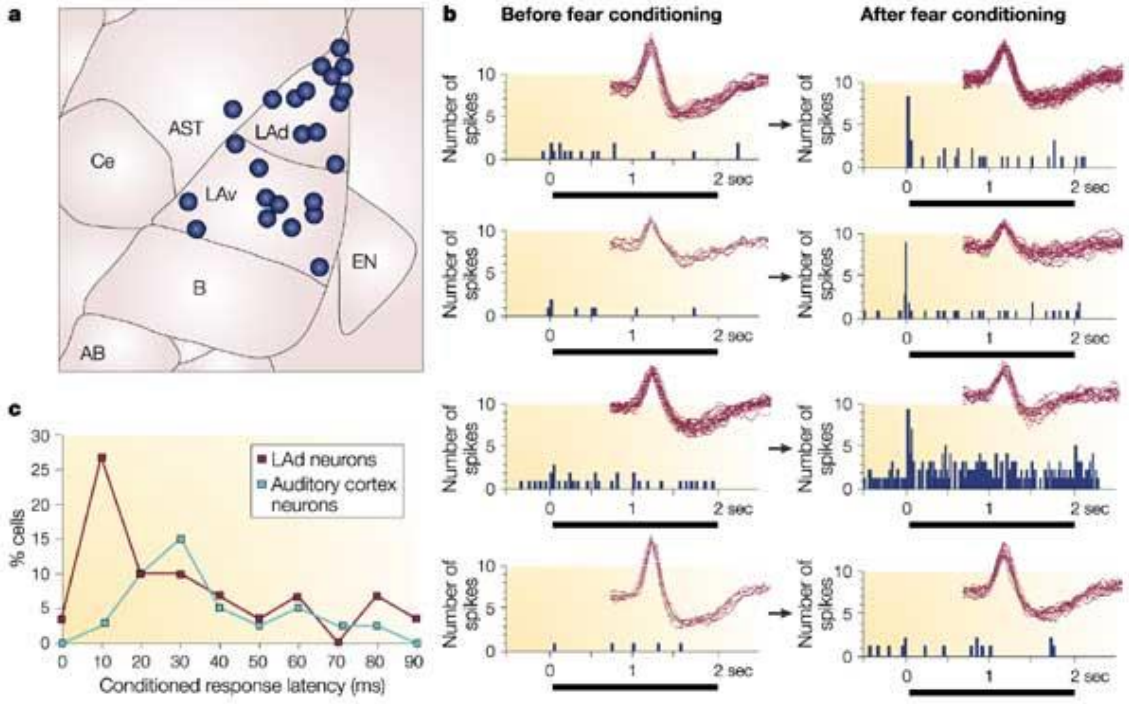

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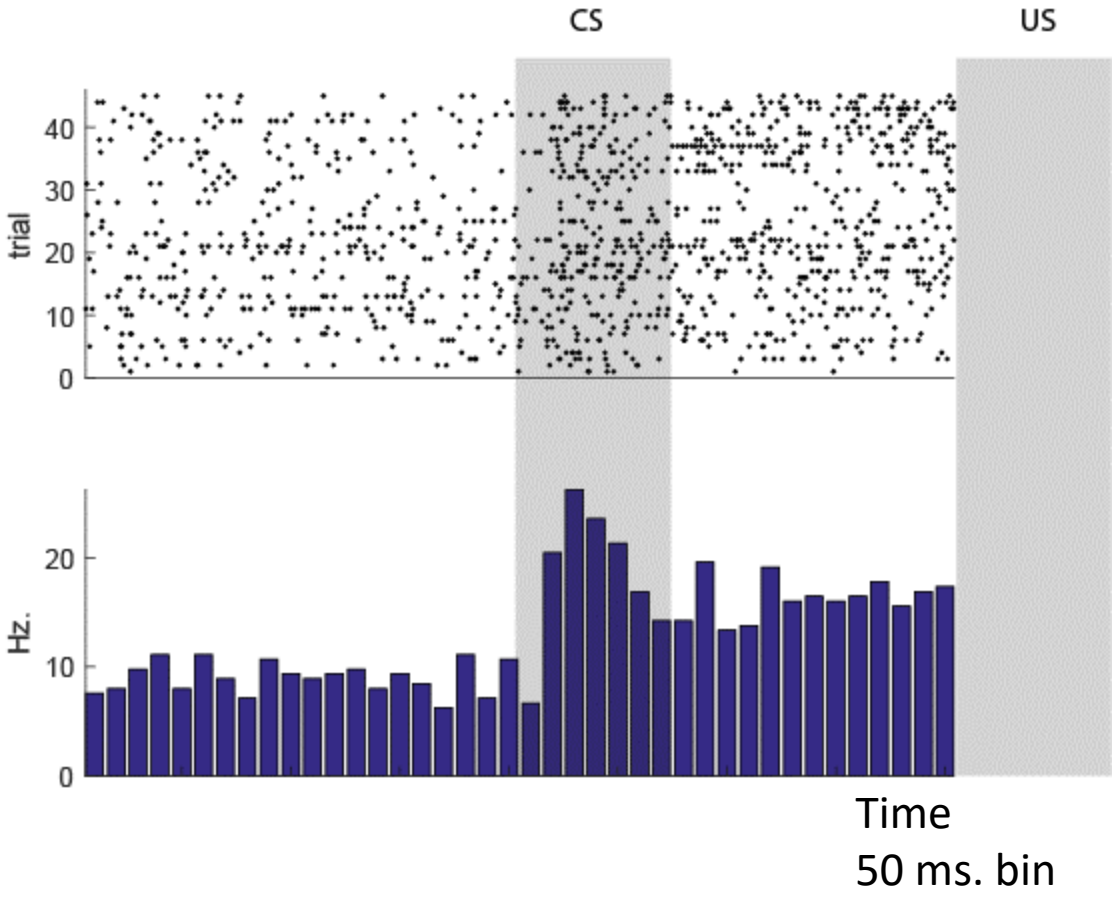
Neurons acquire tone responses after conditioning Primates

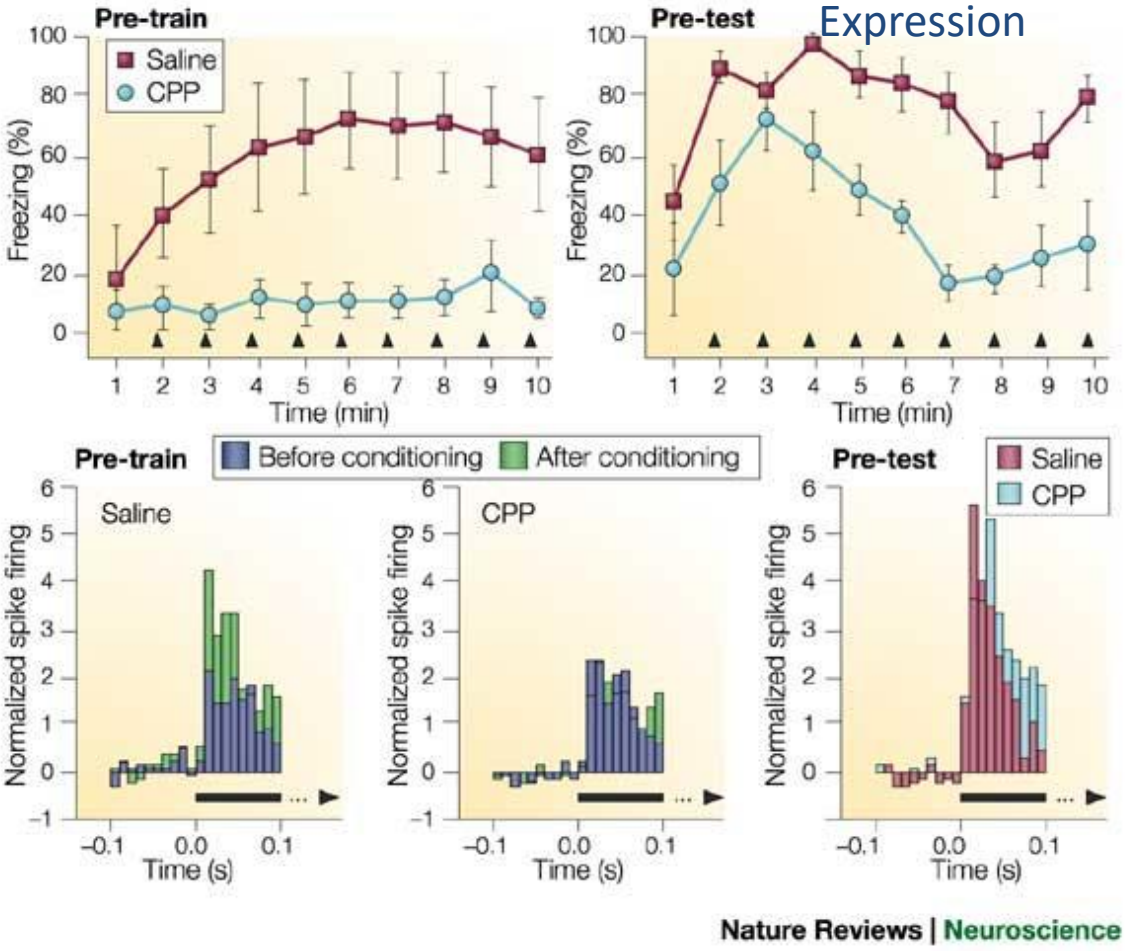
Increased response along trials



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.

