מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE
Department of Neurobiology

Paz Lab
Neural Mechanisms of Learning

Behavioral Neuroscience: Fear thou not

Rony Paz

What is the NeuroPsychological approach?

- **Neuropsychology** is the basic scientific discipline that studies the structure and function of the brain related to specific psychological processes and overt behaviors.
- The use of *artificial* well-controlled tasks.
- Why?
  - Well-controlled
  - Pre-planned quantification
  - We observed something, now lets do it properly
  - Target Human behavior
- For example:
  - Sensation and perception
  - Control of movement
  - **Learning** and **memory**
  - Decision making
  - Emotions
  - Attention

Active and Passive approaches

- The active approach manipulates the brain and observes behavior.
  - Stimulation (electrical, optogenetics)
  - Lesions
  - Pharmacological intervention
  - Genetic manipulations

- The passive approach manipulates behavior and observes the brain.
  - Trained behaviors: electrophysiology, imaging (1P,2P,MRI)
  - Observing patients

Reward vs. Punishment

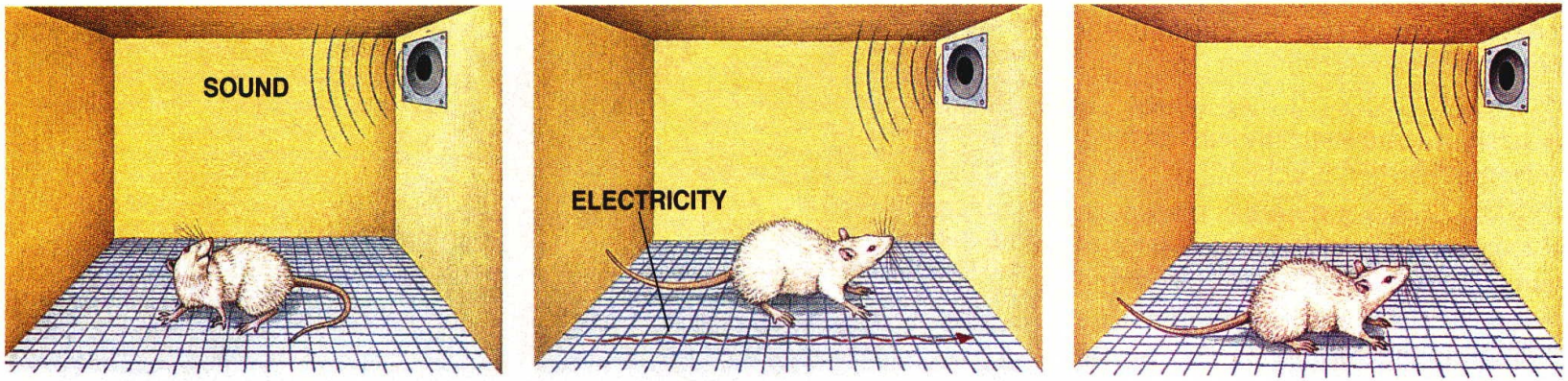
- What is a “reward”?
- Learning is best motivated by threats to survival?
- Threats are much better reinforcers?
- Fear is a prime motivator

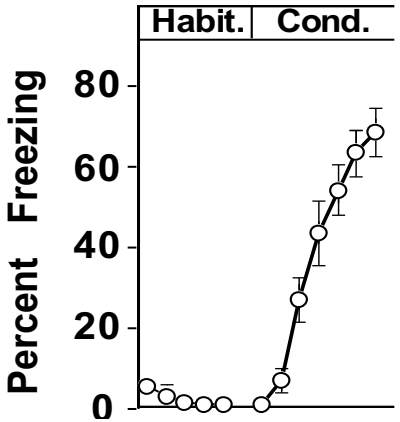
	Decreases behavior	Increases behavior
Presented	Positive punishment	Positive reinforcer
Taken away	Negative punishment	Negative reinforcer

Taking drugs?

More fun,
less withdrawal

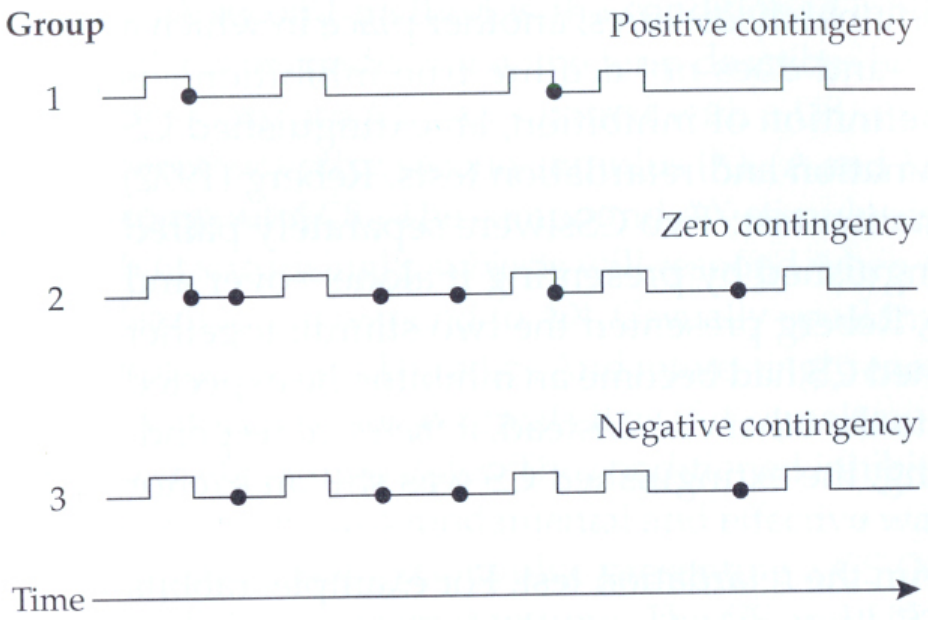
Classical fear conditioning

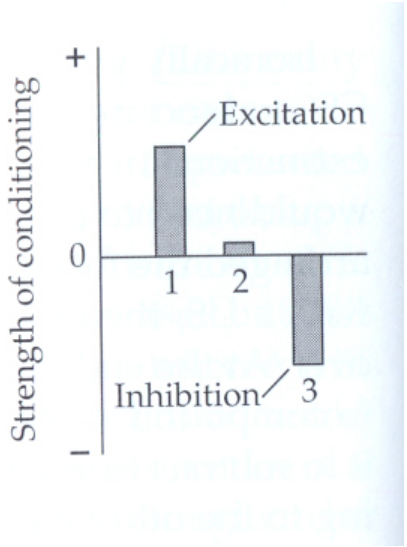




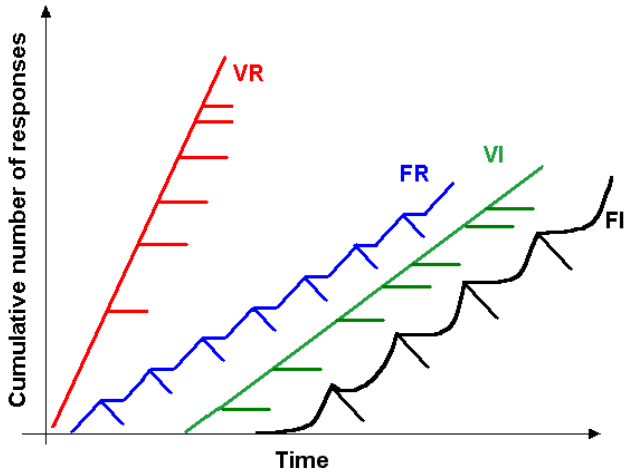
CS-US pairing
Tone = conditioned stimulus (CS)
Foot-shock = unconditioned stimulus (US)
Freezing = conditioned response (CR-UR)

Contingency: co-occurence

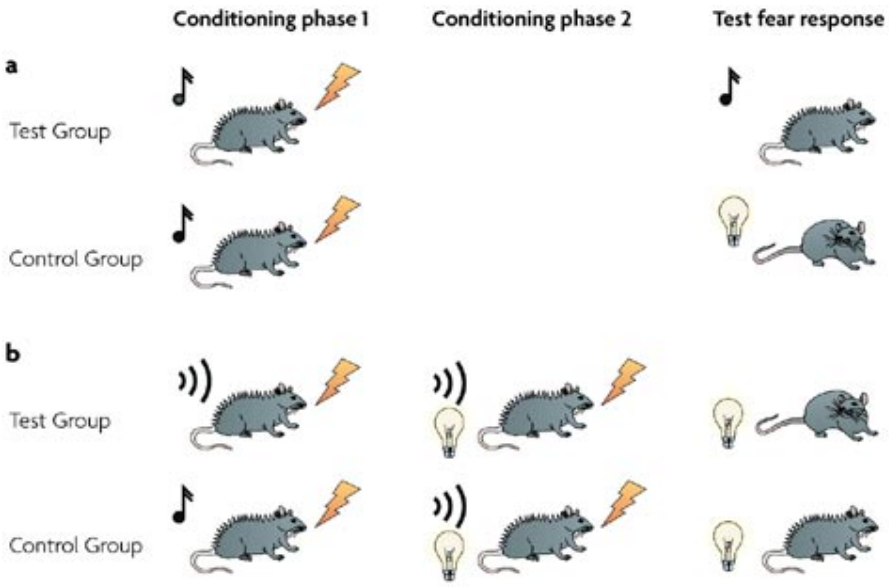




Schedules of reinforcement:
Variable/fixed interval/ratio



More than contingency: Surprise / added information



Aversive conditioning

Blocking

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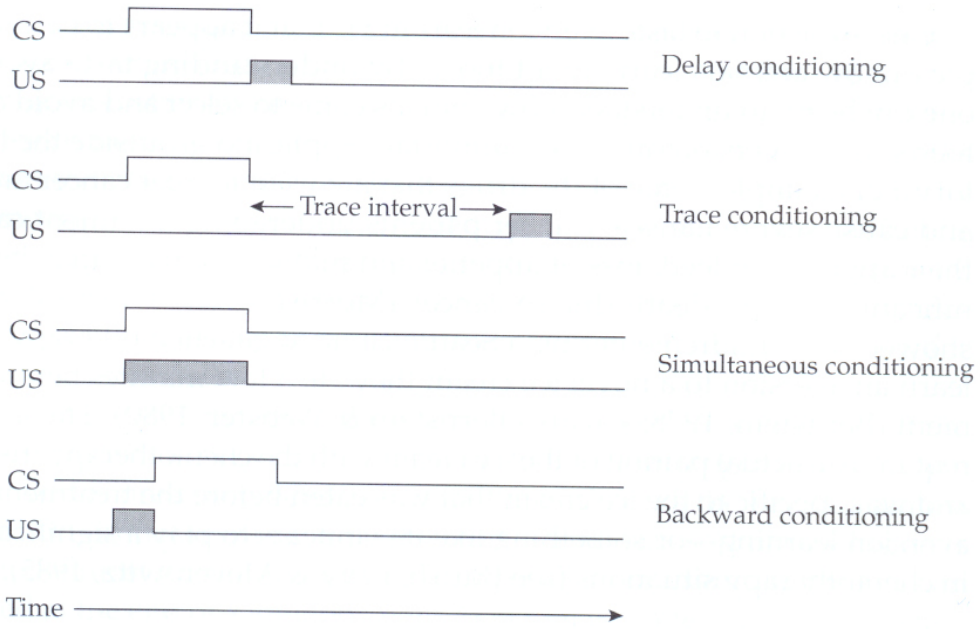
Rules of thumb for conditioning strength

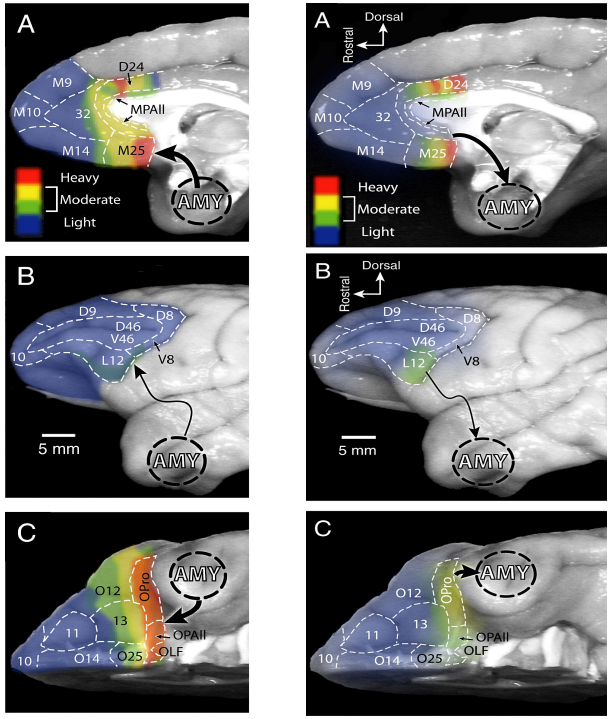


- Backward < simultaneous < trace < delay
- In trace: short interval > long interval
- In delay: short CS > long CS
- Salience of the CS
- Strength of the US
- Spaced trials is better than massed trials (the ratio between inter-trial-interval and the CS)

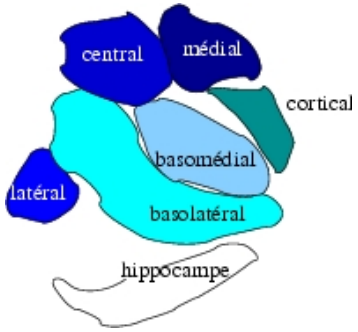
But notice it is hard to estimate backwards learning

