A Concrete Example

Fear Extinction

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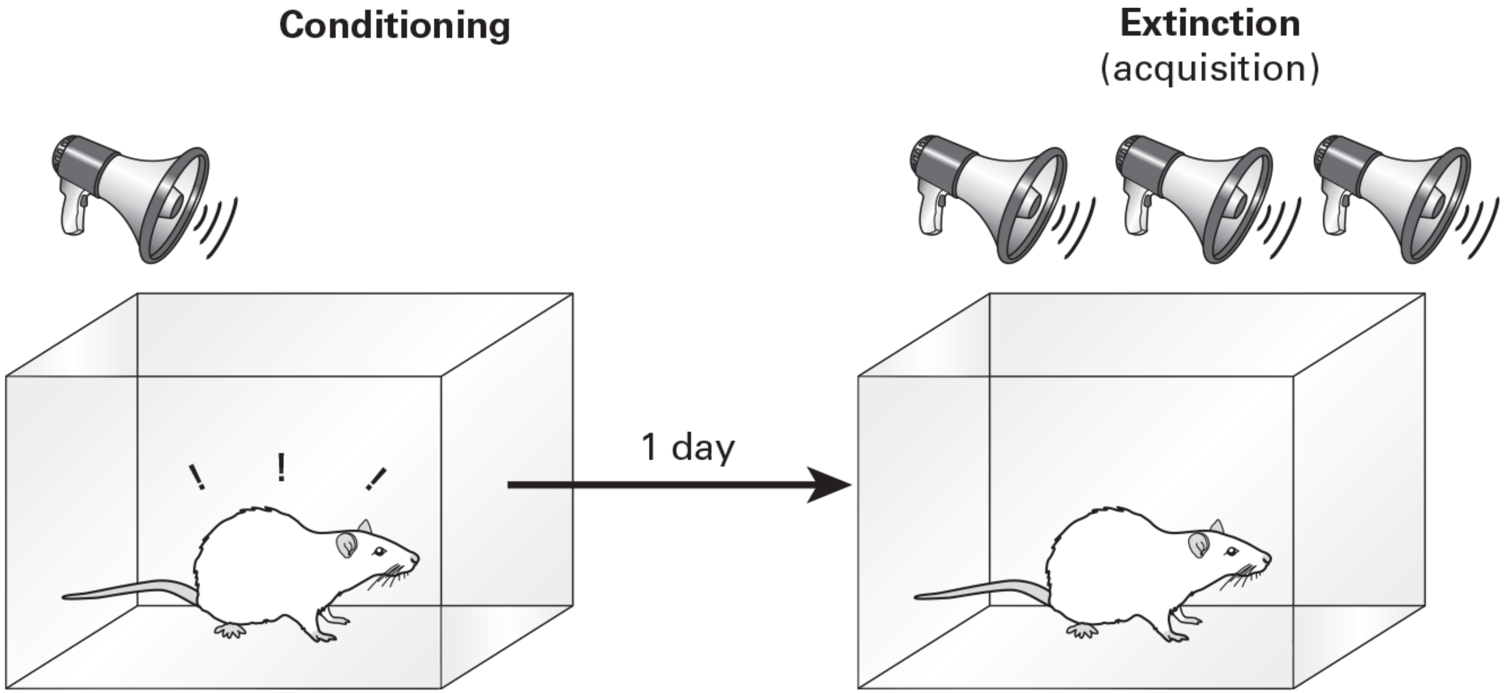
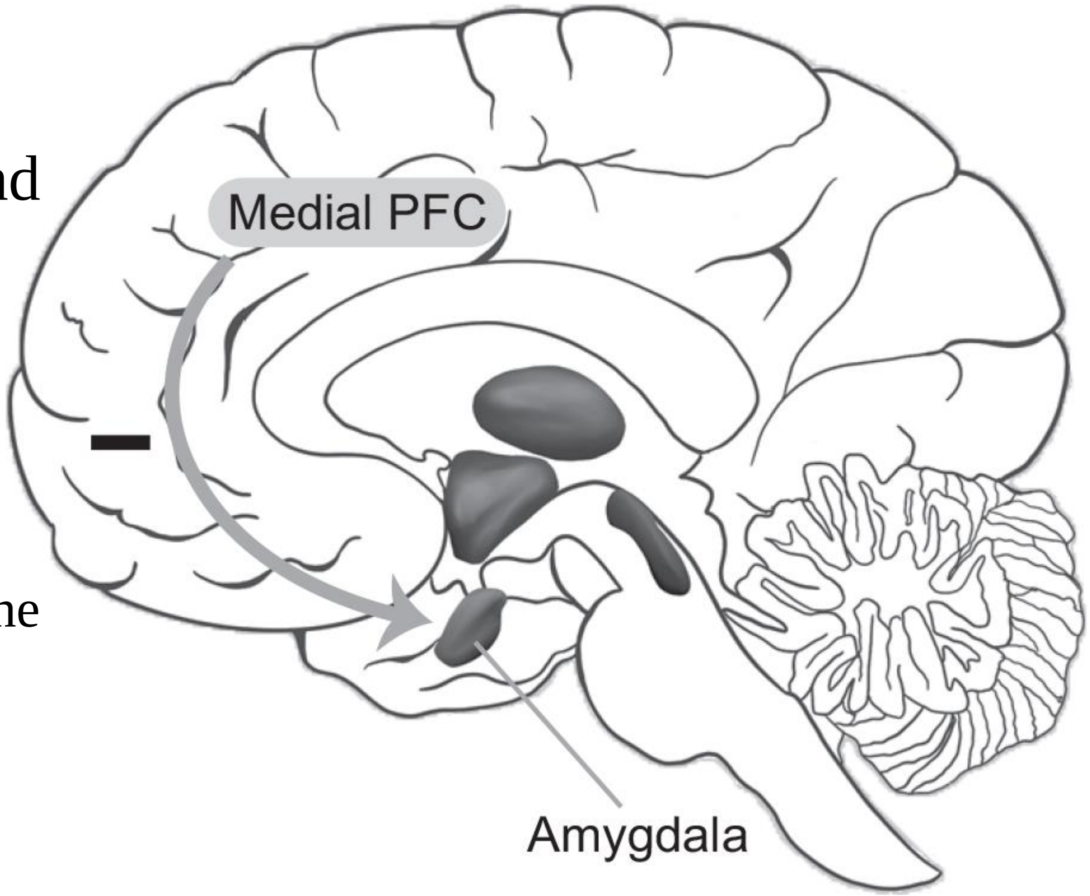
Unlearning Fear