Massive effect when injected before learning

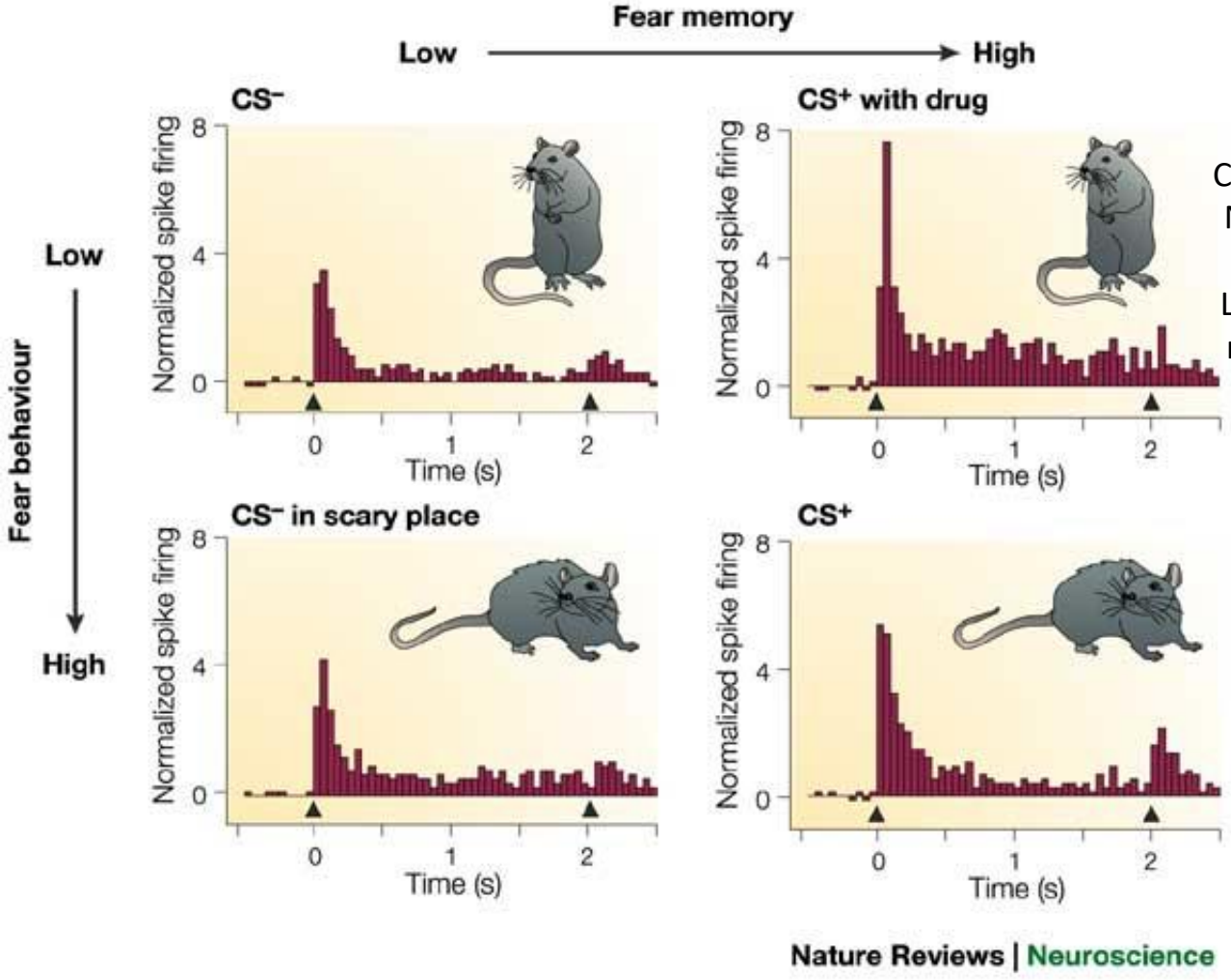


Some effect when injected before retention test

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

Is it fear memory or just fear behavior?

Lateral amygdala encodes memory independent of fear behavior

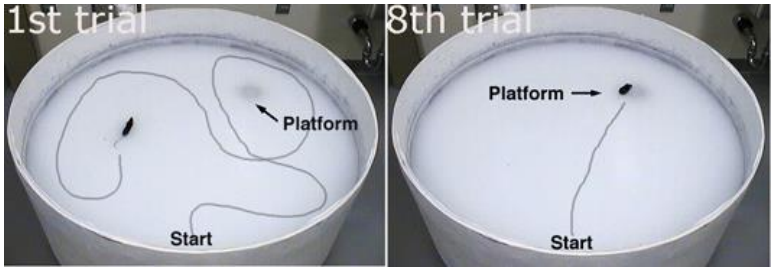


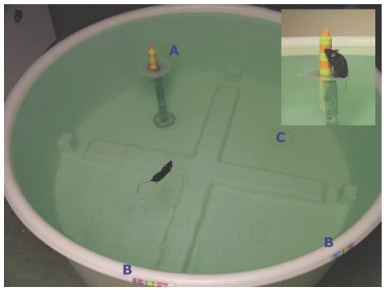
CeM inactivation = No Behavioral CR

LTP in the LA with no behavioral CR

Amygdala modulation of memory

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





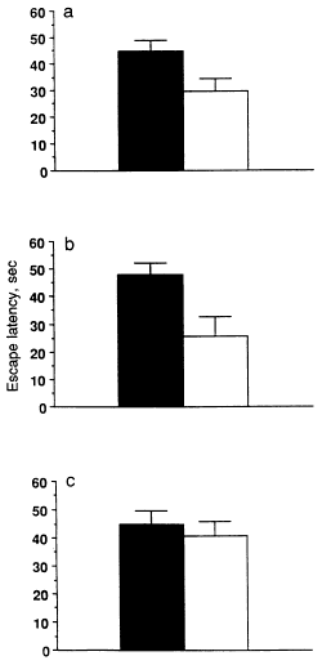


FIG. 1. Mean (±SE) escape latencies of *d*-amphetamine (10 μg) (□) and saline-treated (■) rats on the retention test trial in the spatial task. (*a*) Hippocampal injections. (*b*) Amygdala injections. (*c*) Caudate nucleus injections.

