Emerging Treatments of Anxiety Informed by Scientific Knowledge about the Brain

Outline

- Psychotherapy, learning, and neuroplasticity
- Neural circuitry of therapeutic change
- Pharmacological enhancement of psychotherapeutic learning
  - D-cycloserine
  - SSRIs
- Pharmacological interference with psychotherapeutic learning
  - Benzodiazepines
- Erasing bad memories

Psychotherapy, Learning, and Neuroplasticity

- Learning
  - Acquiring new information and/or skills: emotional regulation, coping strategies, cognitive restructuring, mindfulness, acceptance, behavioral activation
  - Altering/adapting behavior to meet environmental demands or contingencies
  - Repetition and practice
- Neuroplasticity
  - Experience-dependent changes in brain structure and function
  - Synaptic plasticity (e.g., LTP)
  - Neurogenesis
  - Repetition and practice
- Treatment emphasis: learning vs. symptom reduction
  - Repetition and practice

Neural Circuitry of Psychotherapeutic Change

- **Prefrontal cortex**
  - **Emotional regulation, coping strategies, cognitive structuring, directing behavioral activation**
- **Hippocampus**
  - **Learning and memory related to therapeutic change**
- **Amygdala**
  - **Emotional salience related to therapeutic change**
- **Insula**
  - **Moment-to-moment awareness and mindfulness to effect therapeutic change**

Neural Circuitry of Psychotherapeutic Change

- Neural pathways that support dysfunctional thinking and behavior patterns
  - Anxiety, panic, worries, phobias, obsessions, avoidance
  - Depression, self-critical thoughts, suicidal thoughts
  - PTSD, self-blame, safety, trust, power/control, intimacy, esteem
  - Anger, irritability, outbursts, abusive behavior
  - Practice/repetition leads to strengthened neural connections
    - Same mechanisms as in learning math, chess, or piano
  - These neural connections will not go away and cannot be excised
    - They are here for the rest of patient's life
    - This is the bad news (but makes evolutionary sense)
    - Anxiety, depression, and anger co-opted these evolutionarily preserved and often beneficial mechanisms
- Psychotherapy develops and strengthens neural pathways that support accurate thinking and adaptive behavior patterns
  - Thanks to the exact same neuroplastic mechanisms that created the dysfunctional thinking and behavior patterns above

Neural Circuitry of Psychotherapeutic Change

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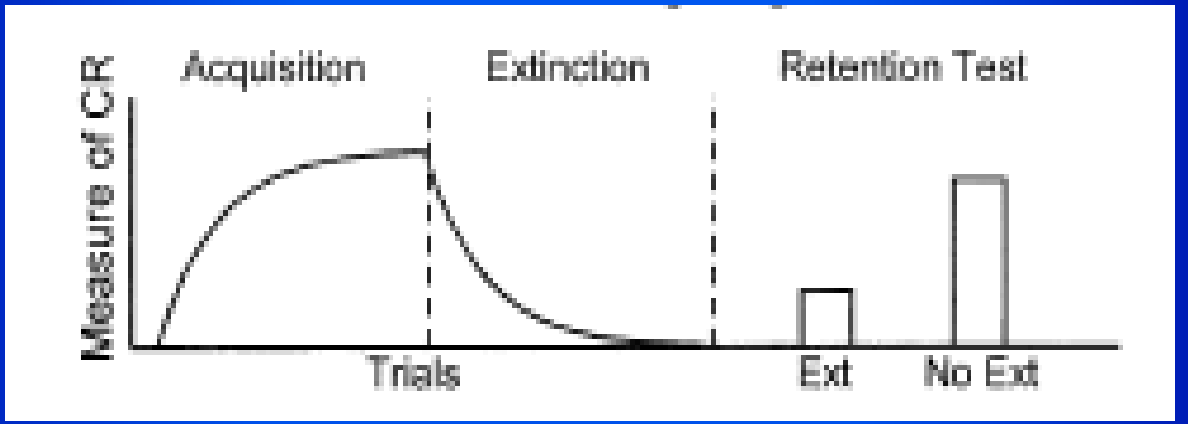
- Remember, your brain will help you get really good at whatever you spend your time doing