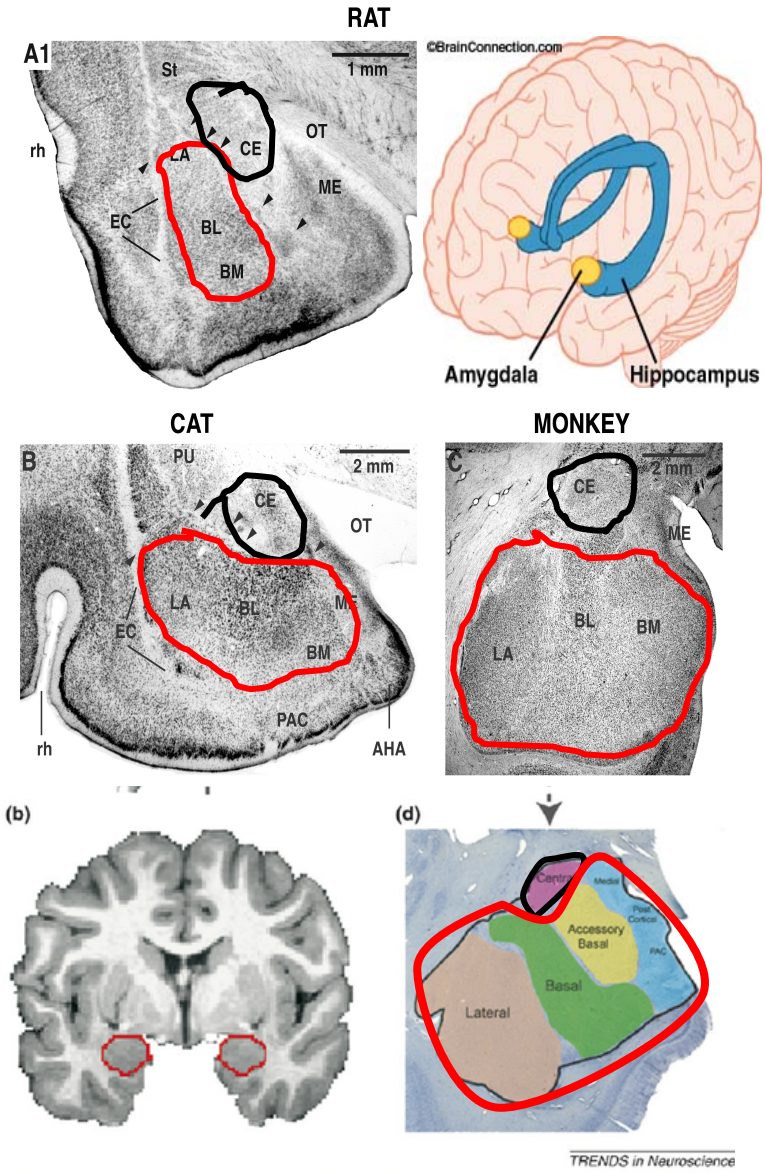
Amygdala

- Evolved in primates
- Correlated with the prefrontal cortex (PFC)
- Amygdala-PFC is a tight 2-way 1-synapse network
- Emotional responses and emotional learning
- Show abnormal activity in most psychiatric conditions, mainly in anxiety and mood disorders



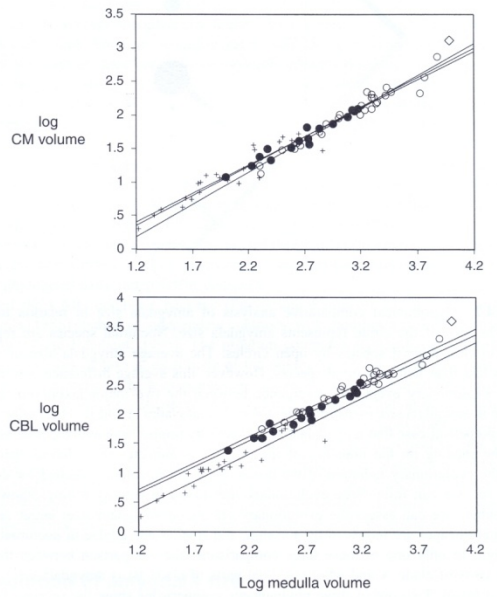
Ghashghaei et al. 2007

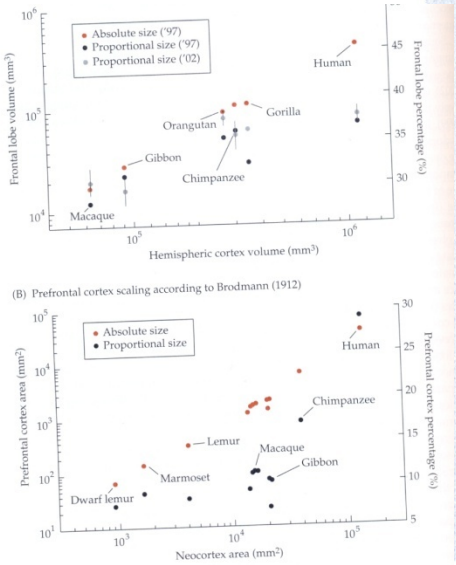


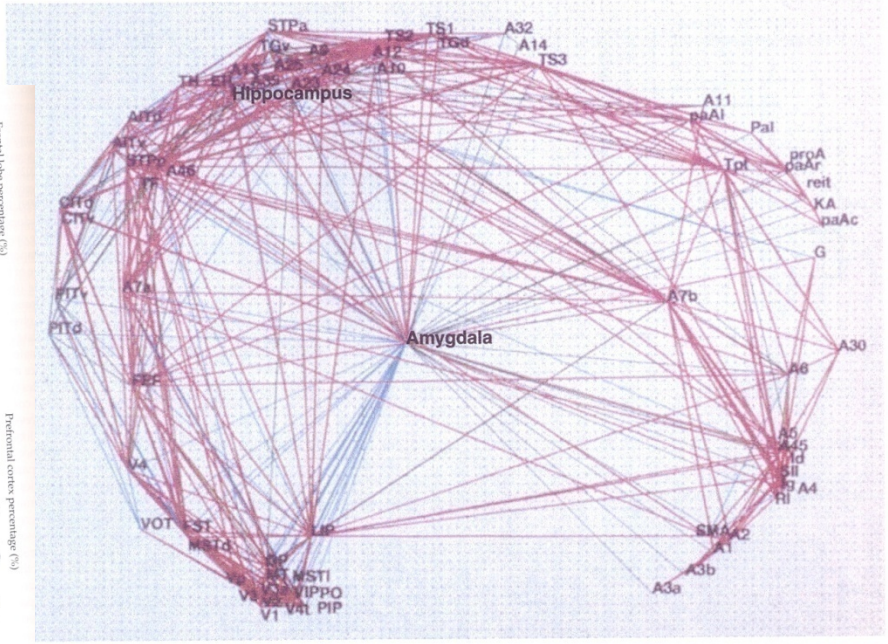


Amygdala and its basolateral complex (BLA)

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



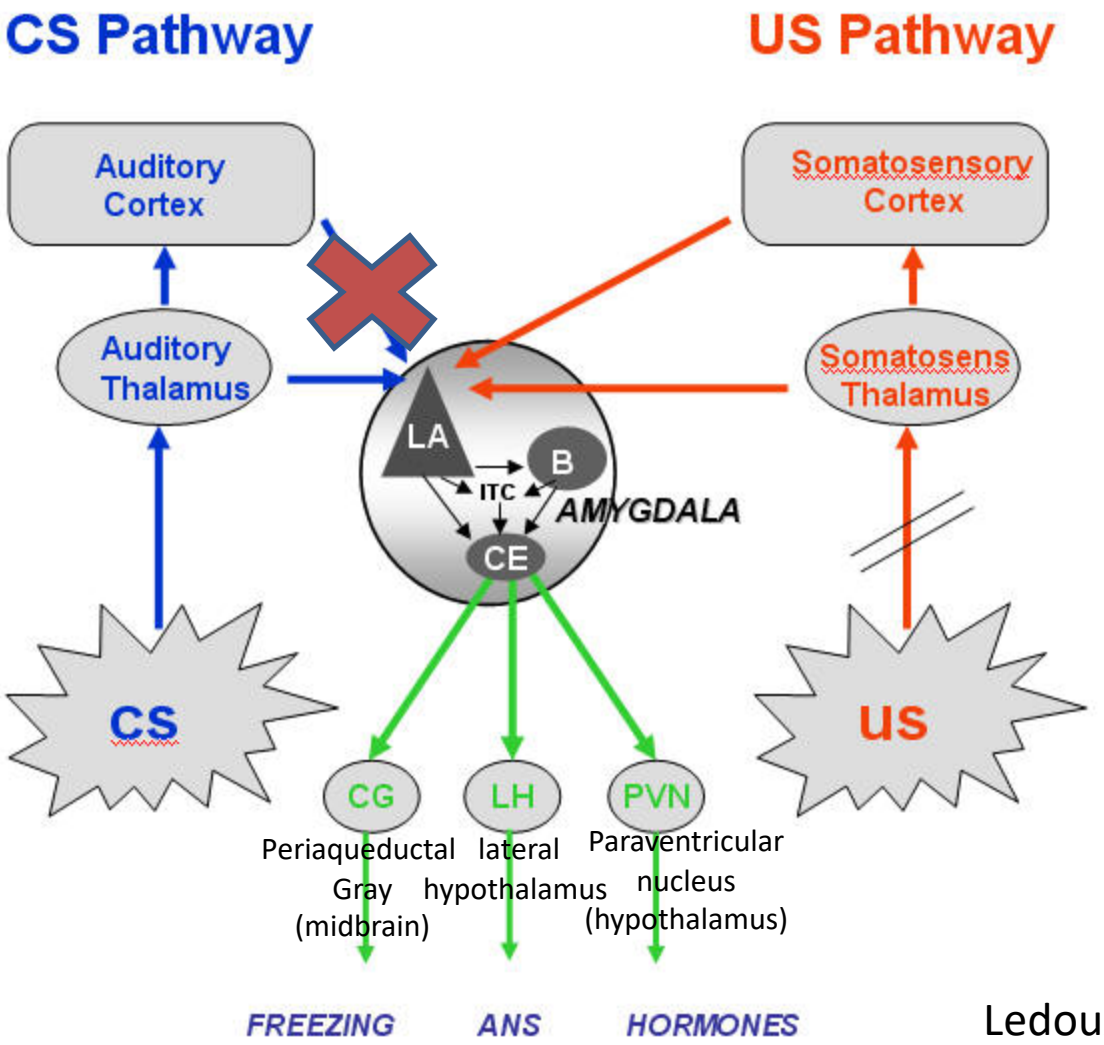




Humans and emotions

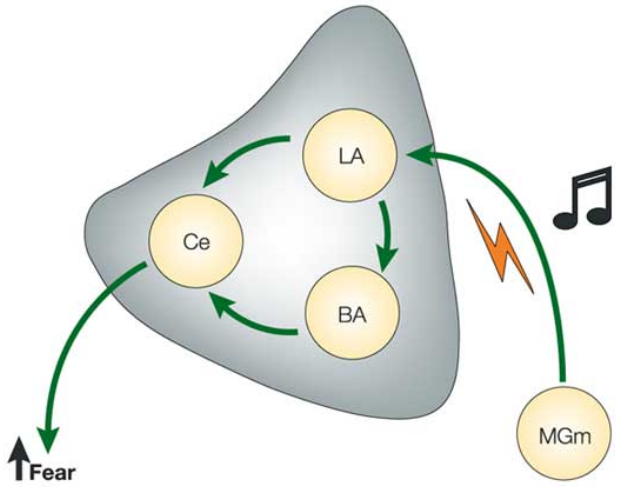
EMOTIONS FACILITATE MEMORY
Emotionally arousing events are remembered more vividly.