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

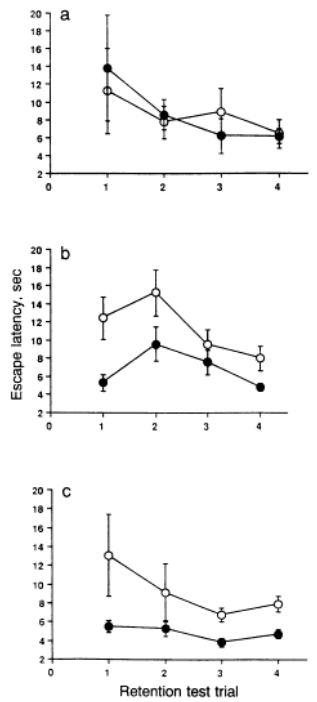
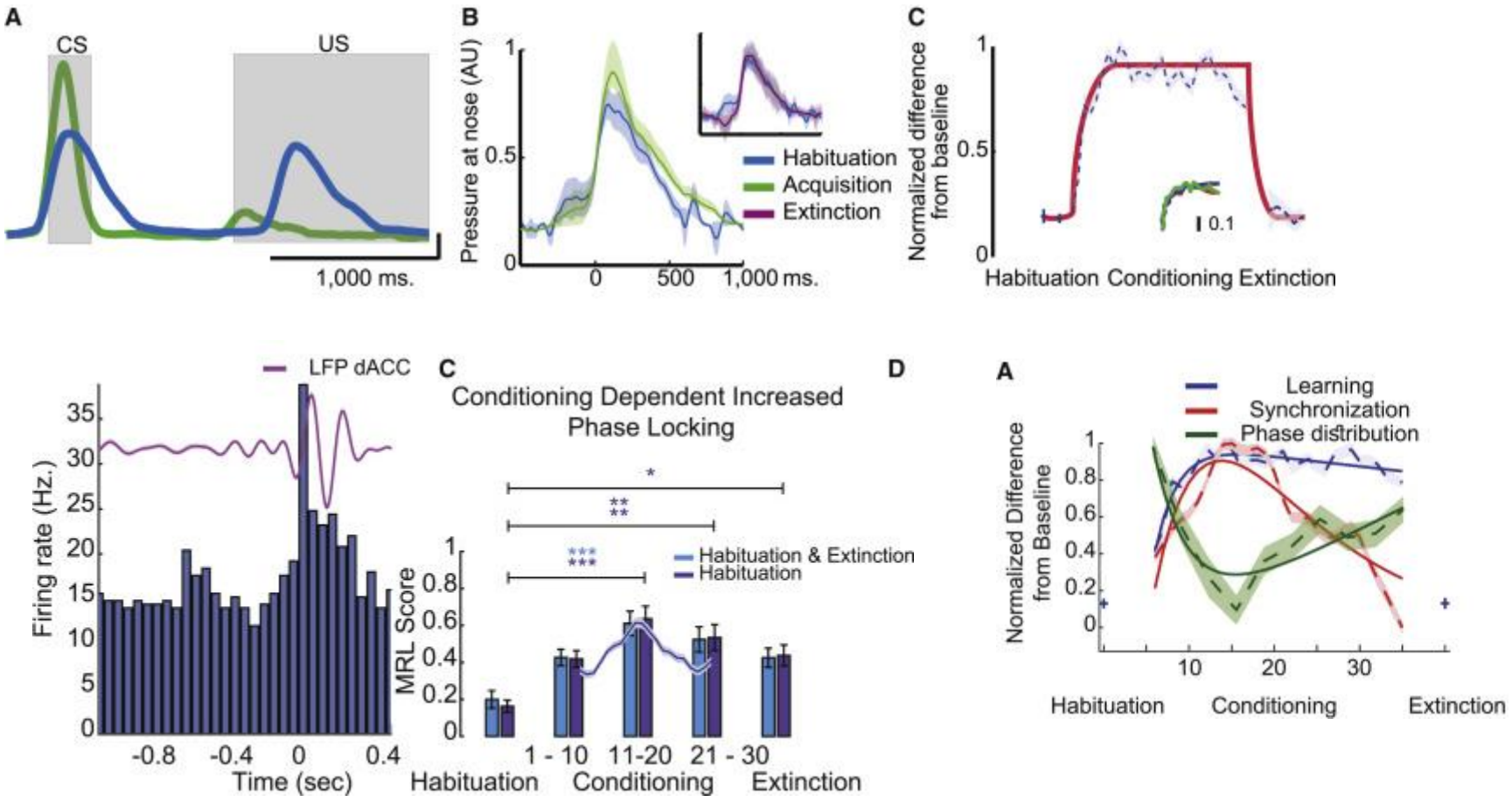


FIG. 2. Mean (±SE) escape latencies of *d*-amphetamine (10 μg) (●) and saline-treated (○) rats on the retention test trial in the cued task. (*a*) Hippocampal injections. (*b*) Amygdala injections. (*c*) Caudate nucleus injections.

Injection of d-amphetamine into the amygdala facilitates hippocampal and striatal learning if right after training, but not if pre-testing

Packard, Mcgaugh

Increased Amygdala-Prefrontal Synchrony during Aversive Learning

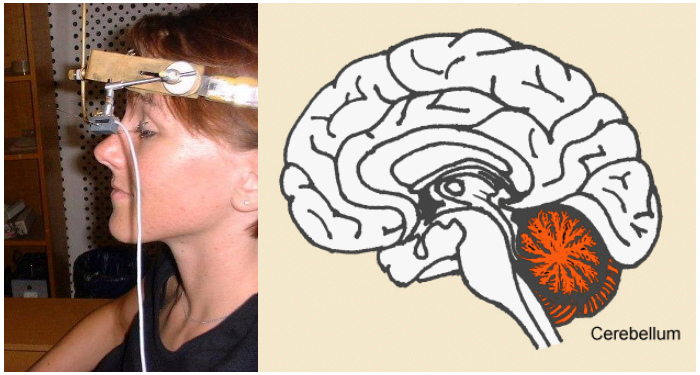


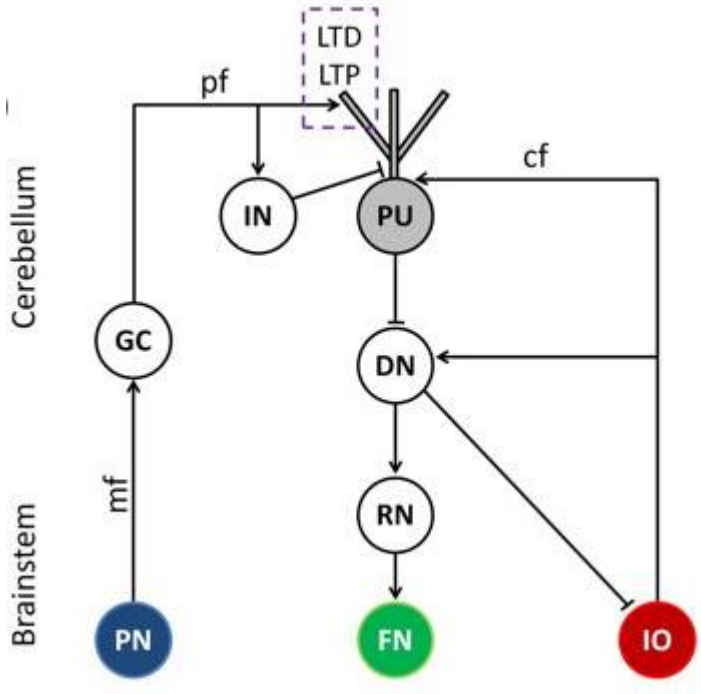
Taub et al., 2017

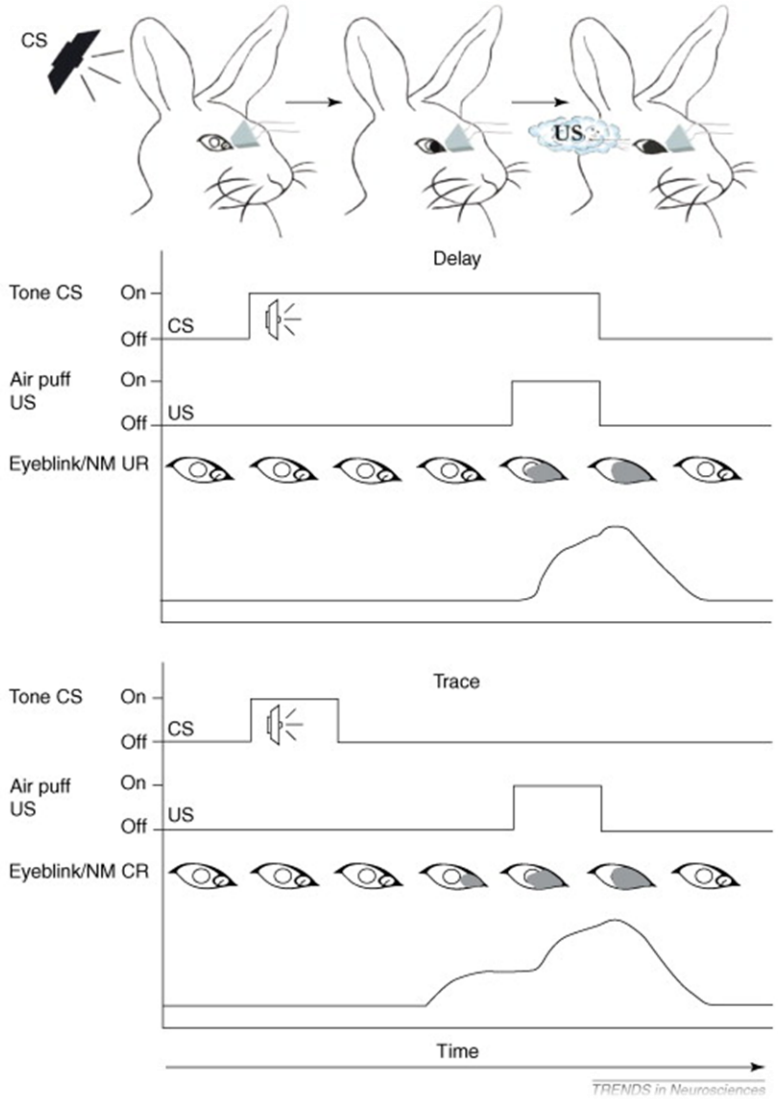
So, does it encode memory or just modulates it?