- How do brain circuits generate complex behaviors in practice?
- We discuss a concrete example: ***extinction learning***
  - This explains why exposure therapy works and what makes it successful.



Unlearning Fear

- The ***acquisition*** of fear relies on the amygdala and several brainstem areas (see Part 1)
- 20C theory for ***fear extinction***: The ***medial prefrontal cortex*** inhibits the amygdala
  - The medical PFC is ***anatomically interconnected*** with the amygdala and several brainstem targets
  - Animals with medial PFC lesions took longer to ***extinguish*** learned associations (LeDoux et al, 1993)
  - The MPFC is involved in learning that the CS ***no longer signals threat***



Unlearning Fear

- Extinction is not simply the ***inhibition of fear***
  - Only the conditioned stimulus's ability to produce freezing behavior is diminished
  - The general fearfulness of rats are left unaltered
- Extinction is a sophisticated form of ***learning***. What is being learned is safety.
  - As any learning process, fear extinction involves acquisition, consolidation, and retrieval
- For a successful extinction, the nature of the ***CS-UCS relationship*** needs to be unraveled
  - ***Protection from extinction***: when CS1(original) is presented with CS2 or accompanied with an action and no UCS ensues, the original CS1 will maintain its association with the UCS
  - ***Backward blocking***: if (CS1 & CS2) → UCS and CS1 → UCS consistently, then CS2 ↛ UCS