Fear circuit



Ledoux, Mcgaugh, Davis

Neurons acquire tone responses after conditioning



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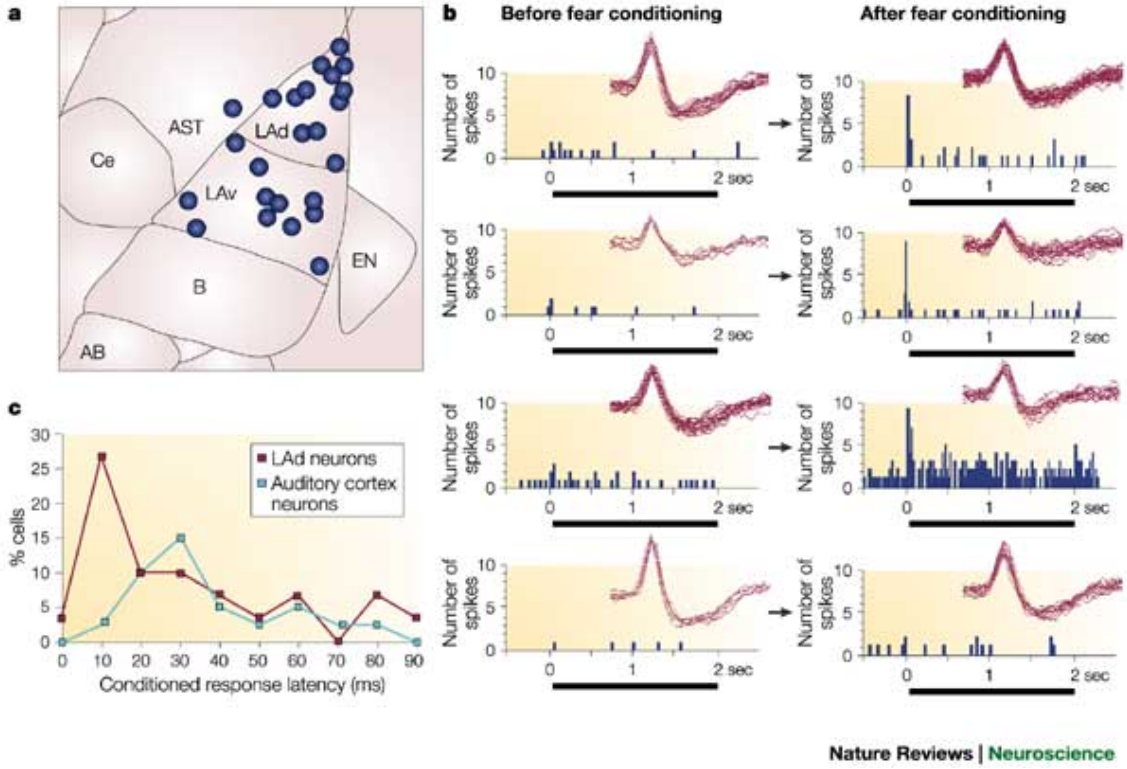

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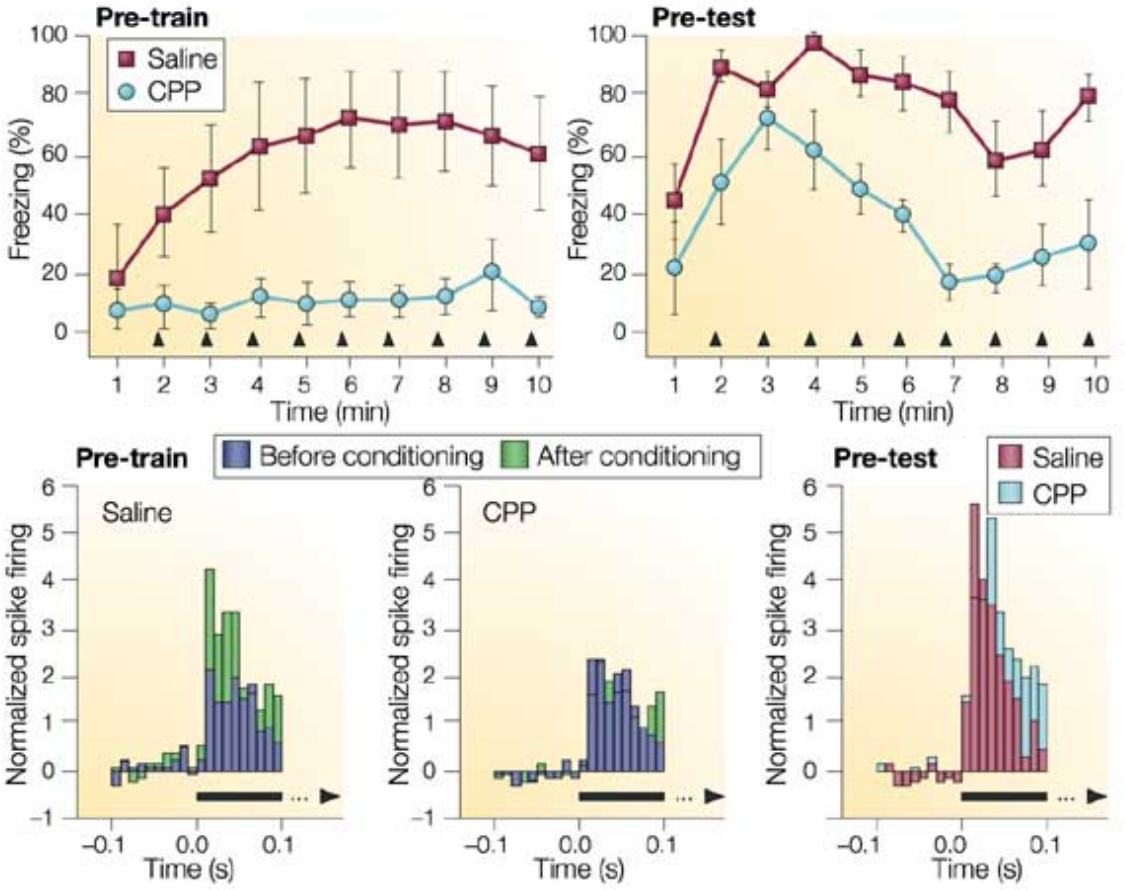
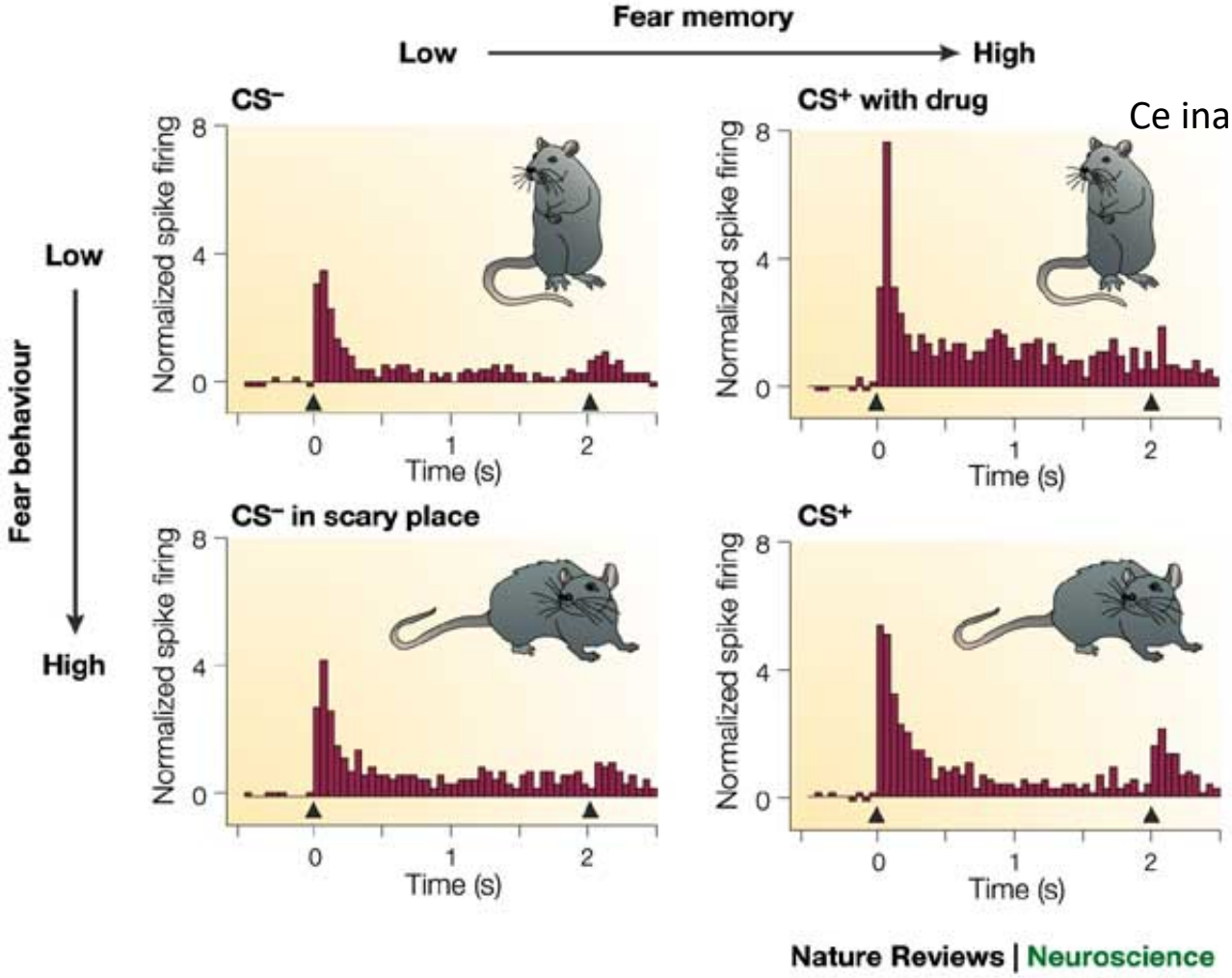
LTP in the LA is required

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.

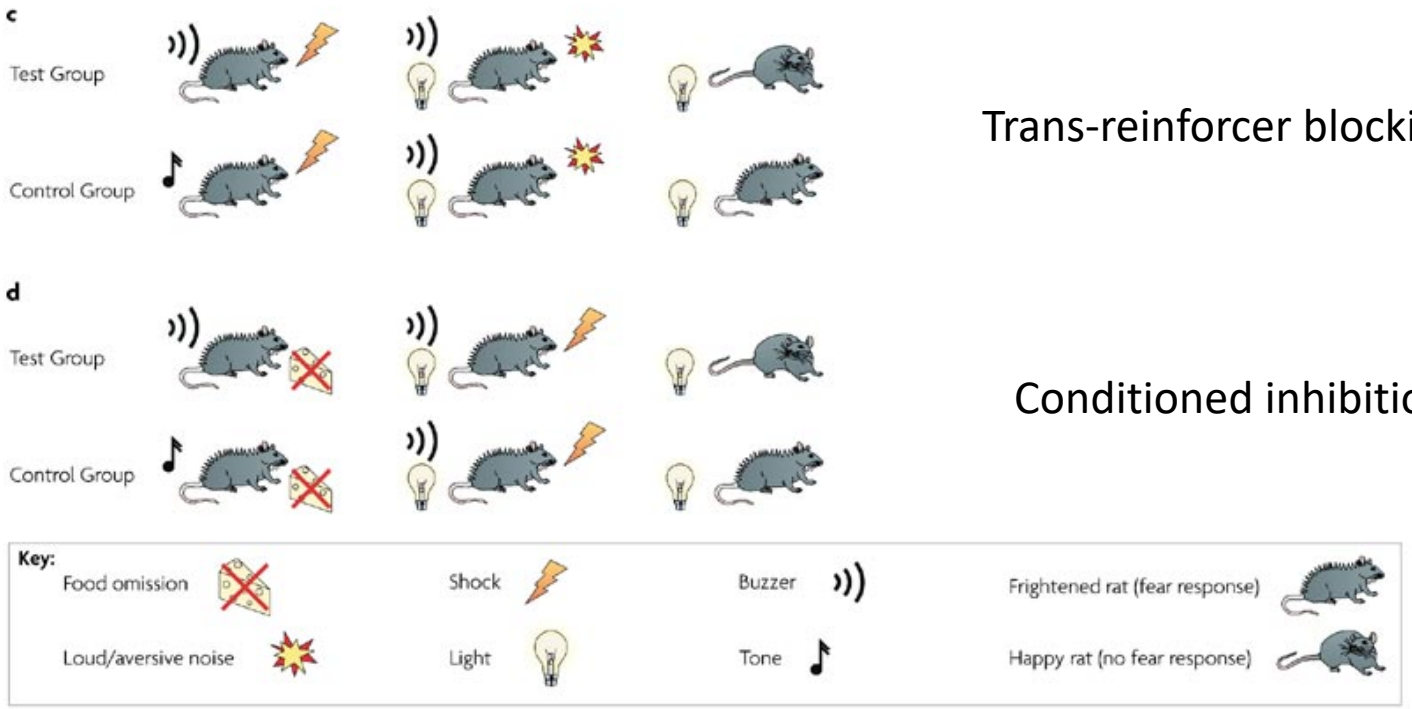


CPP (3-(2-carboxypiperazin-4-yl) propyl-1-phosphonic acid), a competitive NMDA-receptor antagonist

LA encodes memory independent of fear behavior



Ce inactivation

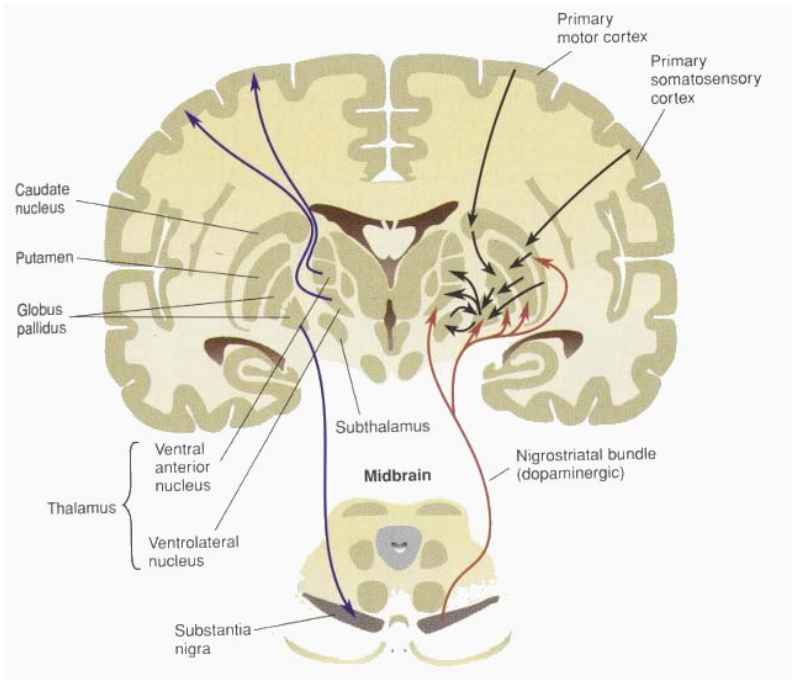


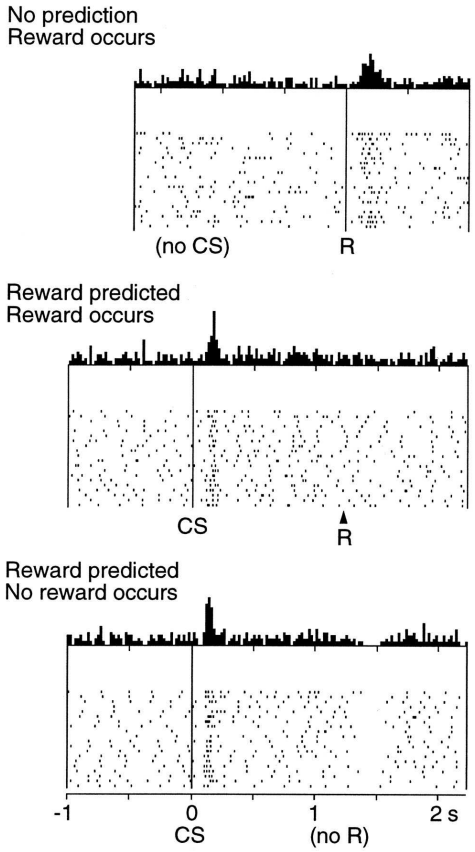
Trans-reinforcer blocking

Conditioned inhibition

Suggests common brain mechanisms

The dopamine system





Schultz et al, JNS 13: 900-913 ,1993

Pearce-hall and rescorla-wagner

the change (Δ) in the associative strength (symbolized V) of a CS

$\Delta V = S.\alpha.\lambda$

S is intensity of the CS and λ of the US. α represents the associability of the CS