- **It depends.**

Eyelid (blink) reflex conditioning





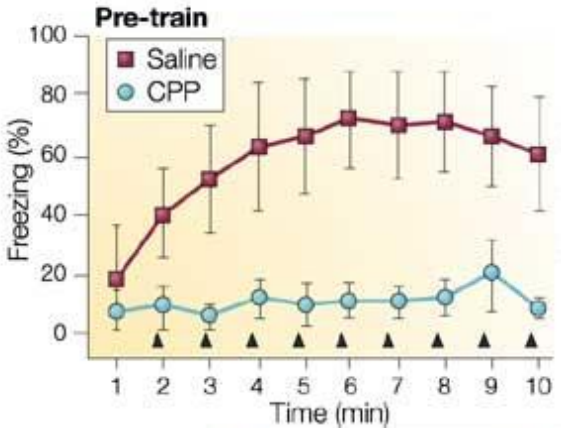


Hogri et al., 2015

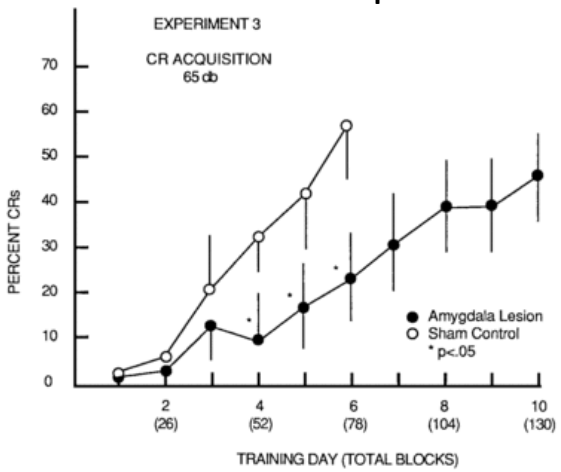
The cerebellum is essential and sufficient for eyeblink conditioning