Extinction and Exposure Therapy

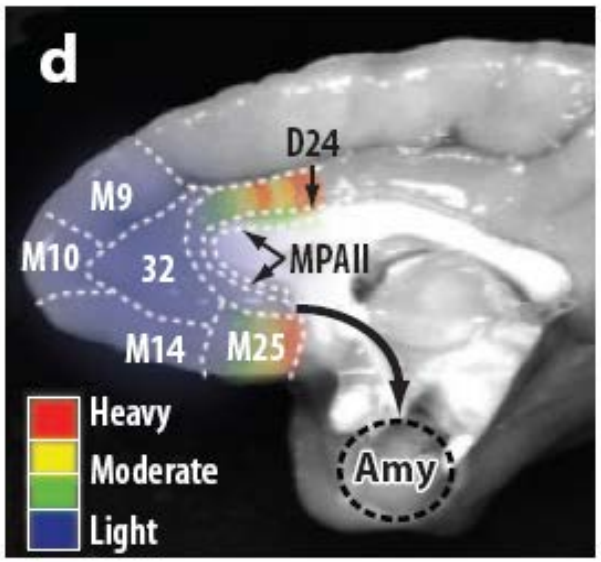
- Extinction is NOT erasing the association between an innocuous cue and danger (shock), but rather learning a new association between that cue and safety (no shock)

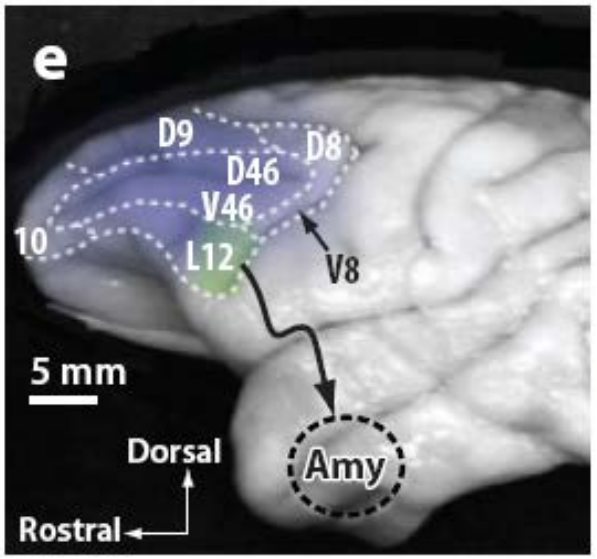


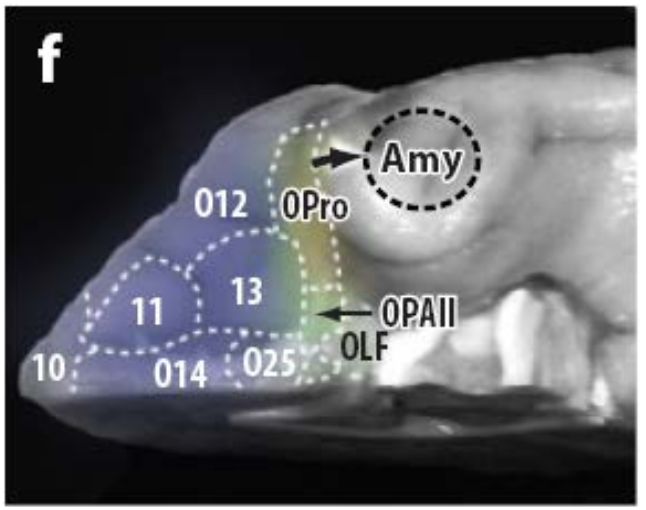
- Exposure therapy is NOT erasing the association between an innocuous cue/trigger and danger (rape, mortar attack), but rather learning a new association between that cue/trigger and safety (no harmful event, safe setting)
- This is implemented via activation of the ventromedial PFC that sends inhibitory projections to the amygdala

Extinction and Exposure Therapy

PFC–Amygdala Connectivity







Ghashghaei et al. (2007) *Neuroimage*

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"The joint use of pharmacological and psychotherapeutic interventions might be especially successful because of a potentially interactive and synergistic—not only additive—effect of the two interventions. Psychopharmacological treatment may help consolidate the biological changes caused by psychotherapy."