$\alpha_n = |\lambda - \Sigma V|_{n-1}$

prediction V of the reward:

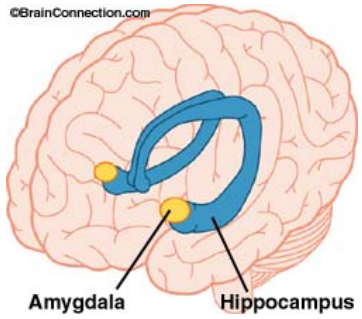
$V = \omega U$

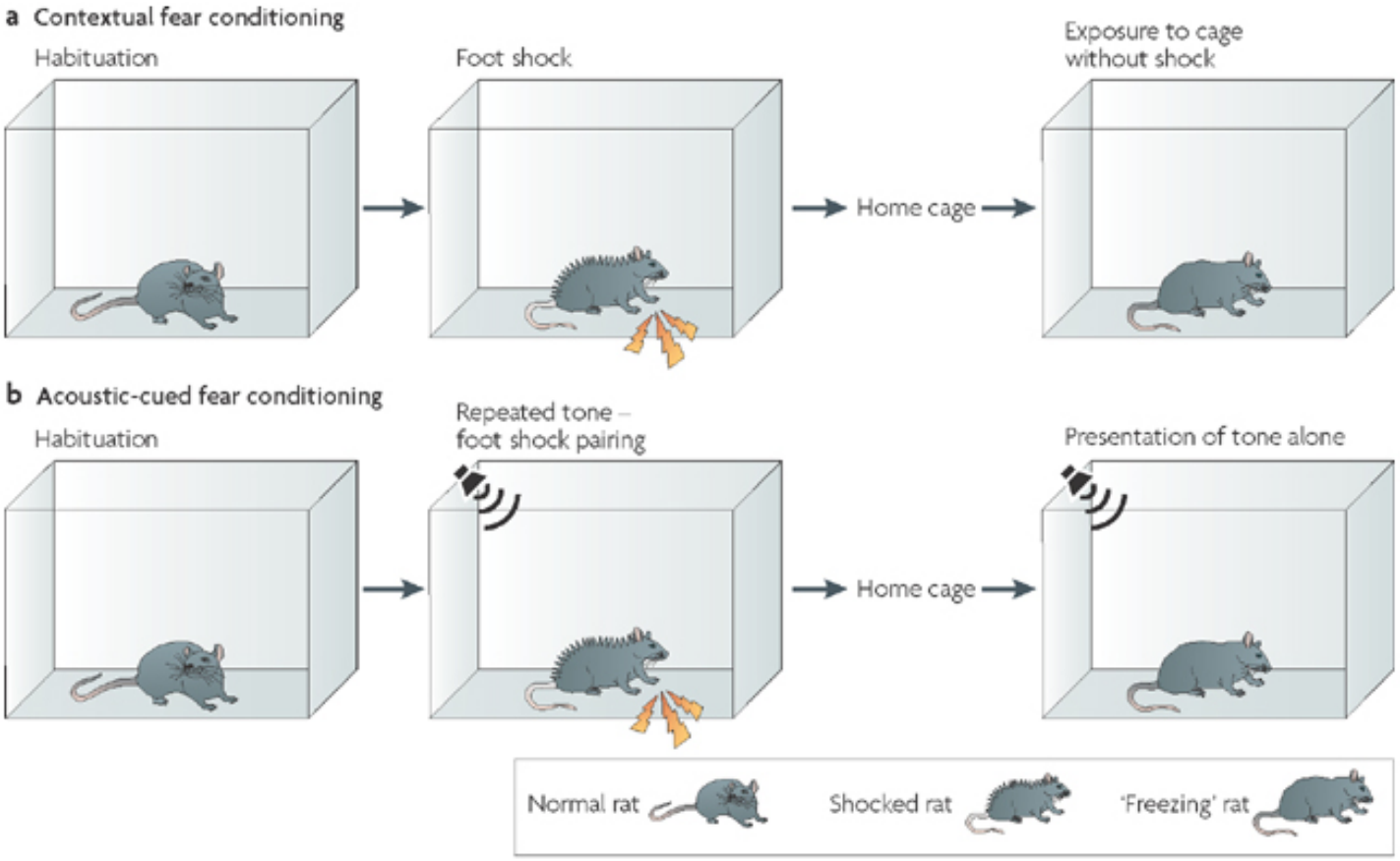
And learn to change ω :

$\Delta \omega = \varepsilon(R-V)U$

Unsigned (attention) “Vs.” signed prediction-error

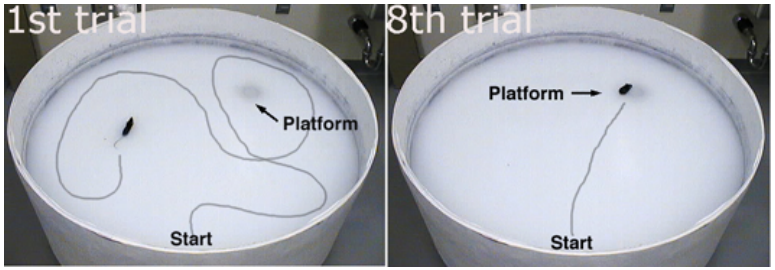
Contextual fear

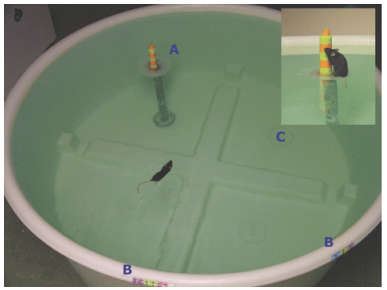




Amygdala modulation of memory

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





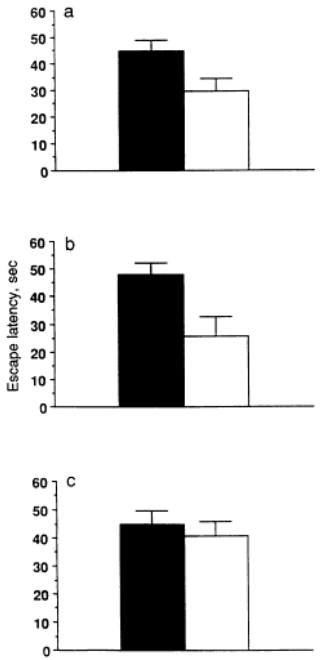


FIG. 1. Mean (±SE) escape latencies of *d*-amphetamine (10 μg) (□) and saline-treated (■) rats on the retention test trial in the spatial task. (*a*) Hippocampal injections. (*b*) Amygdala injections. (*c*) Caudate nucleus injections.

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

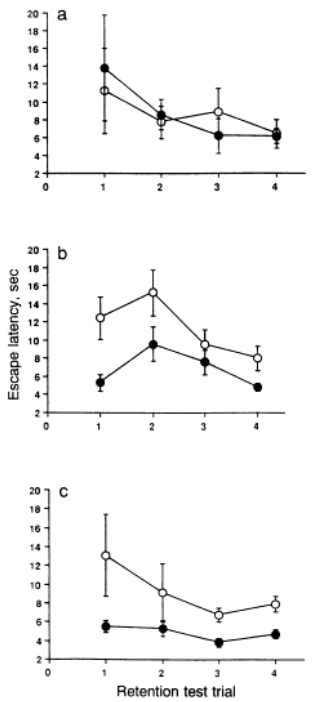


FIG. 2. Mean (±SE) escape latencies of *d*-amphetamine (10 μg) (●) and saline-treated (○) rats on the retention test trial in the cued task. (*a*) Hippocampal injections. (*b*) Amygdala injections. (*c*) Caudate nucleus injections.

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

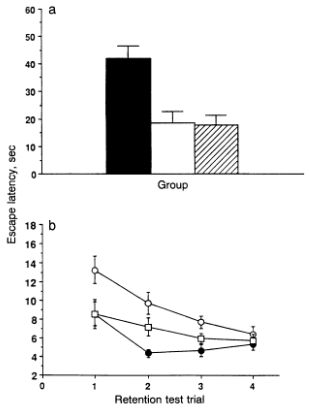
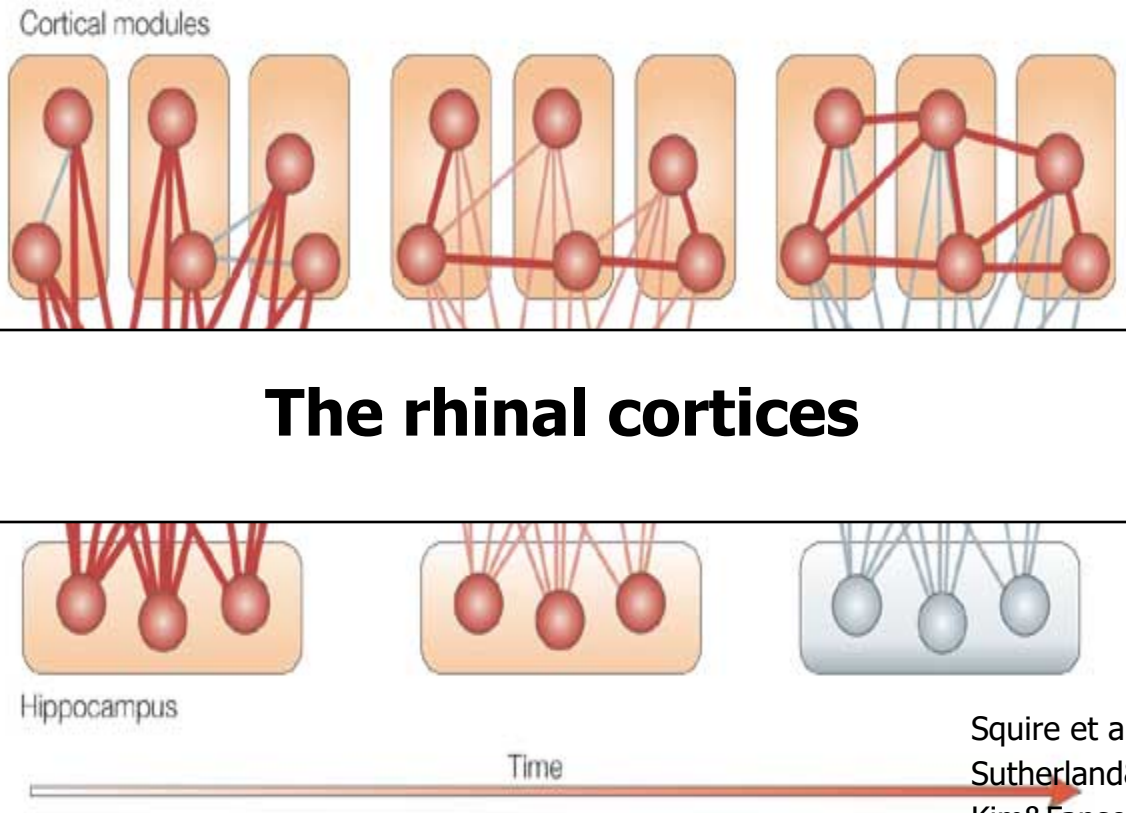


FIG. 3. Mean (±SE) escape latencies of rats receiving intraamygdala posttraining *d*-amphetamine or saline and rats receiving preretention test lidocaine or saline on the retention test trial(s) in the spatial task (*a*) and cued task (*b*). Posttraining/preretention: ■ (*a*) and ○ (*b*), saline/saline;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

Packard, Mcgaugh

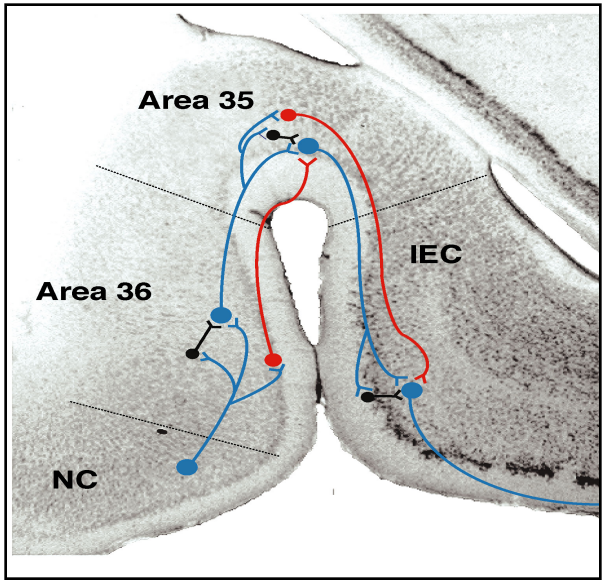
Formation and consolidation of Declarative/episodic memories