Amygdala conditioning facilitates cerebellar eye-blink conditioning

Amygdala dependent



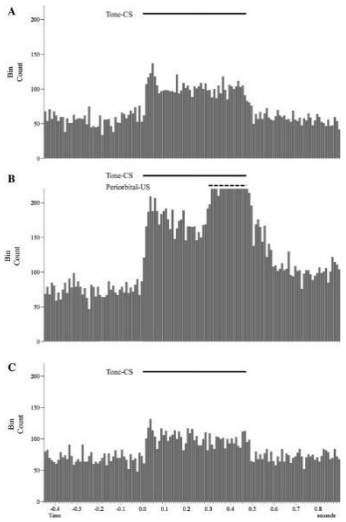
Cerebellum dependent



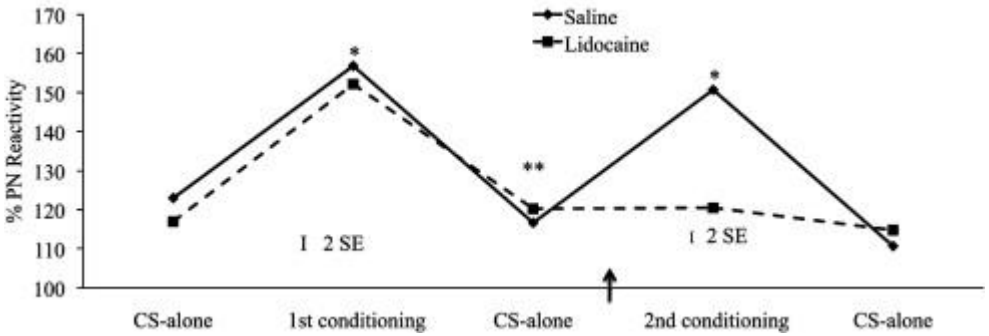
habituation

Conditioning

Extinction



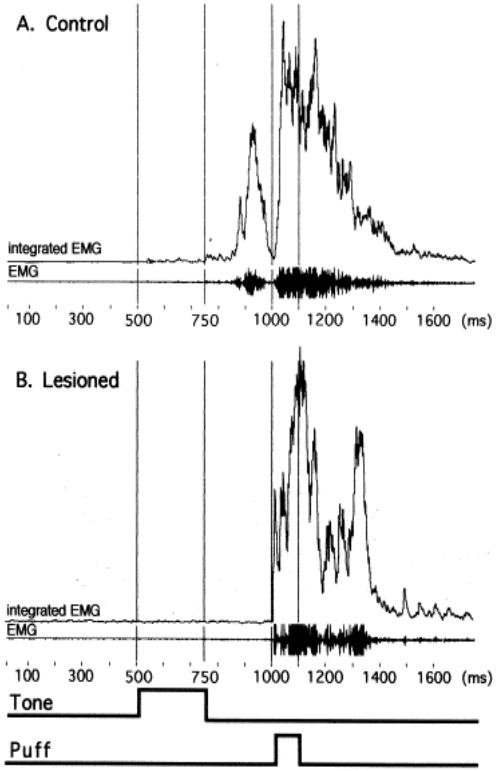
Weisz et al., 1994

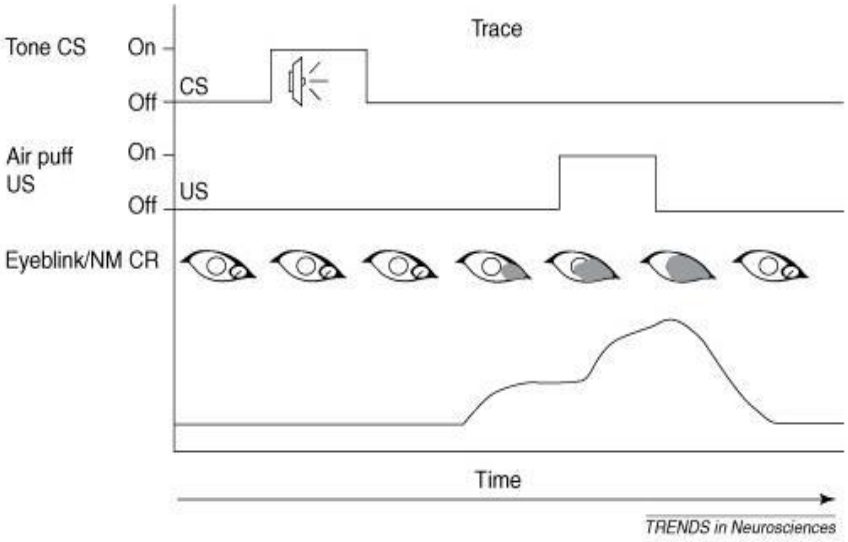


CS facilitation can be abolished by amygdala inactivation

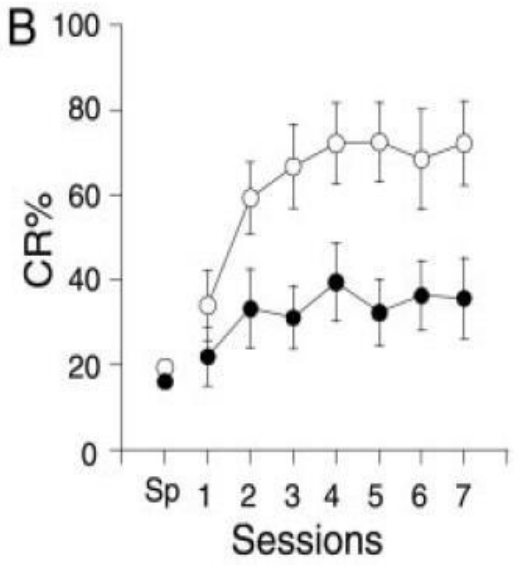
Taub and Mintz, 2010

Eyelid (blink) reflex conditioning – the role of the hippocampus

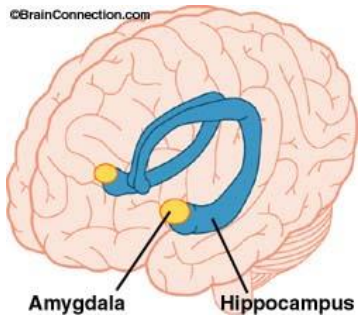


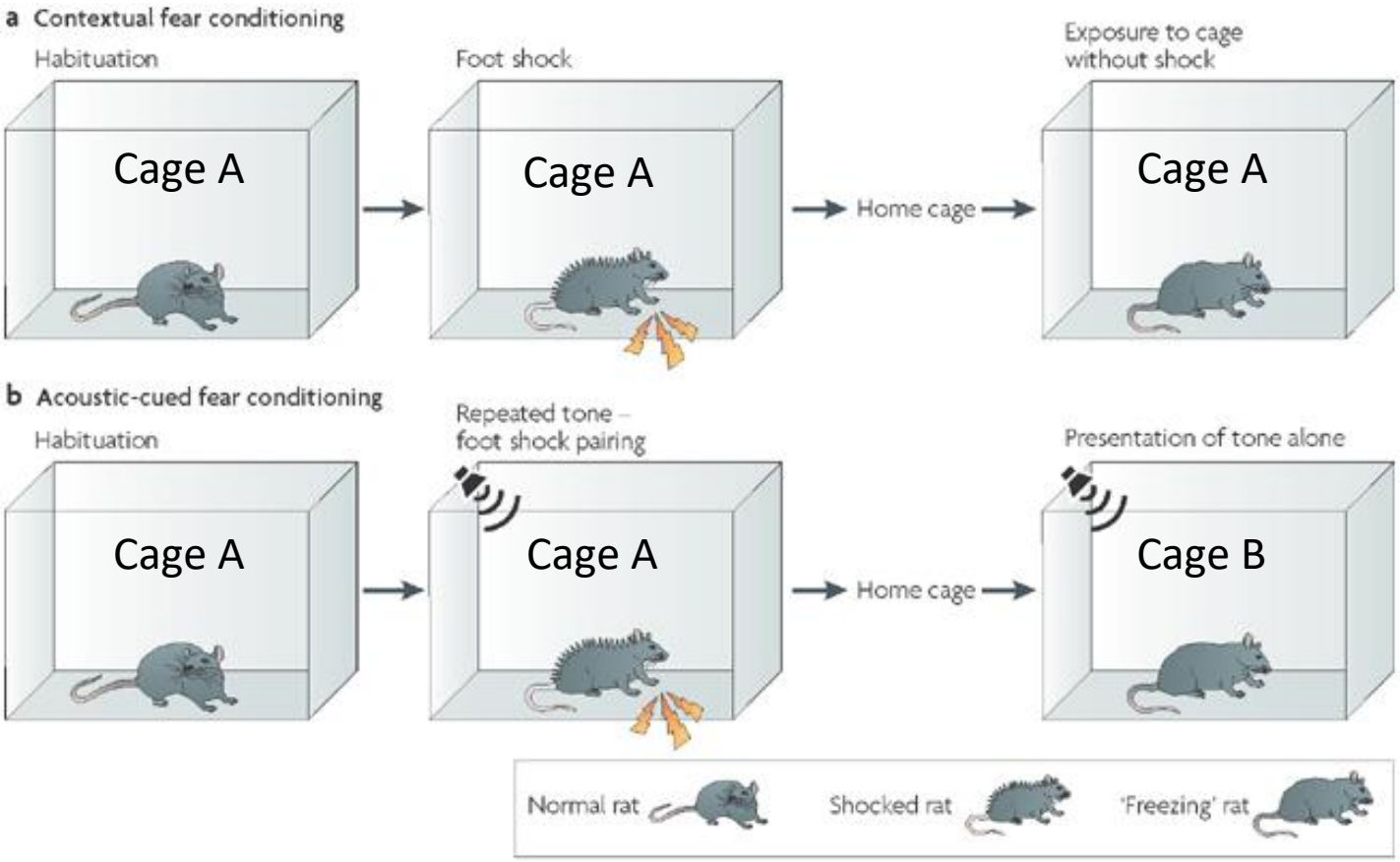


- Why is trace hippocampal-dependent?
- Maintaining the CS? Timing the trace? Harder?
- Eyeblink requires ~0.2sec, and hippocampus is required when 0.4-1sec.
- In tone-shock, trace can be 3sec, and hippocampus is required for ~20sec
- This suggest context-conditioning