Eric R. Kandel, M.D., 1998

Kandel (1998) *Am. J. Psychiatry*

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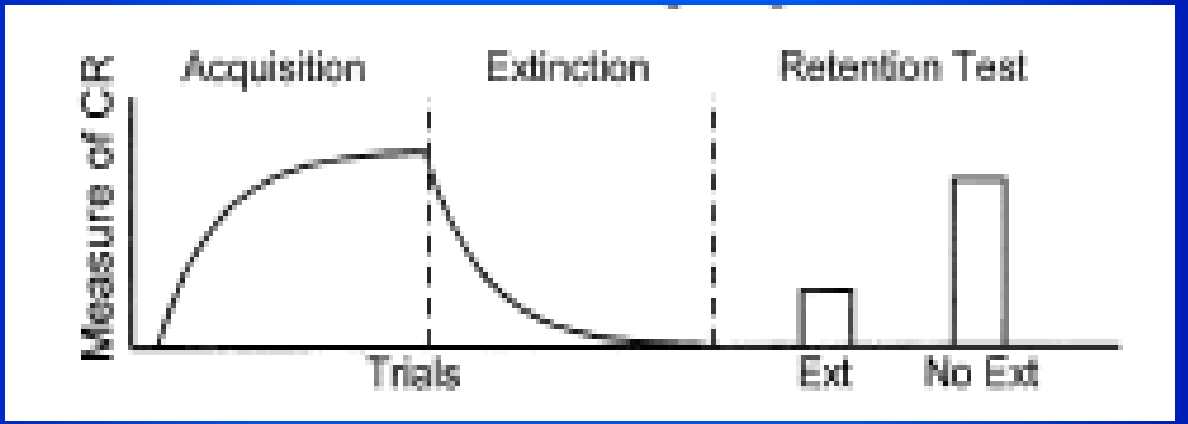
D-cycloserine Facilitates Extinction Learning

- Extinction is NOT erasing the association between an innocuous cue and danger (shock), but rather learning a new association between that cue and safety (no shock)



- D-cycloserine facilitates learning the new association between that cue and safety (no shock)