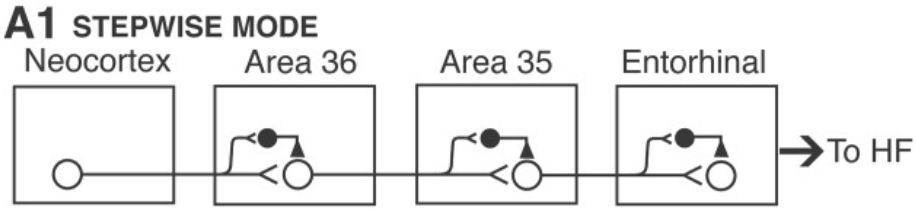


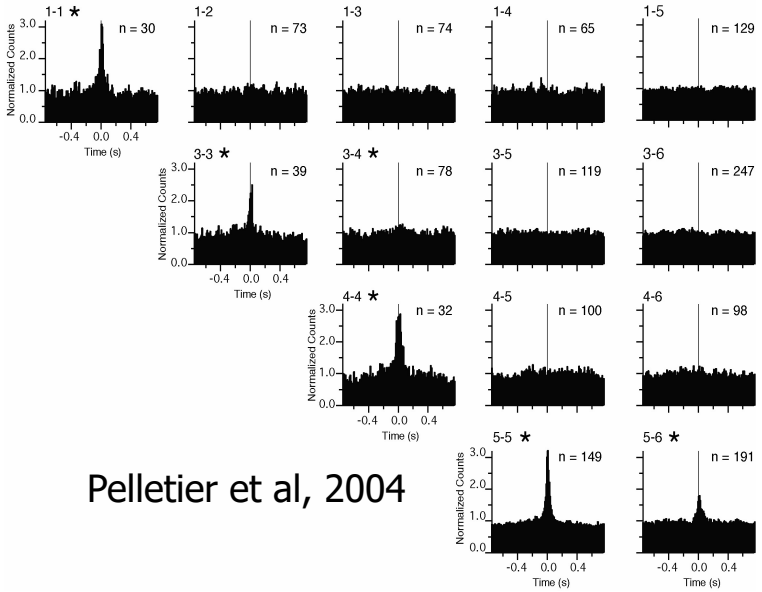
The rhinal cortices

Squire et al, 2004; Buzsaki, 1989; Sutherland&McNaughton, 2000; Kim&Fanselow, 1992; Frankland&Bontempi, 2005.

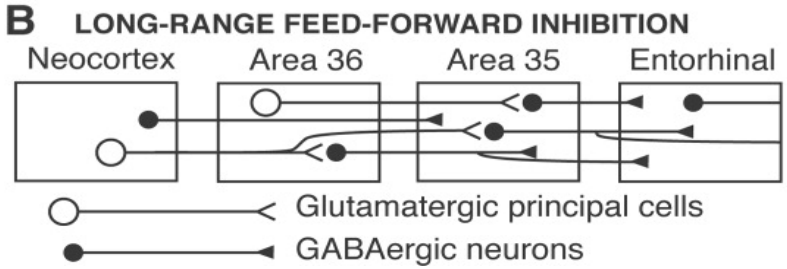
The rhinal cortices: the interface to the Hippocampus



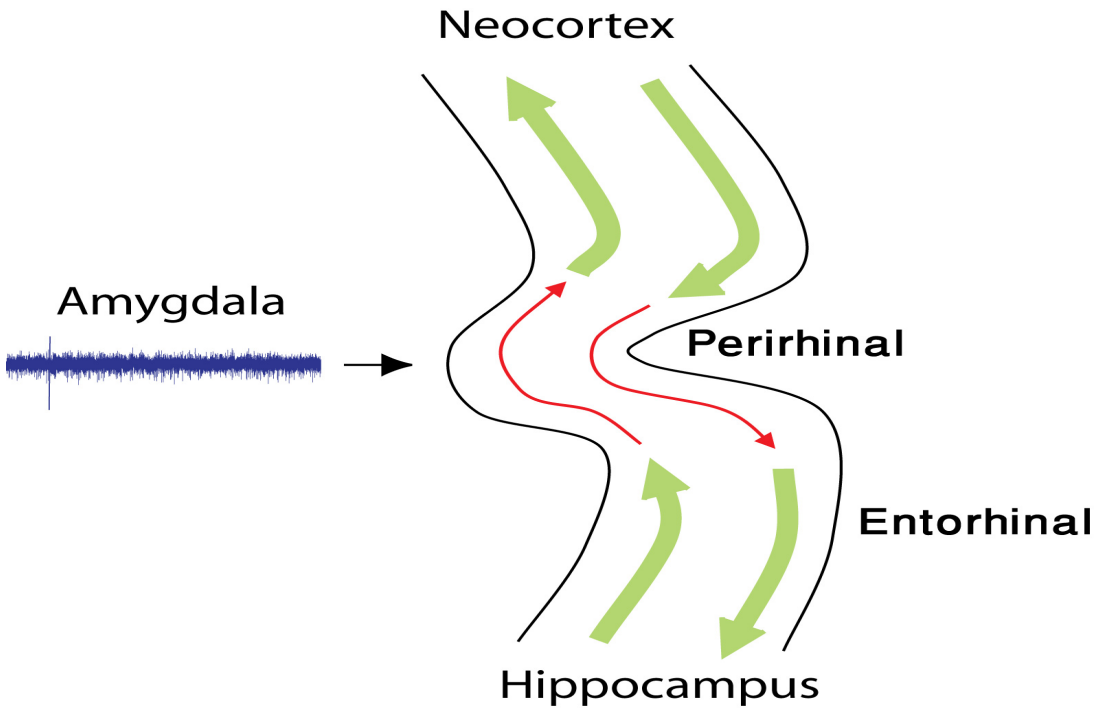




Pelletier et al, 2004

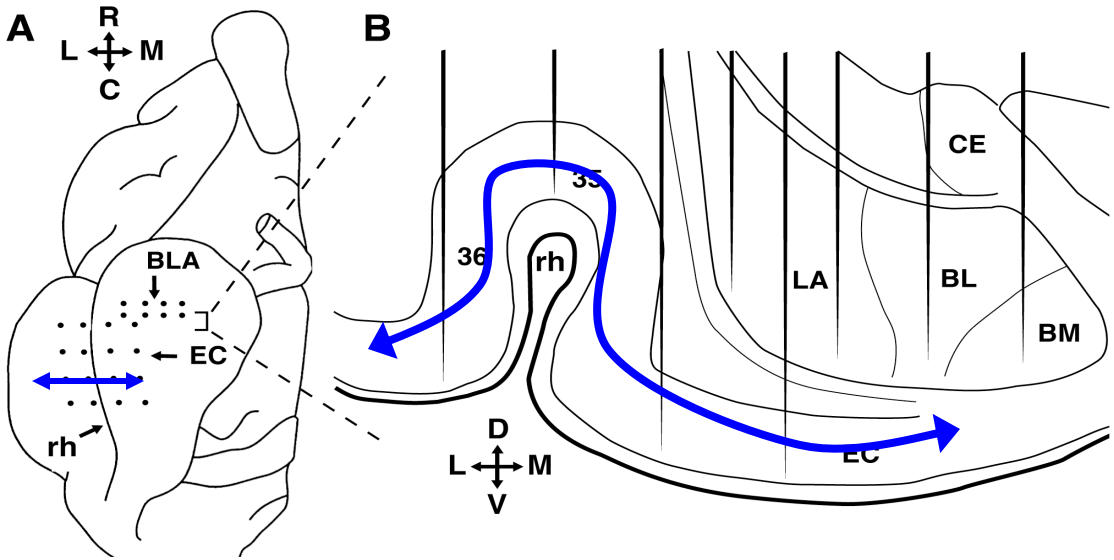


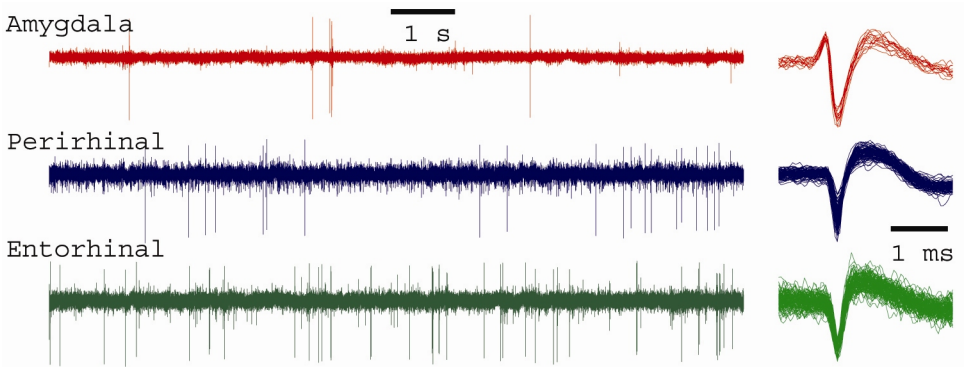
Pinto et al, J. comp. neurol. 2006

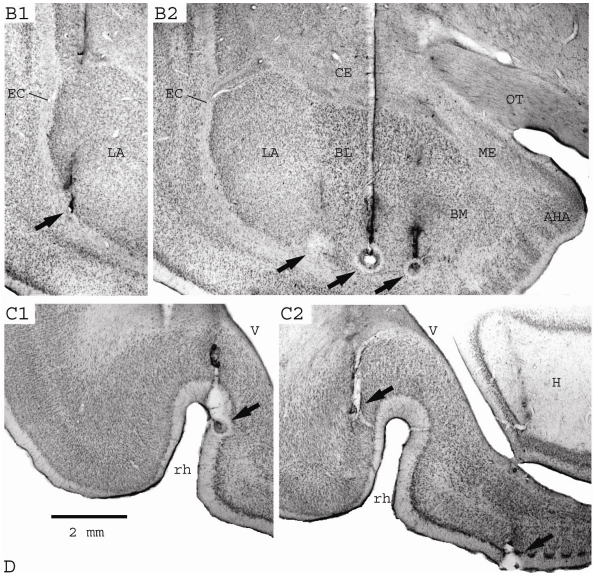


Hypothesis: Amygdala projections to the rhinal cortices facilitate memory by promoting bidirectional impulse transfer between the Neocortex and Hippocampus.

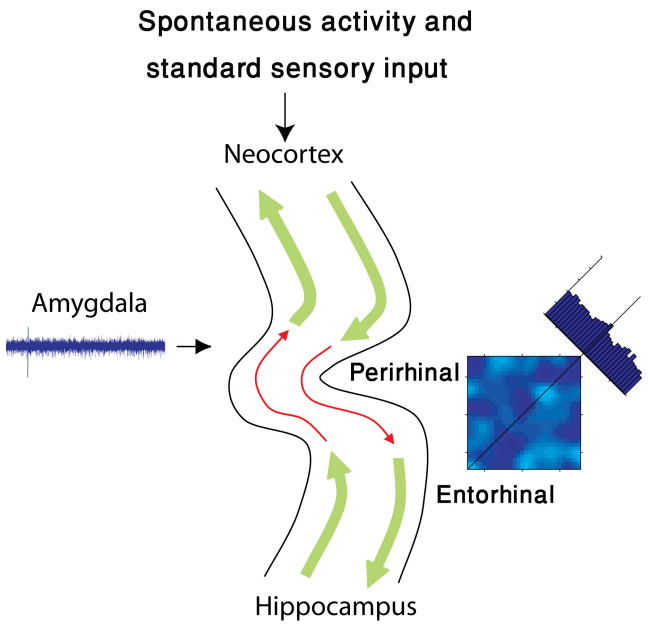
Simultaneous extracellular recordings of BLA, Perirhinal, and Entorhinal.

