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

<table>
<thead>
<tr>
<th></th>
<th>Decreases behavior</th>
<th>Increases behavior</th>
<th>Taking drugs?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presented</td>
<td>Positive punishment</td>
<td>Positive reinforcer</td>
<td></td>
</tr>
<tr>
<td>Taken away</td>
<td>Negative punishment</td>
<td>Negative reinforcer</td>
<td>More fun, less withdrawal</td>
</tr>
</tbody>
</table>
Classical fear conditioning

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

Schedules of reinforcement:
Variable/fixed interval/ratio
More than contingency:
Surprise / added information

Aversive conditioning

Blocking

Key:
- Food omission
- Shock
- Buzzer
- Frightened rat (fear response)
- Loud/aversive noise
- Light
- Tone
- Happy rat (no fear response)
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
Suggests common brain mechanisms

Trans-reinforcer blocking

Conditioned inhibition
Amygdala
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

CS Pathway
- Auditory Cortex
- Auditory Thalamus

US Pathway
- Somatosensory Cortex
- Somatosensory Thalamus

AMYGDALA
- LA
- B

CS
- CG
- LH
- PVN
- Paraventricular nucleus (hypothalamus)
- Periaqueductal lateral hypothalamus (midbrain)

US
- FREEZING
- ANS
- HORMONES

Ledoux, Mcgaugh, Davis
Neurons acquire tone responses after conditioning
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
Long-term potentiation (LTP)

- 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
  - Cooperativity: weak stimulation of many
LA encodes memory independent of fear behavior
Amygdala modulation of memory

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

Morris water maze

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

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

a. Contextual fear conditioning
   - Habituation
   - Foot shock
   - Exposure to cage without shock

b. Acoustic-cued fear conditioning
   - Habituation
   - Repeated tone - foot shock pairing
   - Presentation of tone alone

Normal rat
Shocked rat
"Freezing" rat
Extinction of fear-conditioning
Extinction: a new learning

A. Extinction is not the same as forgetting
B. Spontaneous recovery
C. Renewal
D. Reinstatement

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
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 6.3  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., 1985.)
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.

---

**Consolidation Diagram**

- CS-US 30m -> > 24hrs -> Happy
- CS-US 8h -> Scared
- CS-US 30m Scared -> 30m Saline -> > 24hrs -> Scared
Stress hormones

Mcgaugh JL, science, 2000
Reconsolidation

No effect on STM

Nader, Ledoux, Nature 2000
An updated view of memories

(a)

Short-term memory (STM)
- Lasts for seconds to hours
- ‘Labile’ (sensitive to disruption)
- Does not require new RNA or protein synthesis

Long-term memory (LTM)
- Lasts for days to weeks
- Consolidated (insensitive to disruption)
- Does require new RNA or protein synthesis

(b)

Active state (AS)
- Lasts for seconds to hours
- ‘Labile’ (sensitive to disruption)
  (Does not require new RNA or protein synthesis)

Inactive state (IS)
- Lasts for days to weeks
- Inactive (insensitive to disruption)
  (Does require new RNA or protein synthesis)
PTSD (post-traumatic-stress-disorder)

- Extinction failure
Reconsolidation and extinction: What Freud always knew
Context Generalization / specificity
Stay safe, be fearless