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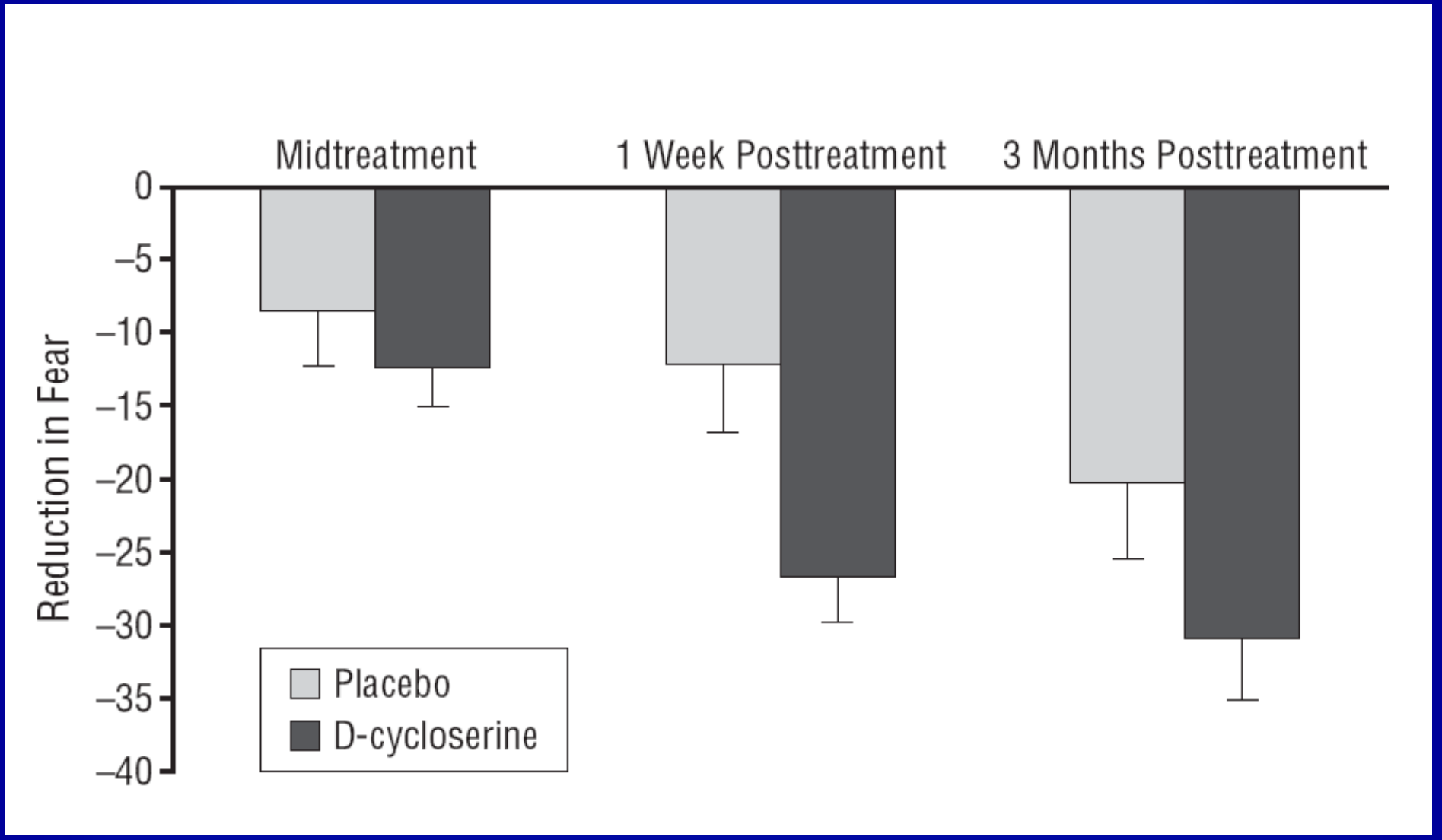
D-cycloserine, Virtual Exposure Therapy, and Acrophobia