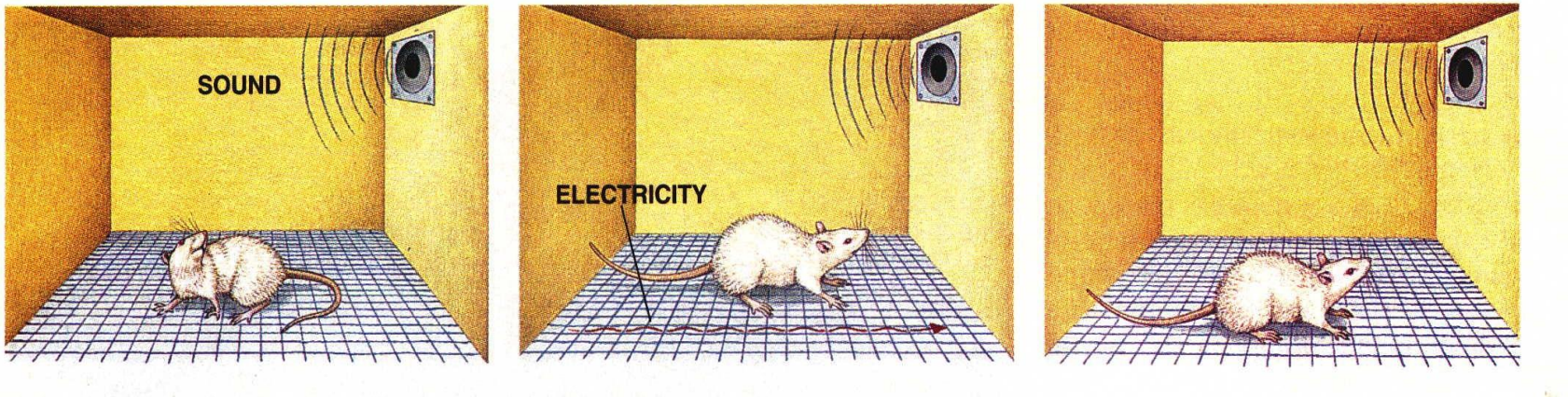


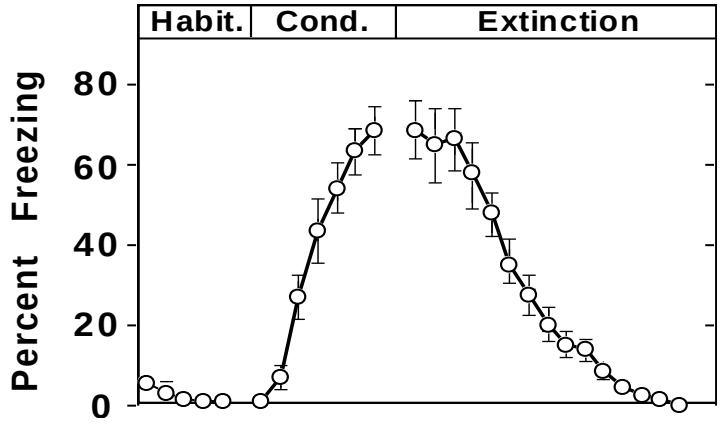
Contextual fear



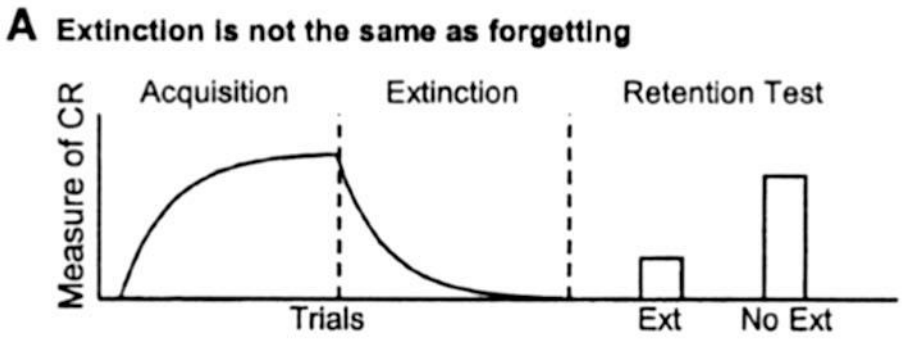


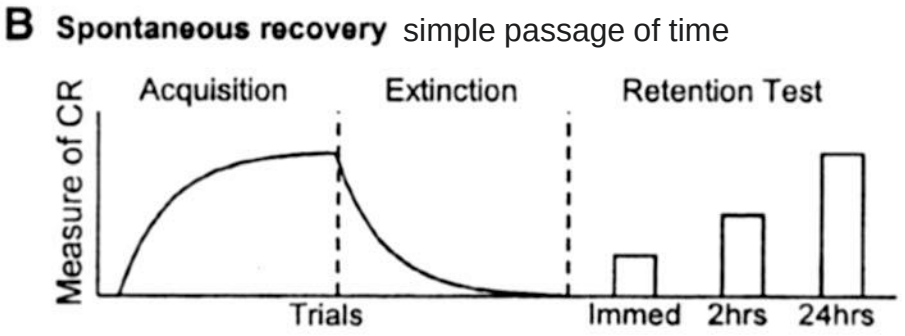
Extinction of fear-conditioning

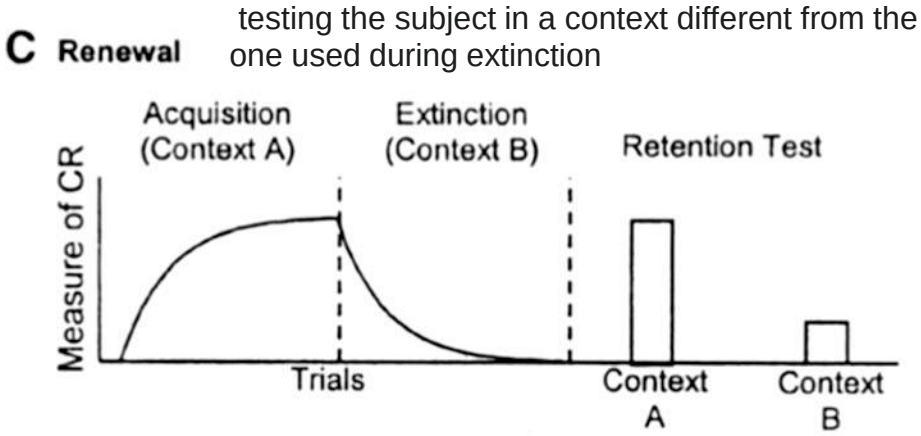


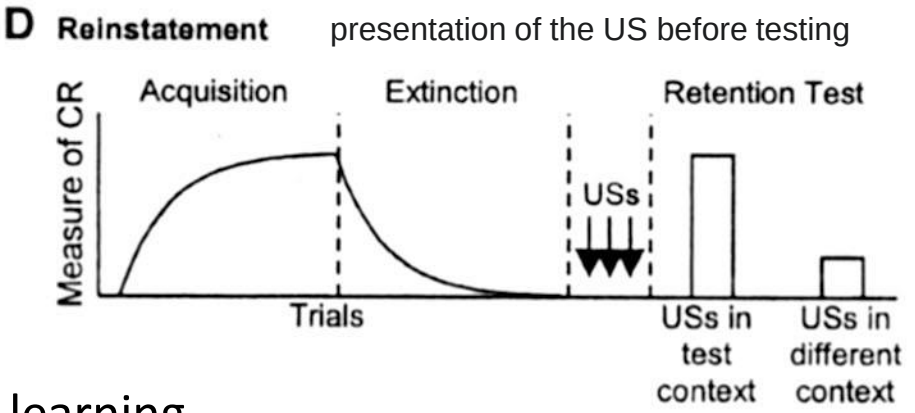


Extinction: a new learning



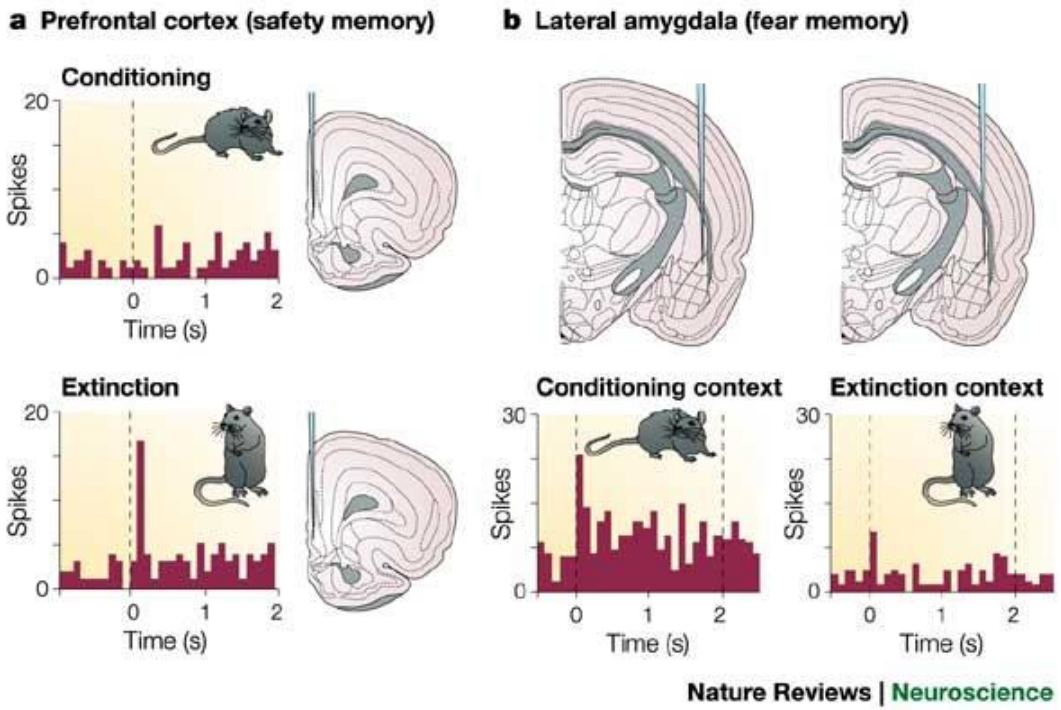


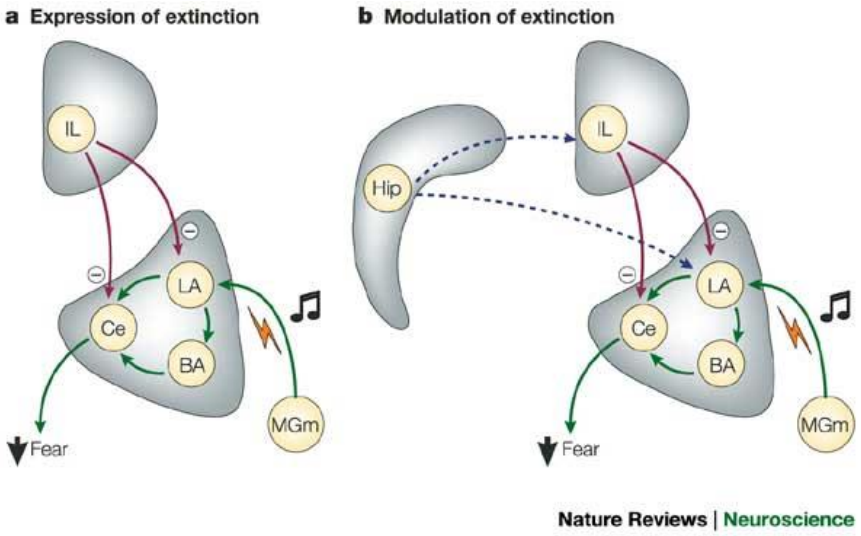


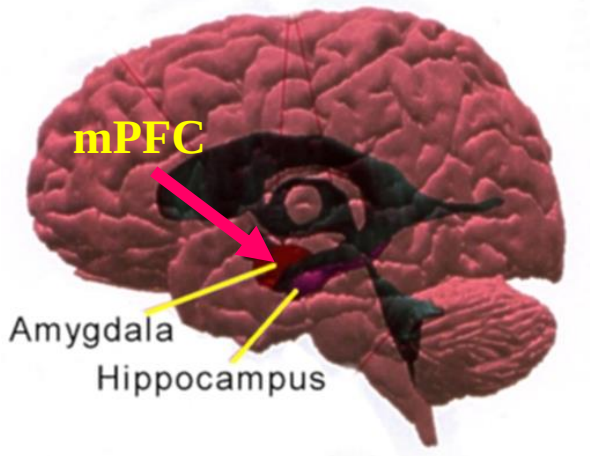


Faster re-learning

Extinction: brain mechanisms

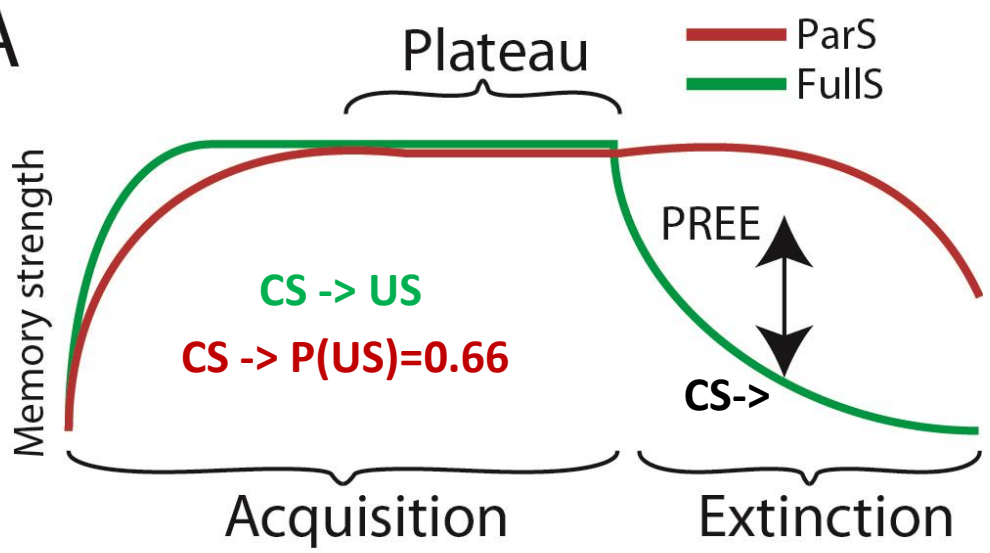






Partial reinforcement extinction effect

- Partial reinforcement
  - Fixed/variable ratio
  - Fixed/variable schedule



- Results in longer extinction learning

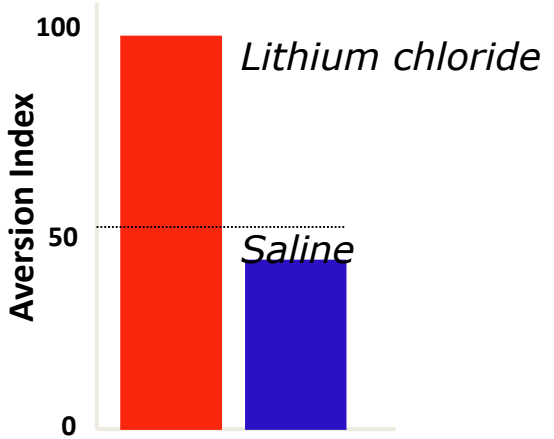
Livneh & Paz, 2012