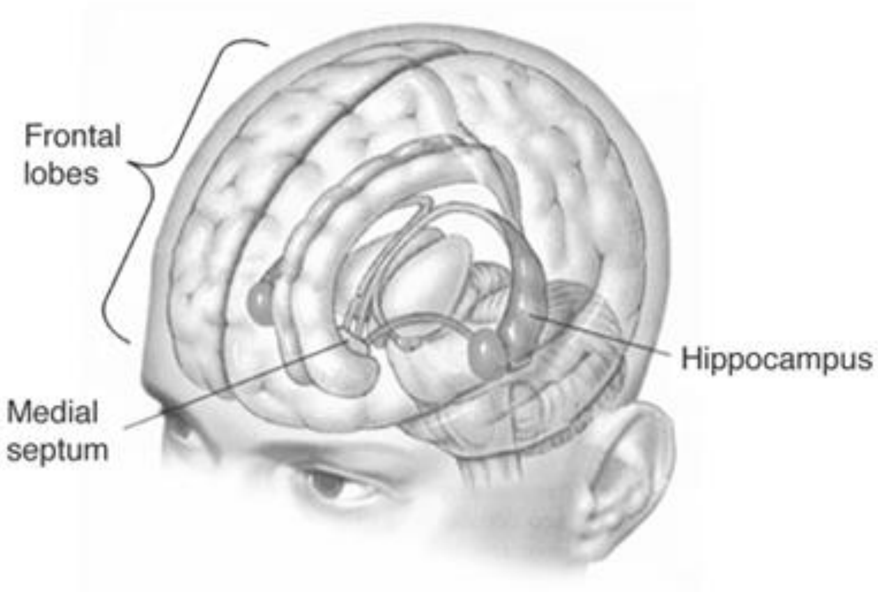
Mechanisms of Extinction

- Although the ***medial PFC*** plays an important role during extinction, there is no evidence that it inhibits the amygdala
- The ***amygdala*** participates in not only acquisition but also extinction
  - chemical blockage of the basolateral amygdala impairs or prevents extinction
  - the consolidation of extinction involve morphological changes in the amygdala
  - the amygdala also projects onto the medial PFC
- Animals learn that the CS ***in this environment*** is now safe.
  - The ***hippocampus*** keeps track of the context. It is likely involved in fear extinction.

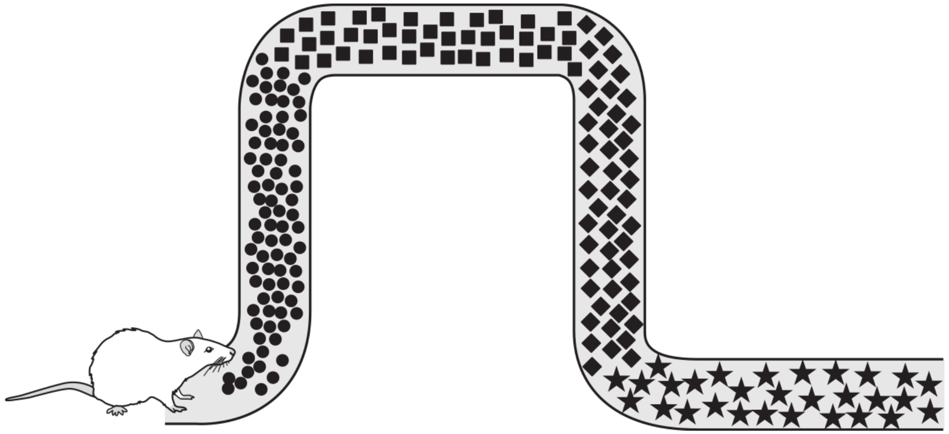
The Hippocampus

Does the hippocampus implement ***memory functions*** vs ***spatial functions***?

- ***Patient H.M.*** had most of his hippocampus removed by surgery to treat his seizures.
- Displayed impaired memory formation