Ressler et al. (2004) *Arch. Gen. Psychiatry*

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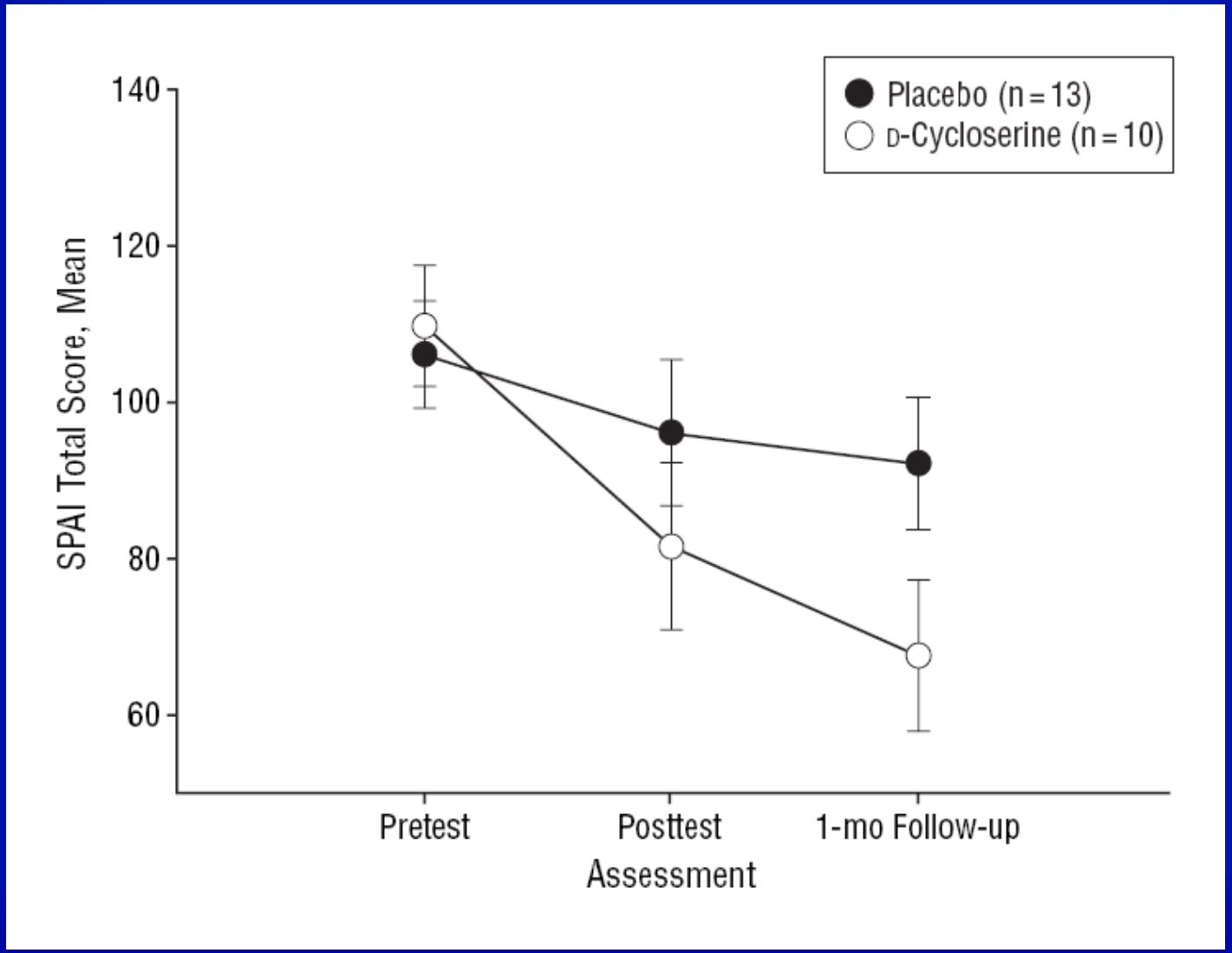
D-cycloserine, Exposure Therapy, and Social Anxiety Disorder