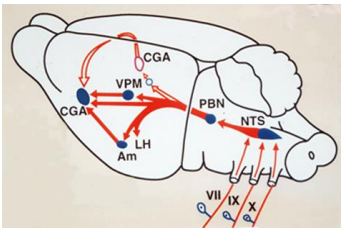
  - Frustration theory (Amsel): The omission of the US induces frustration. Therefore, during extinction, the frustration predicts the US.
  - Sequential theory (Capaldi): conditioning to strings of NNNRNNNR

Garcia J

Conditioned Taste Aversion

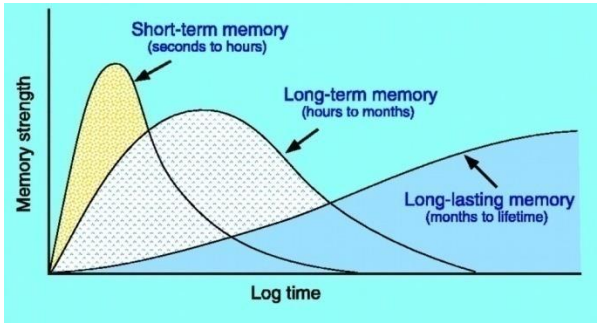
- One-trial learning
- Long-delay learning (few hours)
  - A [lack of] interference effect?
  - Still a problem for neuroscientists

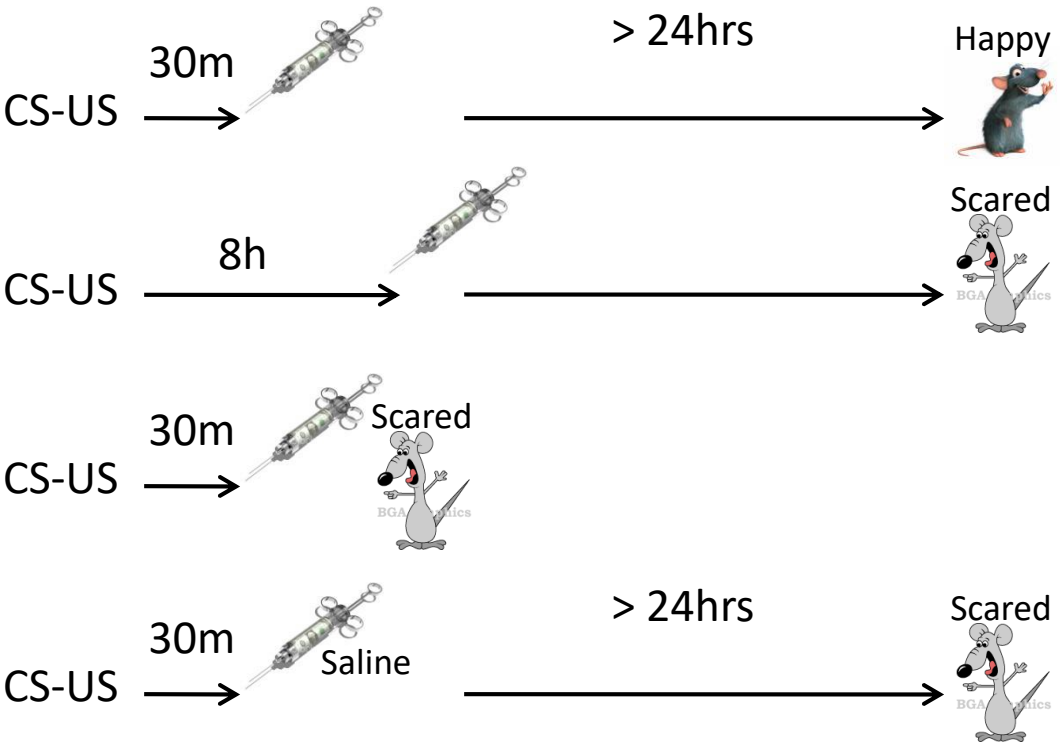


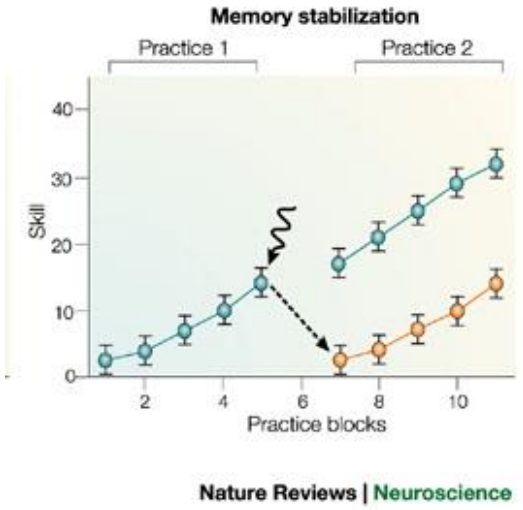


Consolidation

- 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.



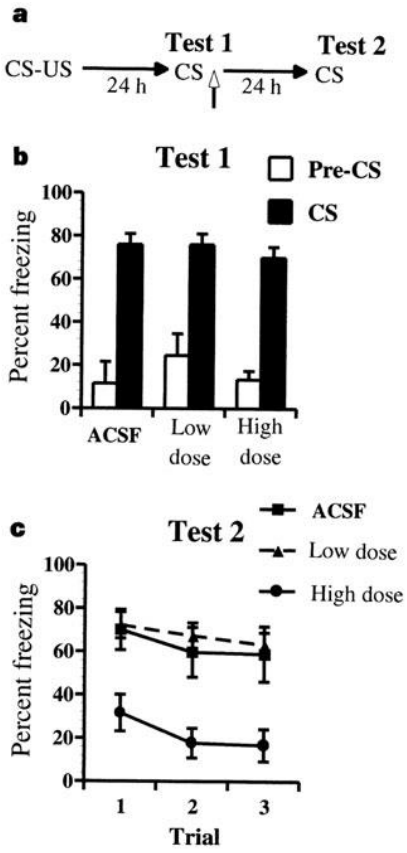




Reconsolidation

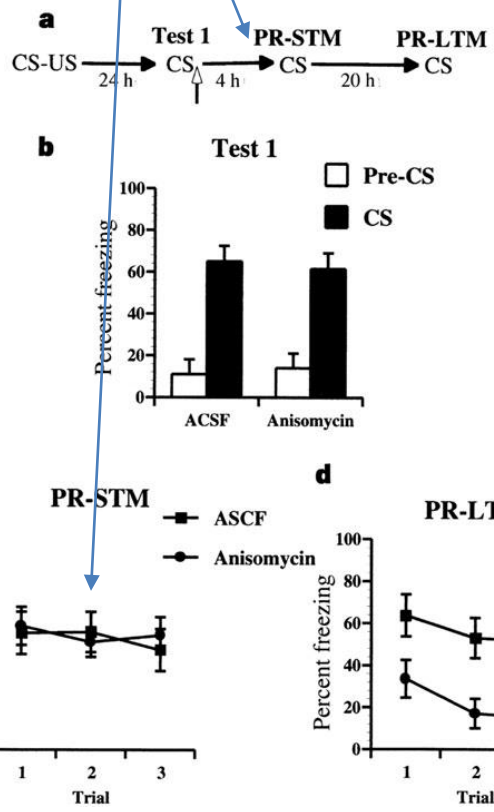
Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval