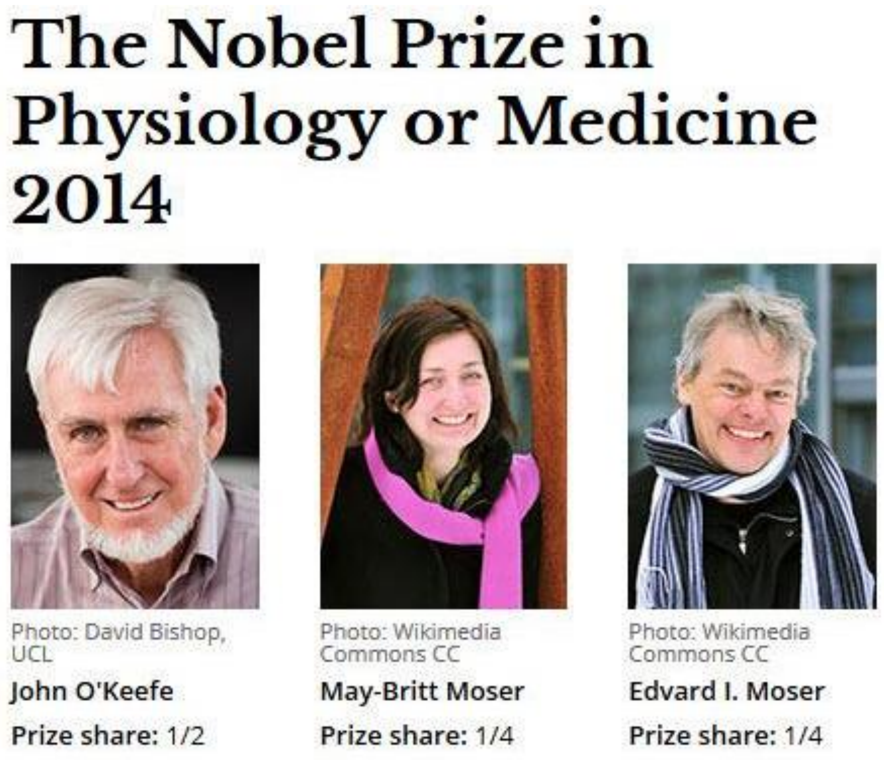


- O'Keefe and Dostrovsky (1971) observed selective, vigorous firing of hippocampus neurons to places in the environment (later popularized as "***place cells***")
  - "spatial reference map"



The Hippocampus as Brain's "Inner GPS"

- Cognitive Maps: Conceptualized by Edward Tolman
  - Learning is an active process of extracting the ***underlying structure of the world*** through a map-like representation of causal associations
- The hippocampus encodes ***environmental information***
  - "grid cells", "border cells", "head direction cells", "speed cells", "time cells" in the hippocampus (Nobel Prize 2014)
  - Hippocampal cells are influenced by ***more than space and time***: conditioned stimuli, novelty, attention, internal state, reward, etc.



The Hippocampus ⊂ Temporal Lobe

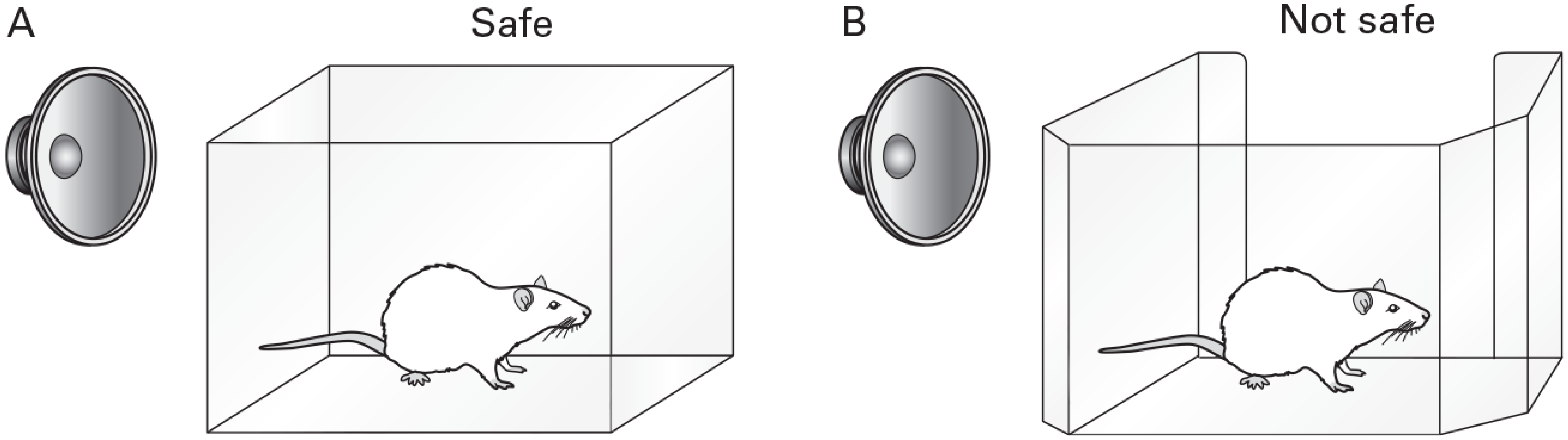
- Memory vs Space
  - One perspective is that the brain uses space to organize memories (episodic memories)
  - Another idea suggests that the hippocampus generates at once a map of space and a map of memories, together with links between them.

↓

- Today's research is less centered on a sole region – it is more about ***how the parts interact*** in the temporal lobe.
  - Episodic memory and spatial navigation are not carried out by single regions

The Hippocampus's Role in Extinction

- The ***hippocampus*** provides context-related information that guides extinction.
  - Context is important because it is better to treat the CS as dangerous under different conditions.