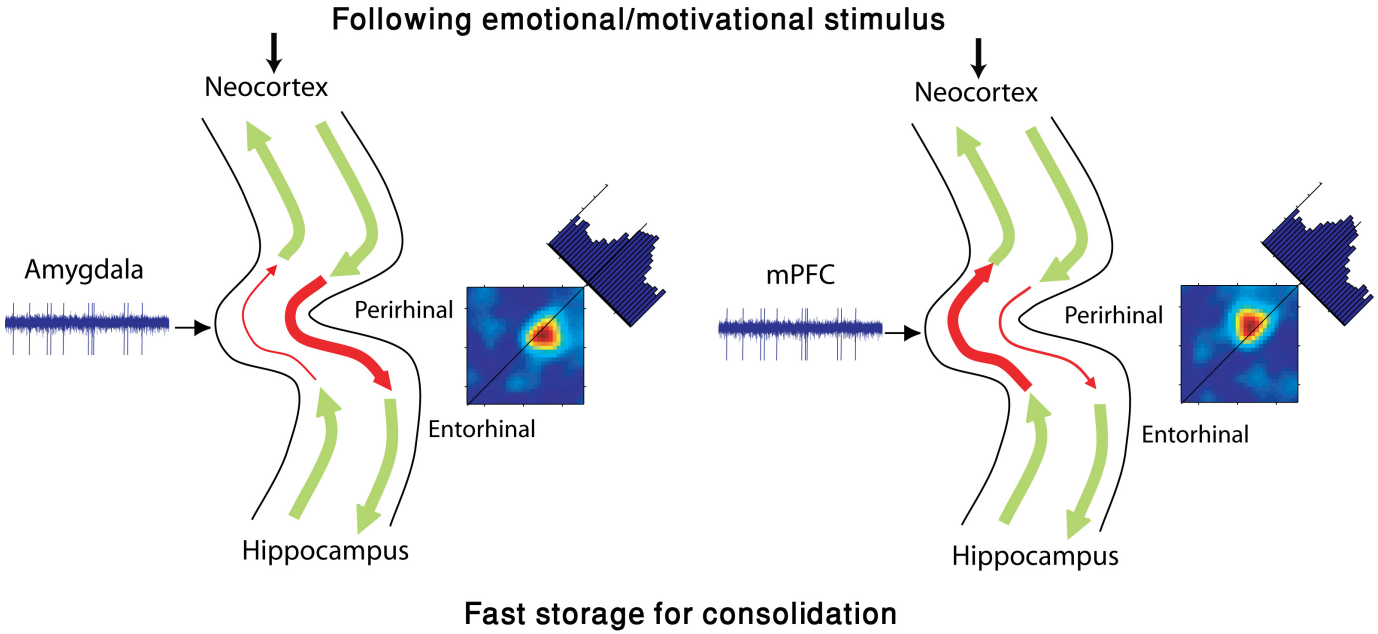






Facilitation of information transfer

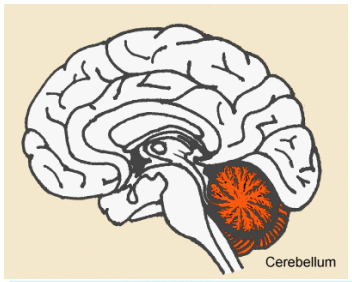


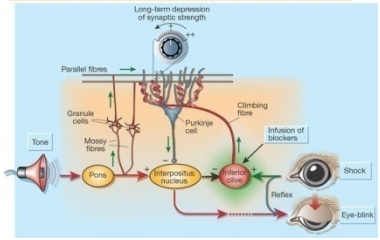


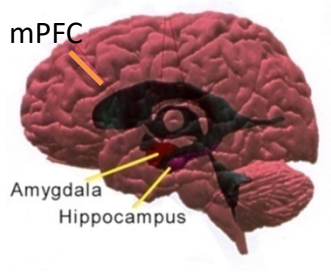
So, does it encode the memory or just modulates it?

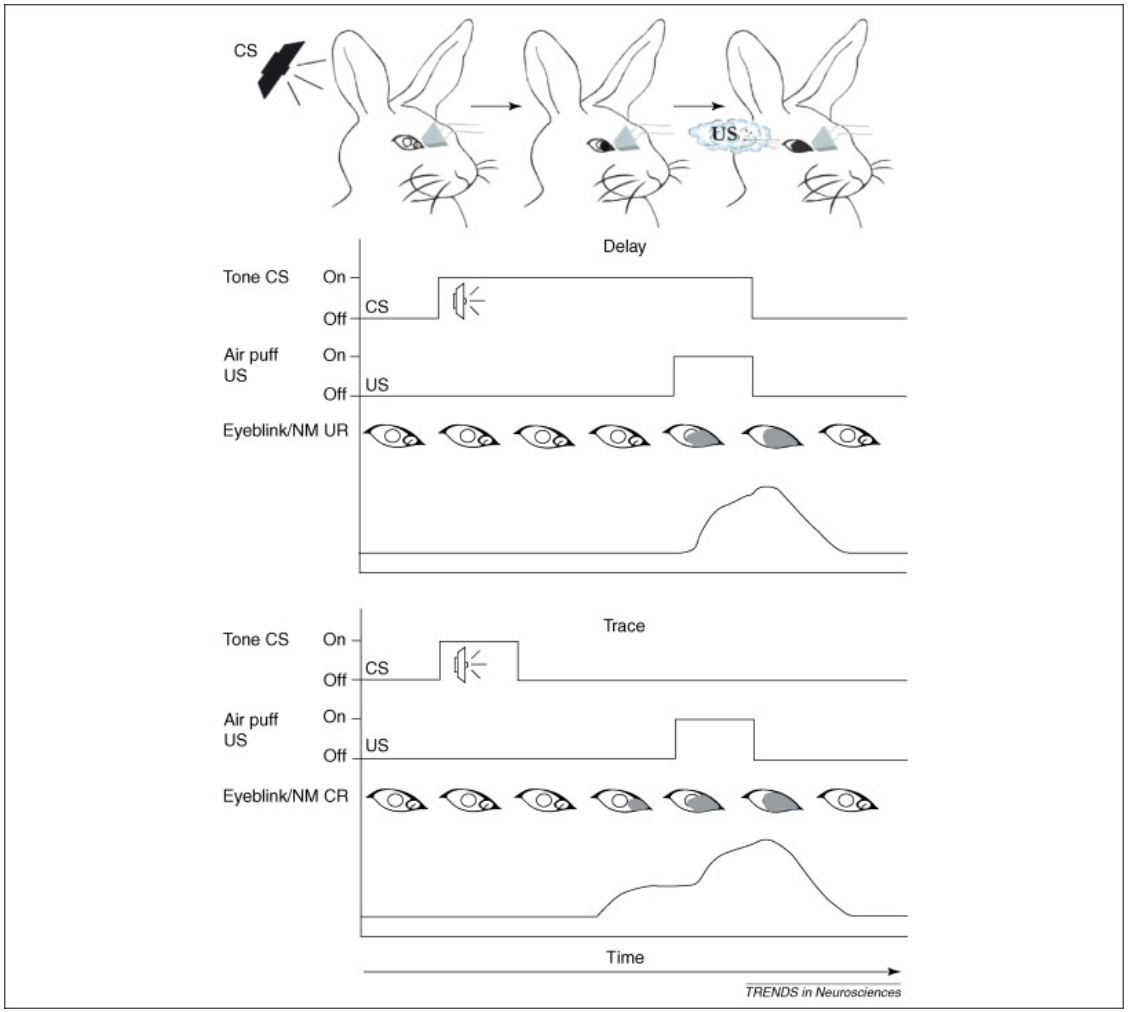
- **It depends.**

Eyelid (blink) reflex conditioning



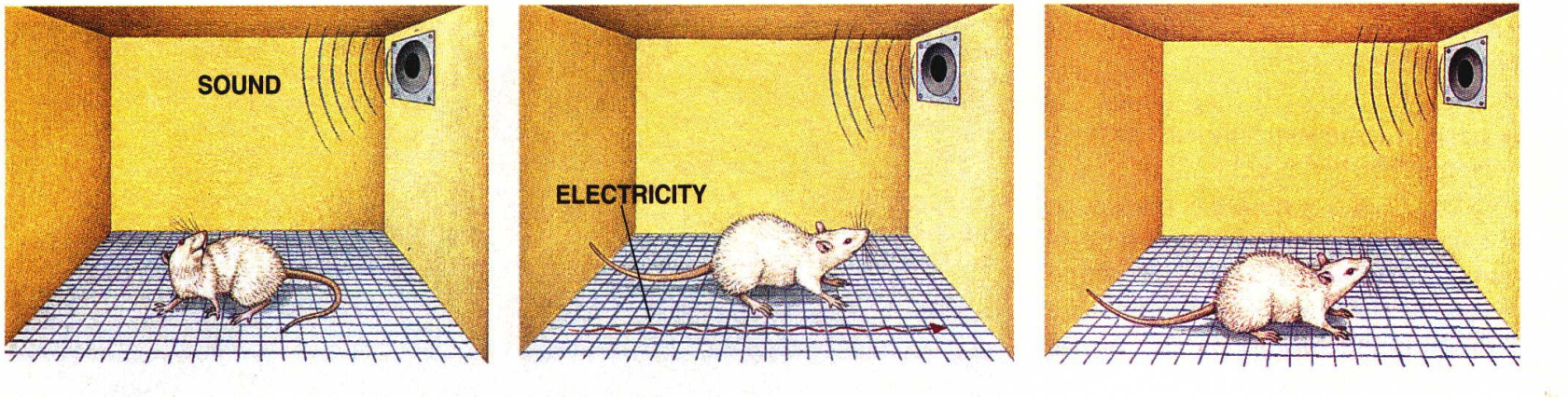


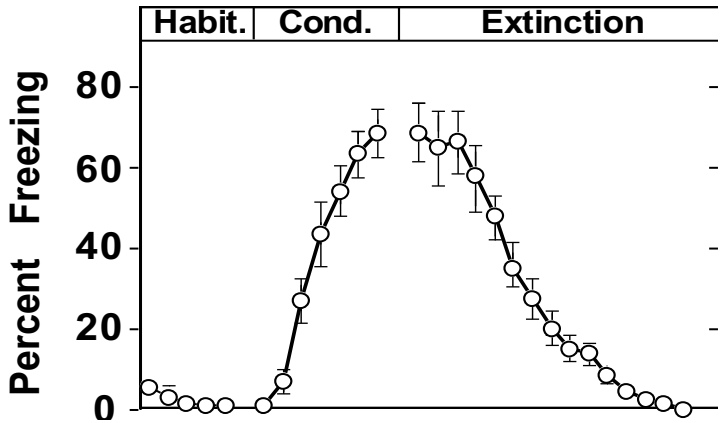




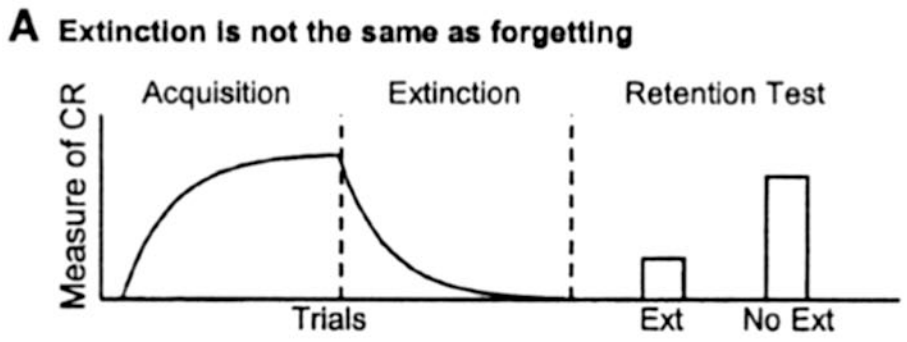
- Why is trace hippocampal-dependent?
- Maintaining the CS? Timing the trace? Harder?
- Eyelid requires ~0.3sec, and hippocampus is required when 0.5-1sec.
- In tone-shock, trace can be 3sec, and hippocampus is required for ~20sec
- This suggest context-conditioning