Hofmann et al. (2006) *Arch. Gen. Psychiatry*

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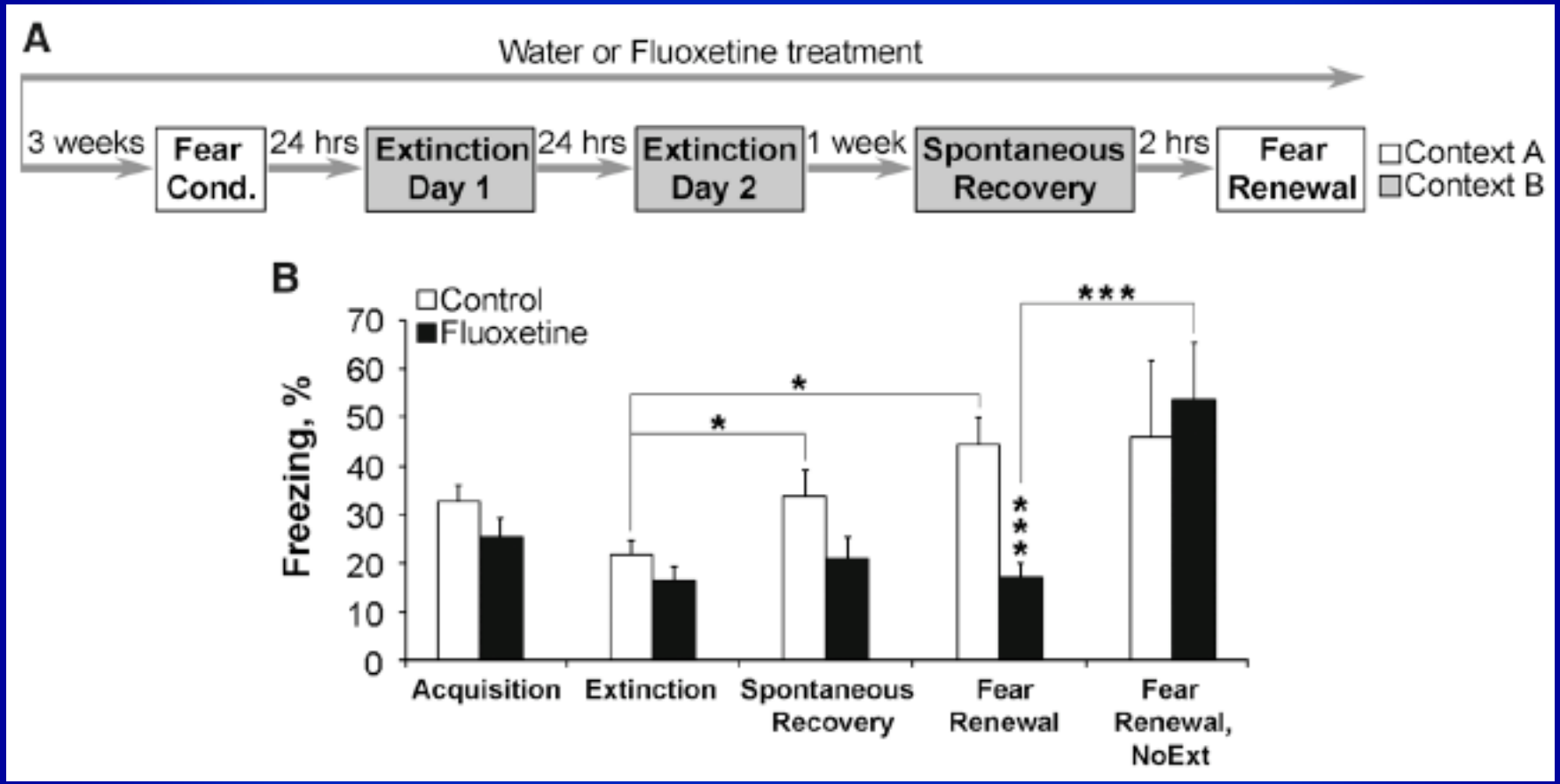
SSRIs and Extinction