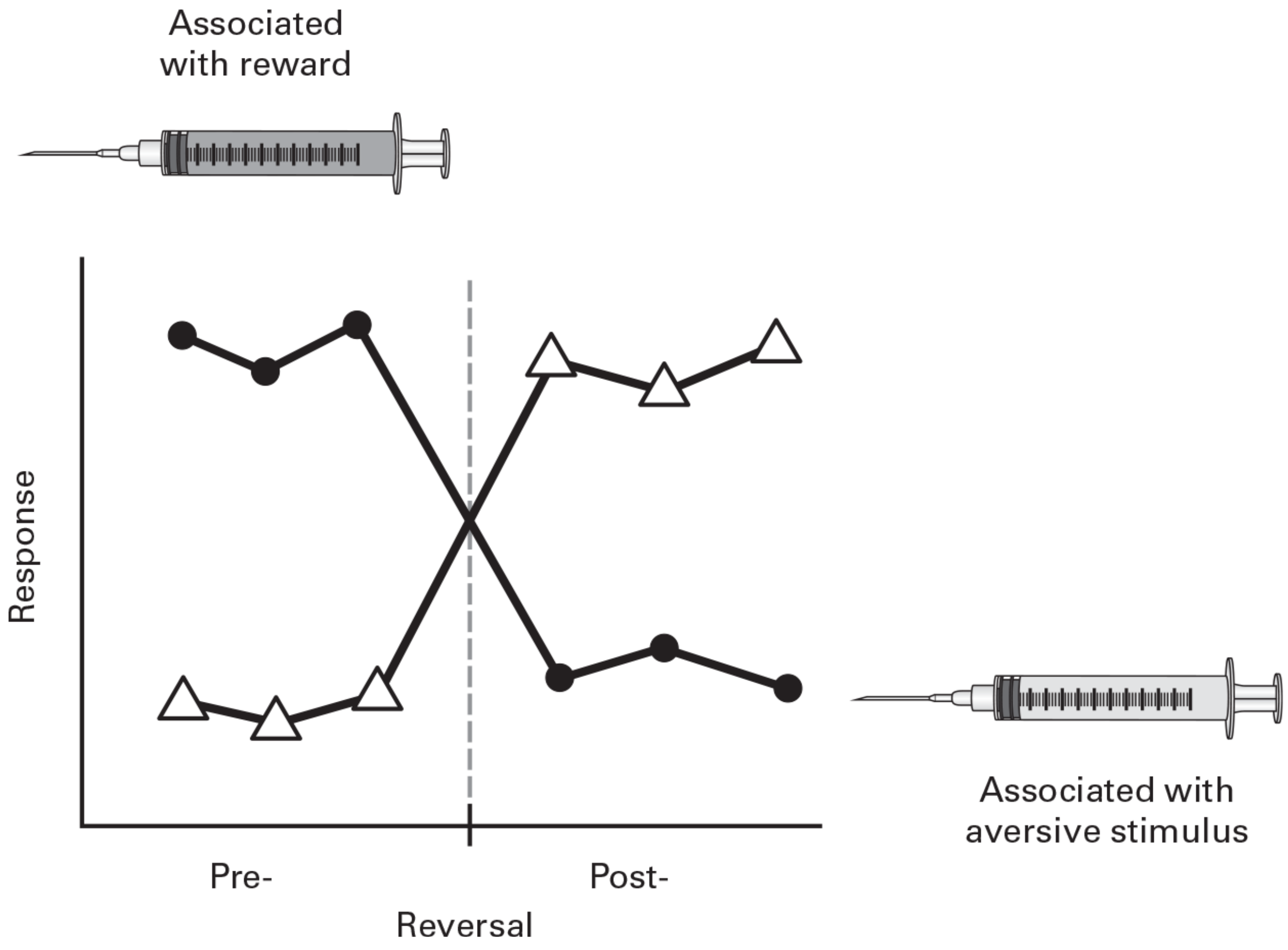


The Hippocampus's Role in Extinction

- The hippocampus has direct connections to the ***amygdala***, and the targeted neurons in the amygdala promote defensive responding ("fear").
  - Through this pathway, the hippocampus signals that the CS is given in a novel context—**fear is renewed.**

- The hippocampus also has dense projections to the ***medial prefrontal cortex***, and the hippocampus can engage the medial PFC to indicate that the environment has not changed.
  - Here, the original context of extinction is the same experienced presently, **so it is likely safe.**

The Orbitofrontal Cortex: Reversal Learning



- Initial training associates the syringe with reward (juice)
- Reversal occurs and the syringe is associated with punishment (salt)
- Without the OFC, animals were impaired in their ability to reverse behavior