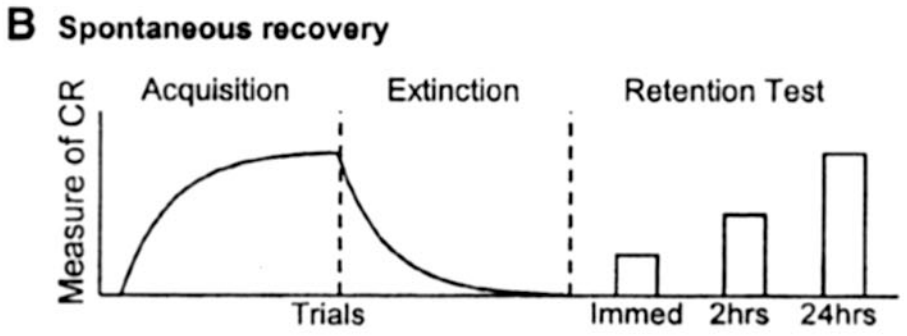
Extinction of fear-conditioning

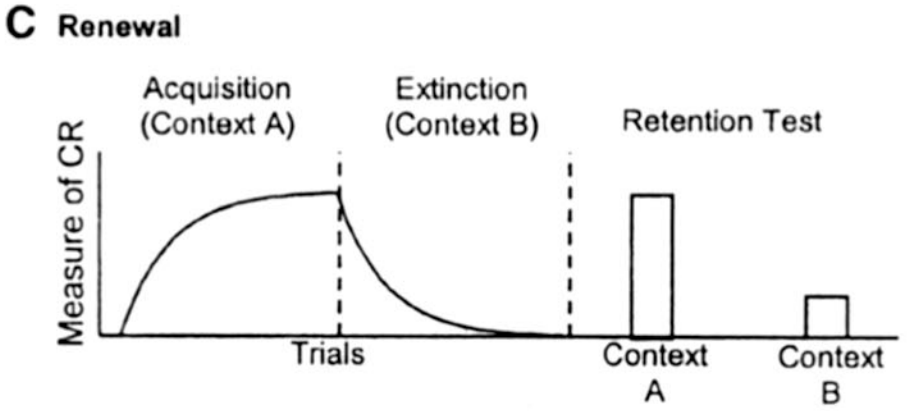


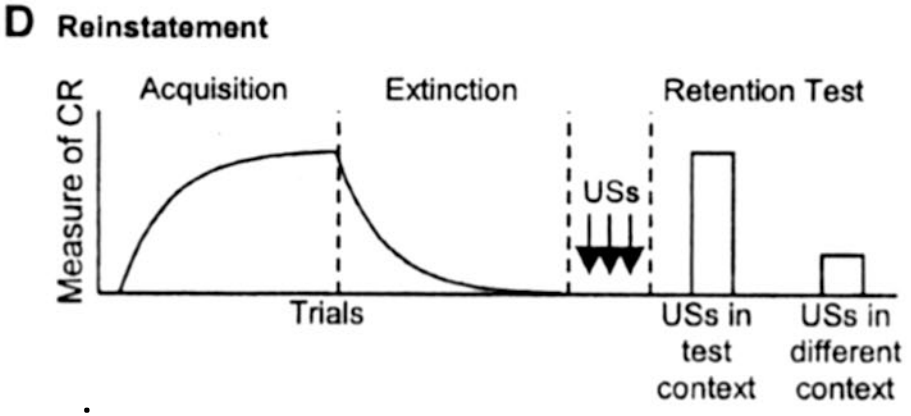


Extinction: a new learning



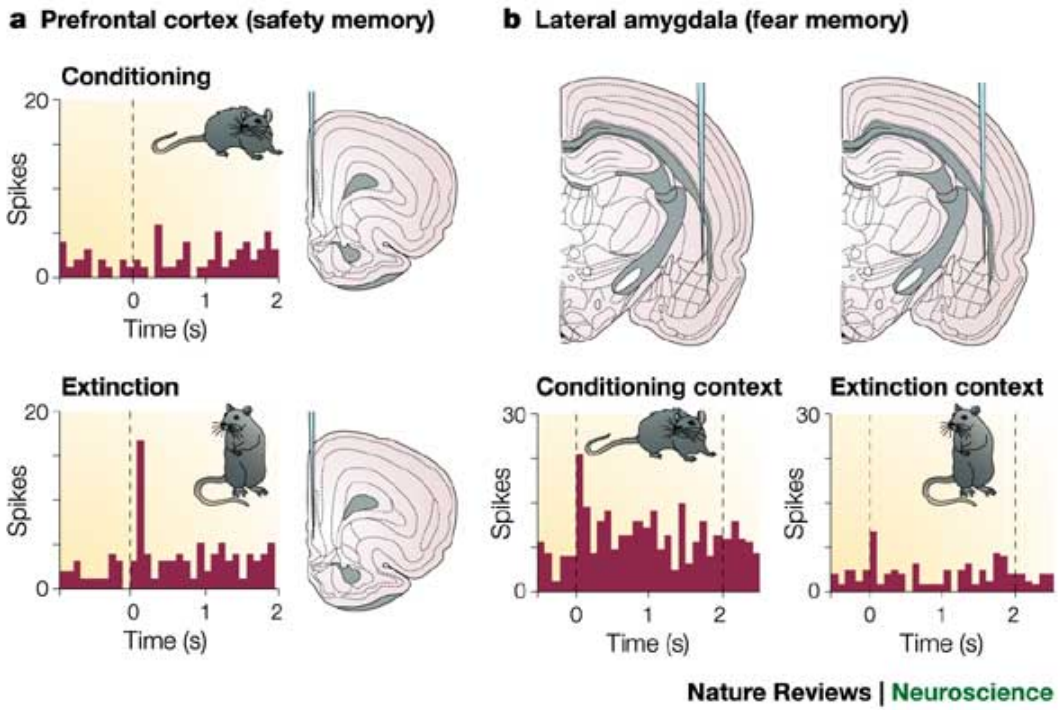


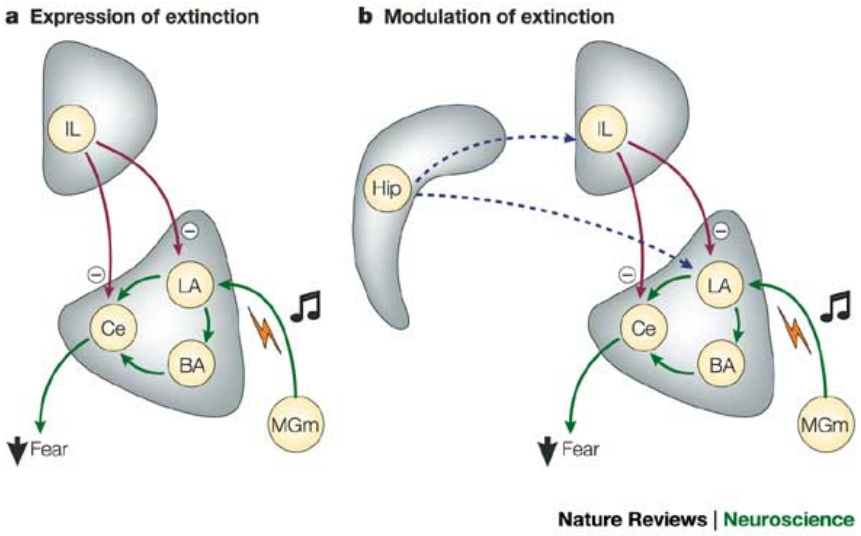


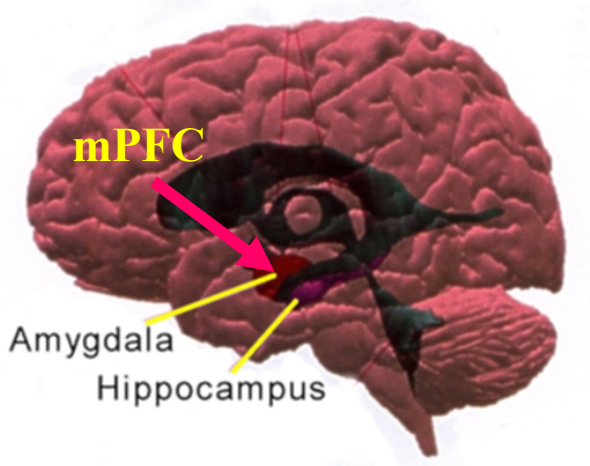


Faster re-learning

Extinction: brain mechanisms

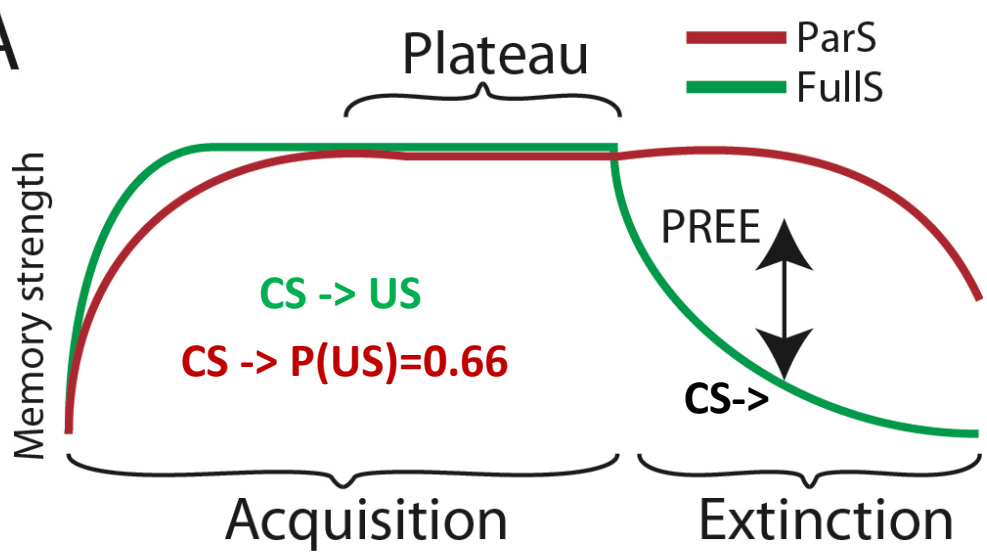






Partial reinforcement extinction effect

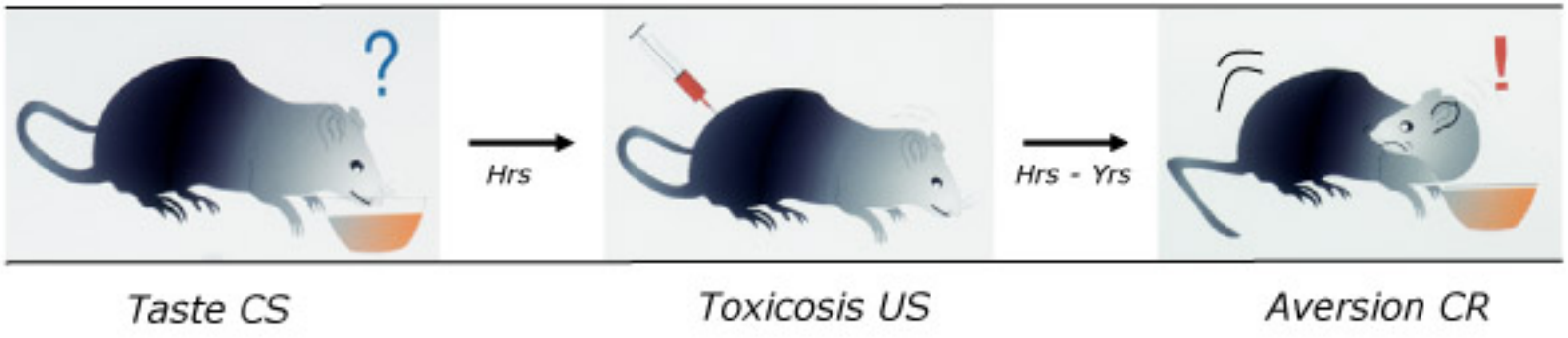
- Partial reinforcement
  - Fixed/variable ratio
  - Fixed/variable schedule
- Results in longer extinction



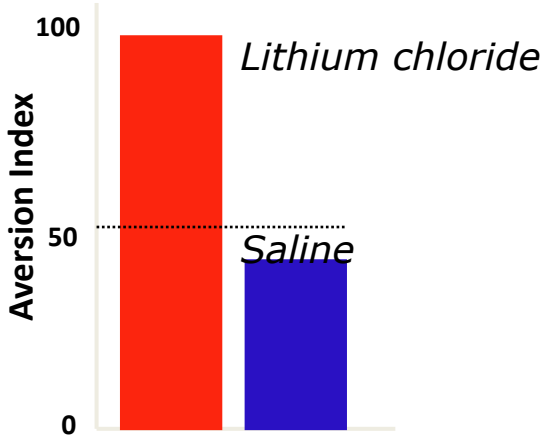
  - Frustration theory (Amsel): The omission of the US induces frustration. Therefore, during extinction, the frustration predicts the US.
  - Sequential theory (Capaldi): conditioning to strings of NNNRNNNR

Garcia J

Conditioned Taste Aversion



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



CTA

- Compound potentiation: odor + taste increase response to odor

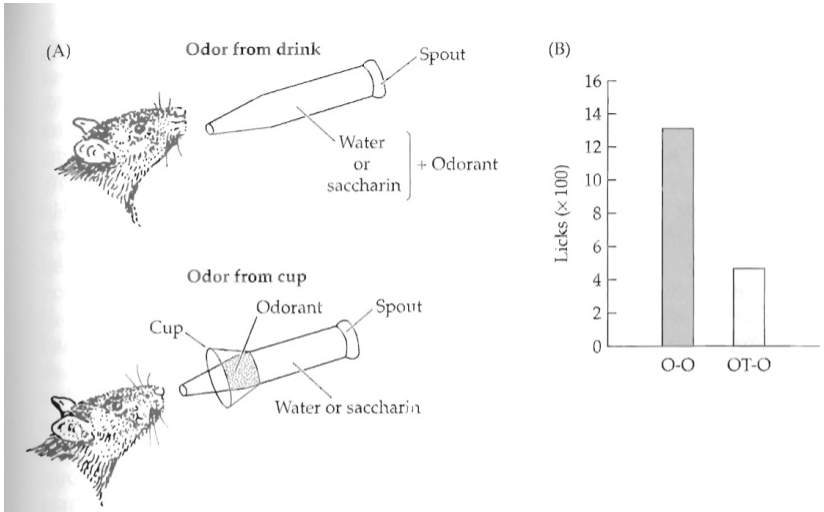
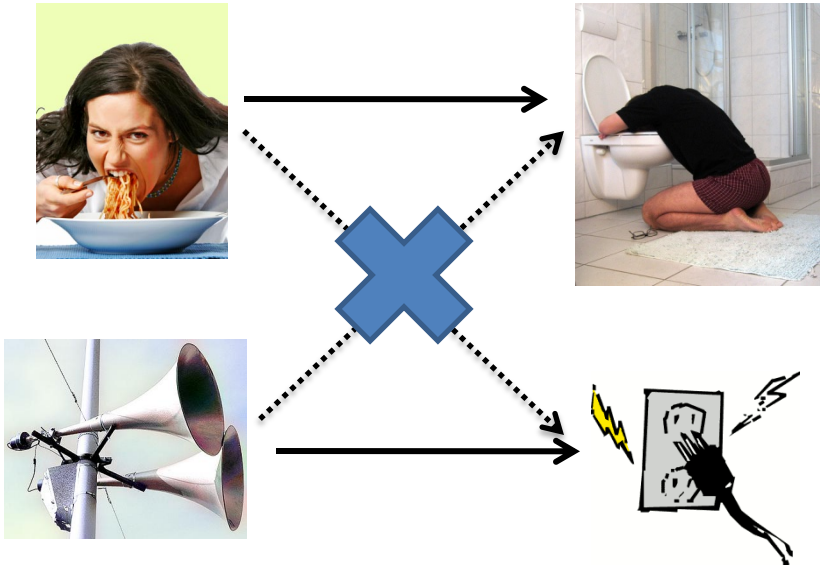


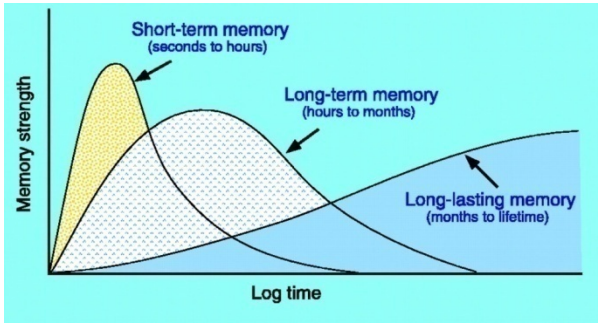
Figure 6.5 Potentiation of odor conditioning by taste. (A) A rat is given a taste in drinking water that also contains an odor. (In many experiments, the odor comes from a cup near the spout instead of being mixed in the drink.) (B) When odor is paired with illness on its own and then tested (O-O), it 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.)