A test of whether consolidated fear memories can become labile when reactivated

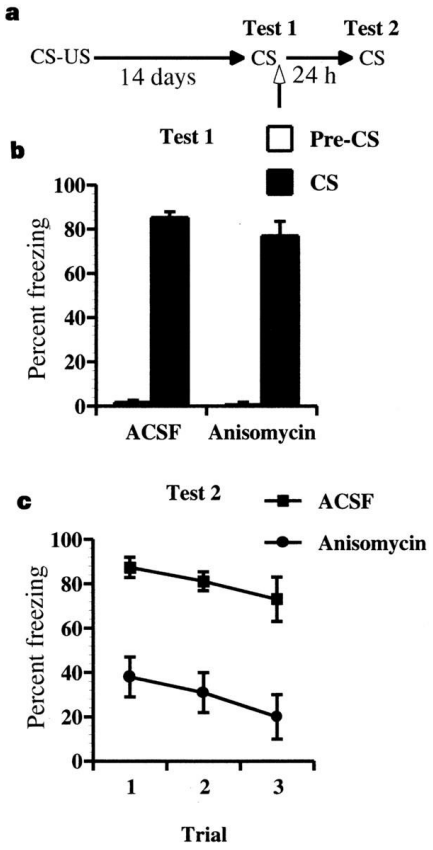


No CR reminder

No effect on STM

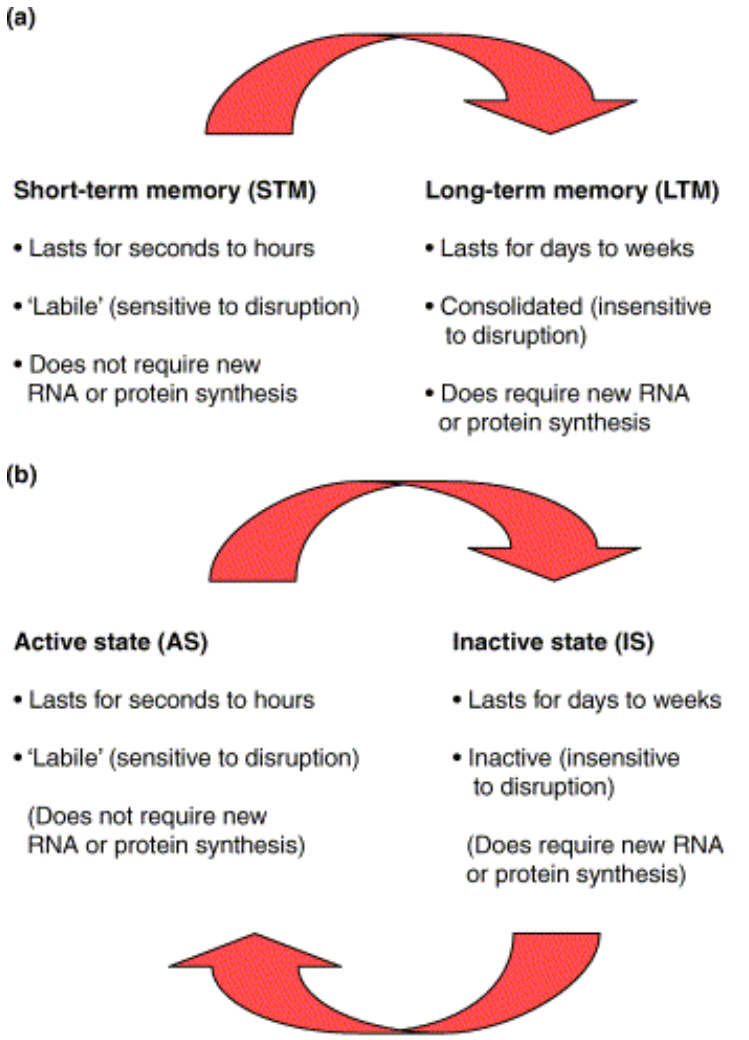


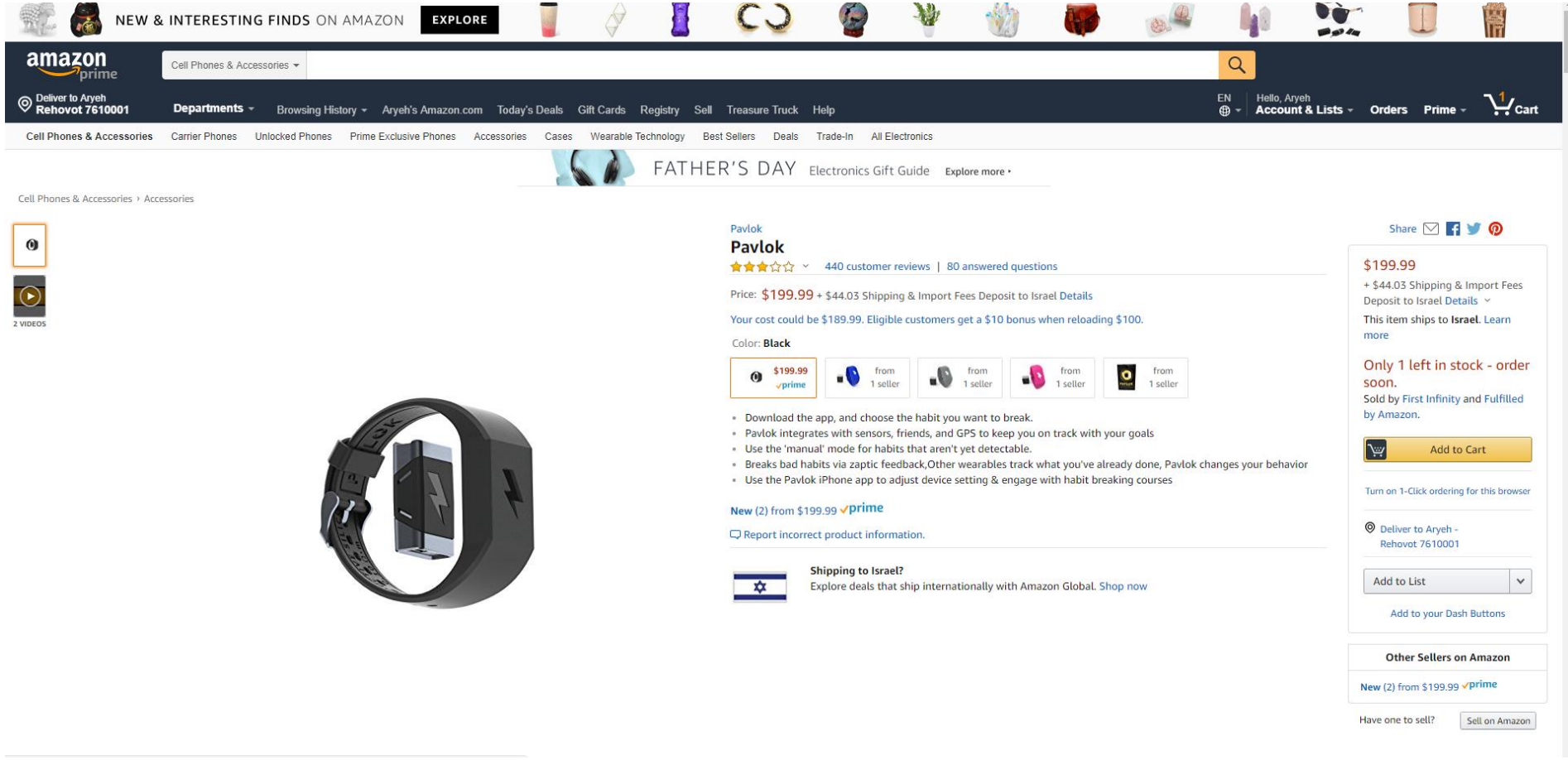
Fourteen days after training, anisomycin infusions after reactivation of the memory still produce amnesia



Nader et al., Nature 2000

An updated view of memories





Stay safe, be fearless