The Orbitofrontal Cortex: Updating Value

- Neurons in the OFC respond to the meaning of the stimulus

  → They ***encode value***

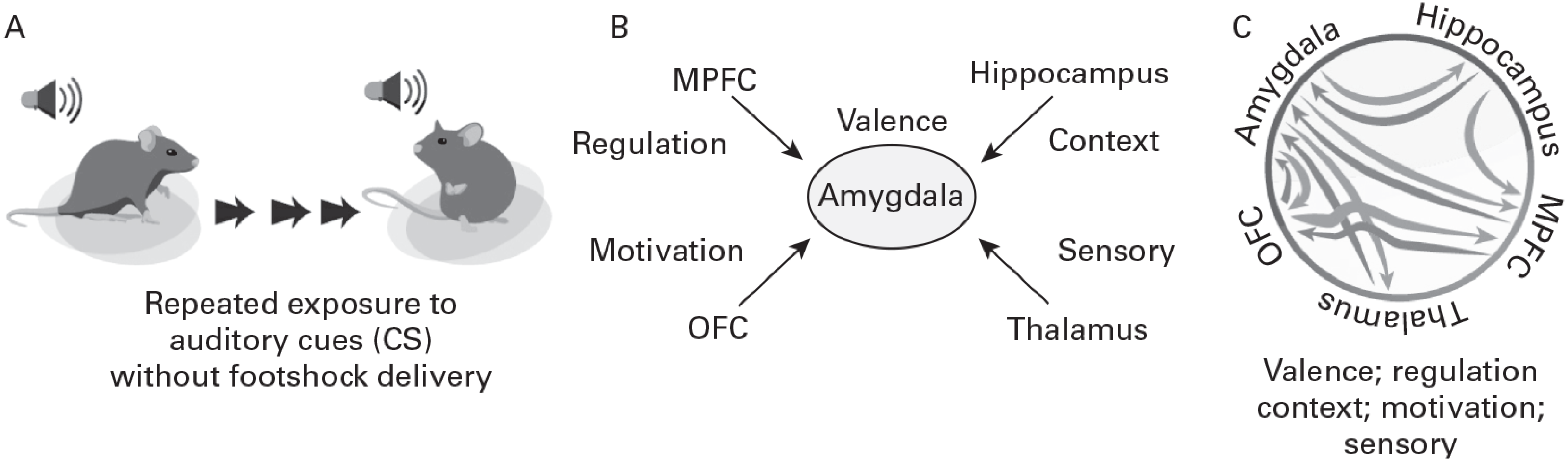
- Firing is not due to object features, but the ***outcome*** it predicts ***(reward/punishment)***
  - neurons in the OFC integrate the ***magnitude and the probability of reward.***
- The ***animal's current state*** is considered when the ***value of the outcome*** is predicted
  - Monkeys with OFC lesions will fail to update their food preference even after overfeeding on it

The OFC and Hippocampus: T-maze

- The hippocampus & the orbitofrontal cortex: T-maze experiment
- Rats often paused at the choice point. What were they doing?
- ***Simulating*** the consequences of potential actions before decision
  - Hippocampal cell firing encoded information about pathways ahead
  - Orbitofrontal neurons fired along a path based on the probability that it would lead to reward
- Direct connections between the hippocampus and orbitofrontal cortex suggest that the former conveys spatial information that the latter evaluates its expected behavioral significance

Collective Dynamics: Unlearning Fear

- We are used to thinking like **Figure B**: top-down regulation, one-to-one correspondence between brain areas and “valence”, “regulation”, “context”, etc.
- Alternatively, **Figure C** might be the more realistic picture: nonhierarchical view, no straightforward one-to-one relation ⇒ the brain regions ***collectively*** determine the extinction process



How to Define a Jointly Interdependent System

- Why? Because the underlying processes (valence, regulation, etc.) are ***not separable***
  - These variables are so intertwined that they are ***jointly determined***
  - ***Natural behaviors*** are better described as ***dynamical systems***
- A simpler example of foxes and hare:

$$F'(t) = \alpha FH - \beta F$$

$$H'(t) = \gamma H - \delta FH$$

- How can we proceed with this ***complex systems perspective***?
  - Computationally, we can specify equations for signal changes in the amygdala, hippocampus, etc.
  - Experimentally, we can focus on multiregional temporal evolution of brain data

Far from Simple

- Discussion/Quiz