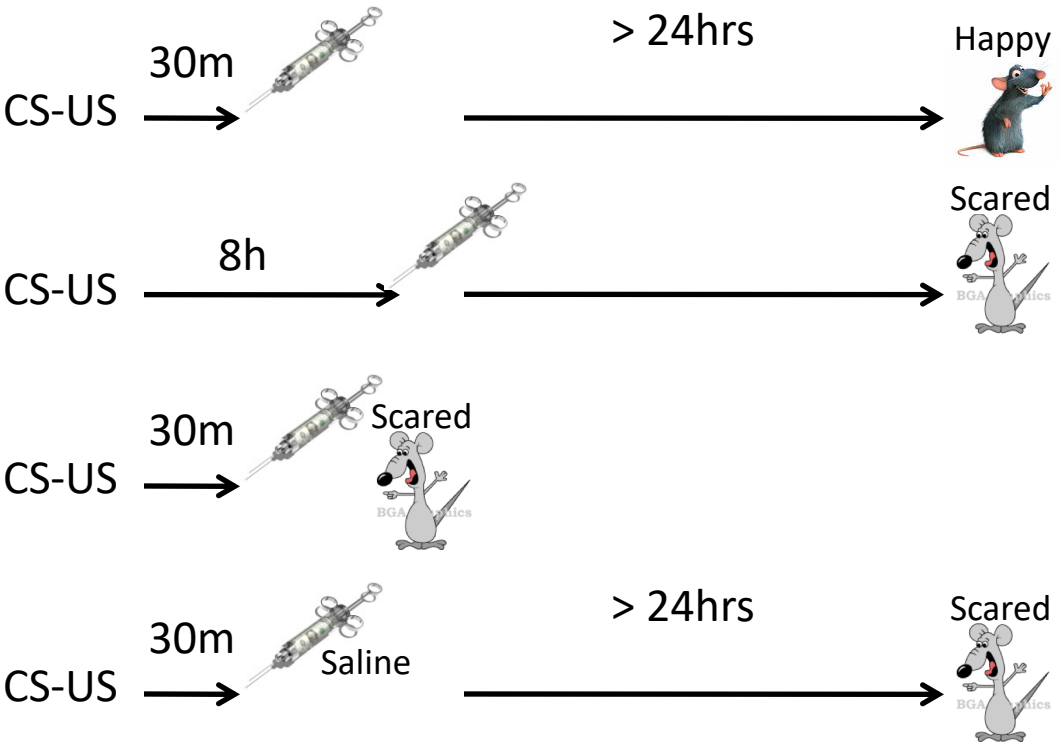
- Preparedness:

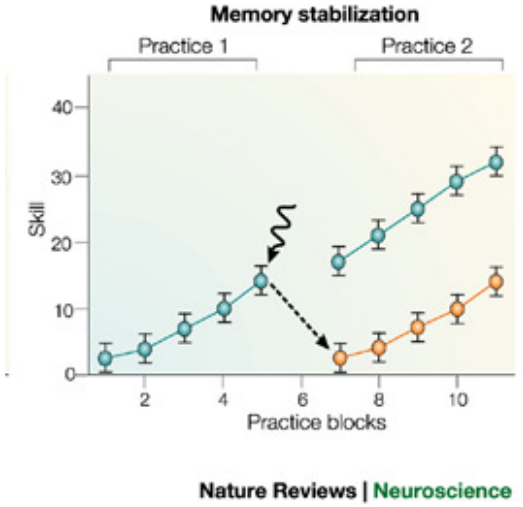


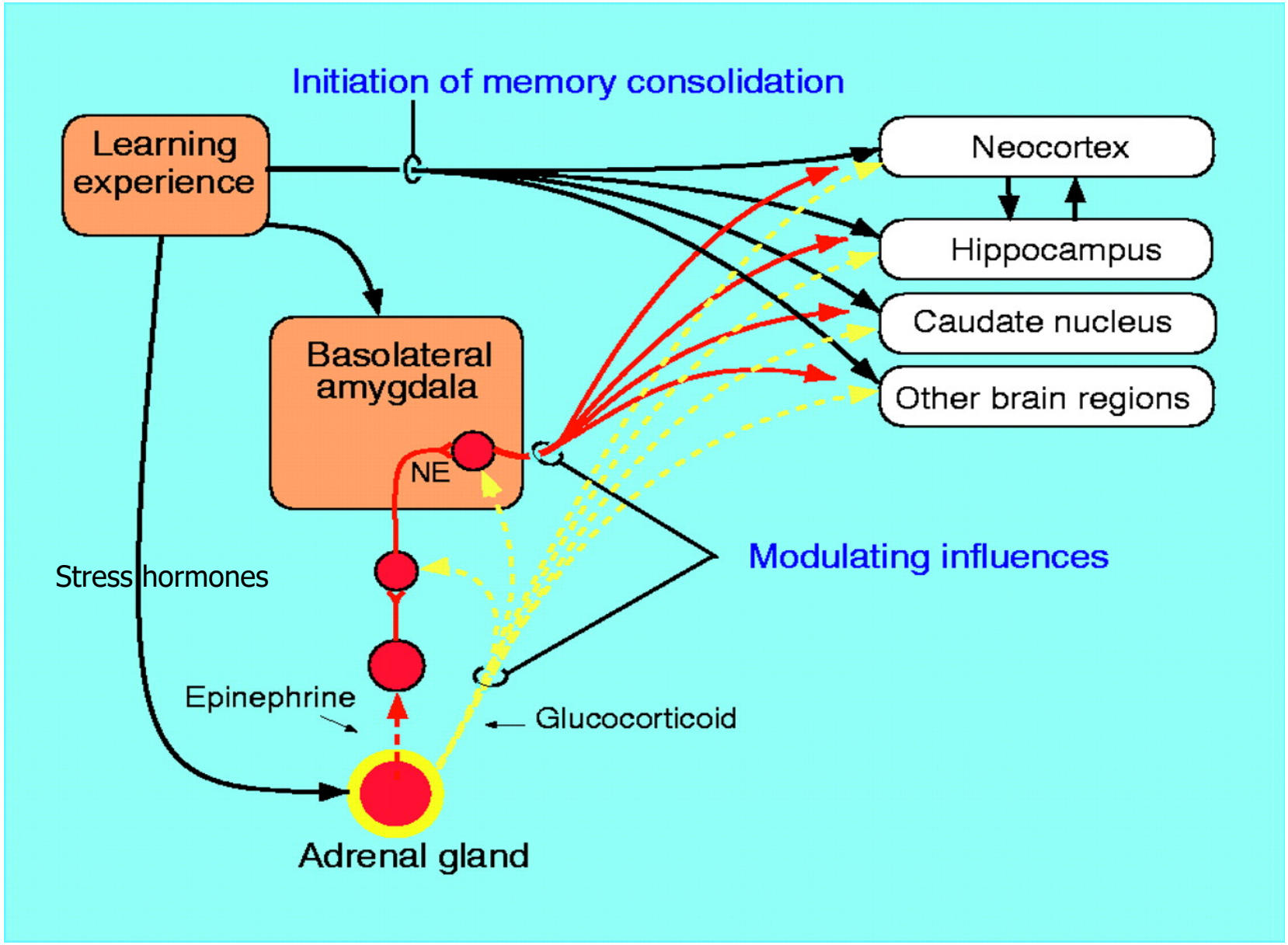
Consolidation

- 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.





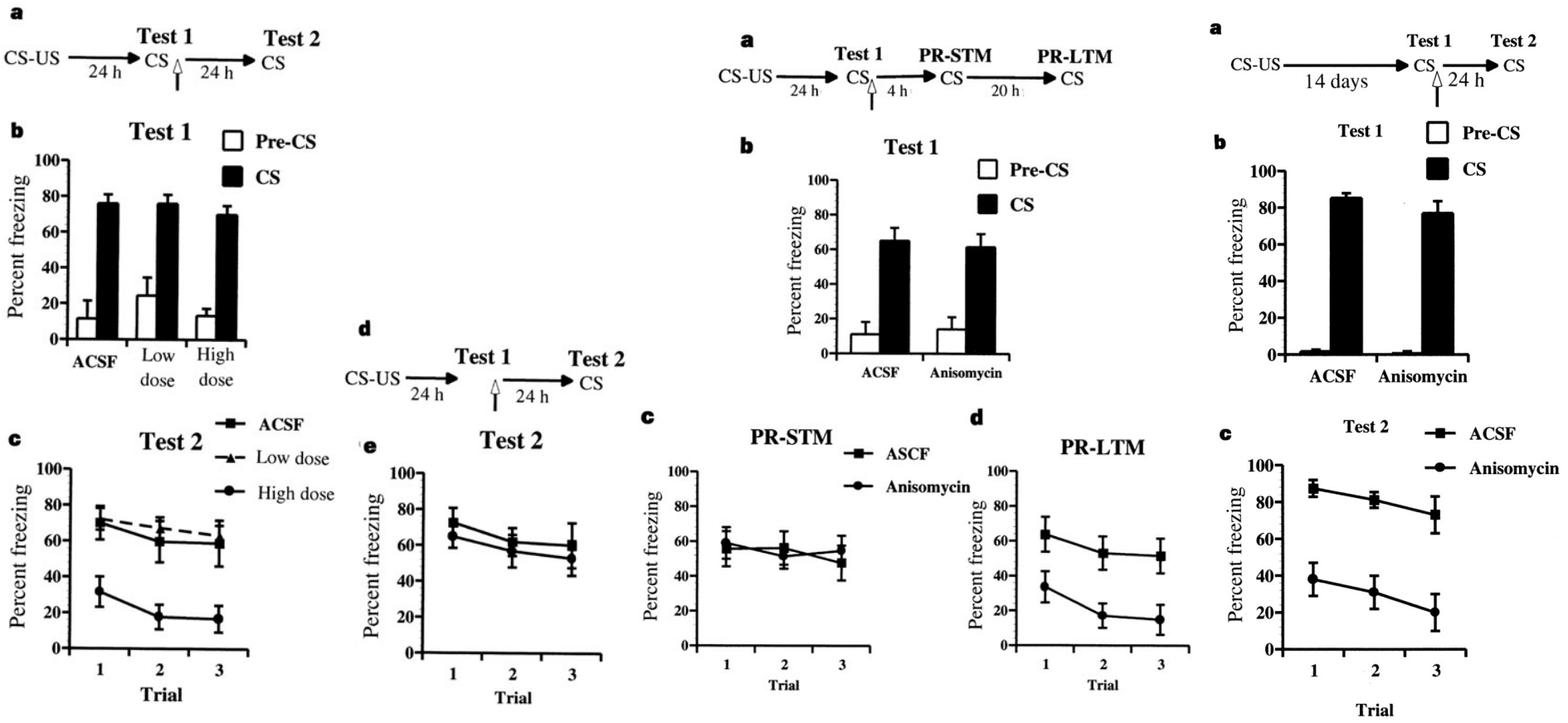




Mcgaugh JL, science, 2000

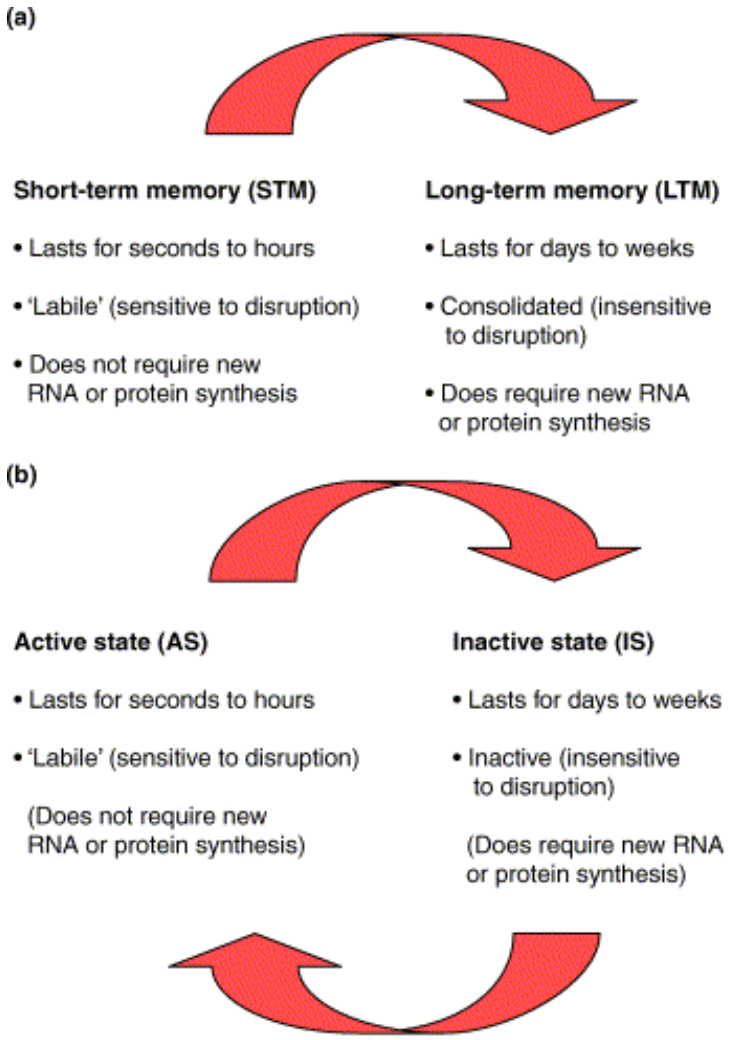
Reconsolidation

No effect on STM



Nader, Ledoux, Nature 2000

An updated view of memories



Stay safe, be fearless