Karpova et al. (2011) *Science*

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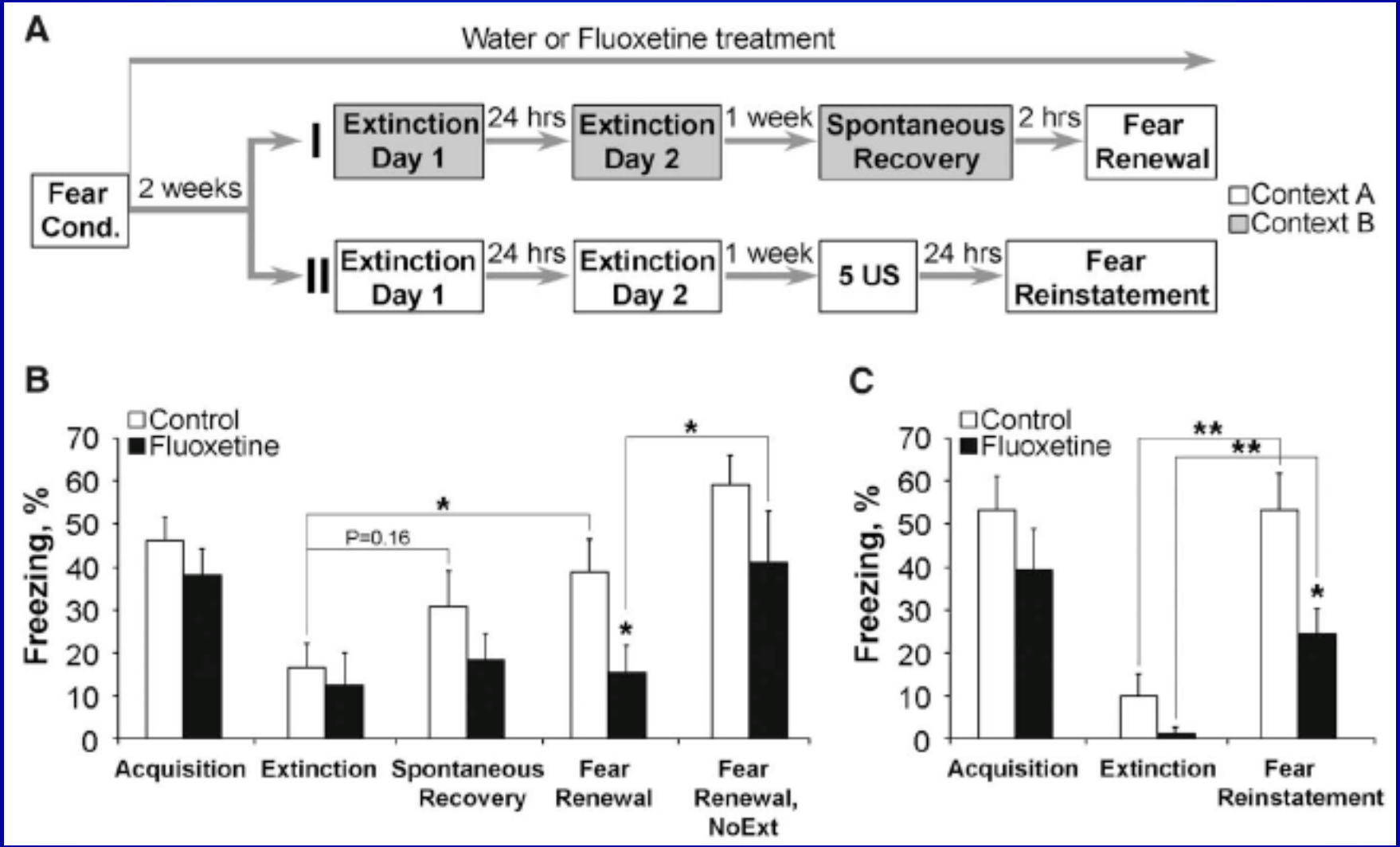
SSRIs and Extinction



Karpova et al. (2011) *Science*

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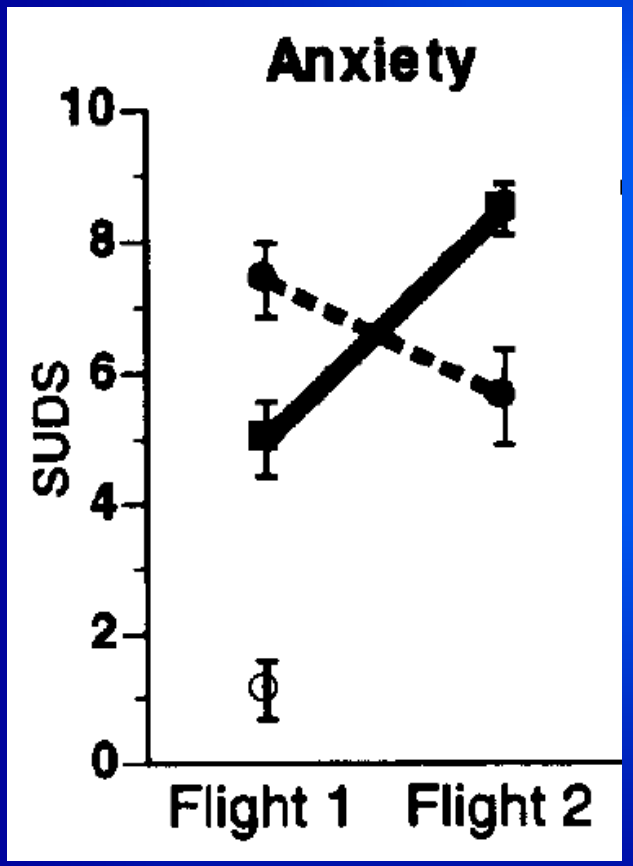
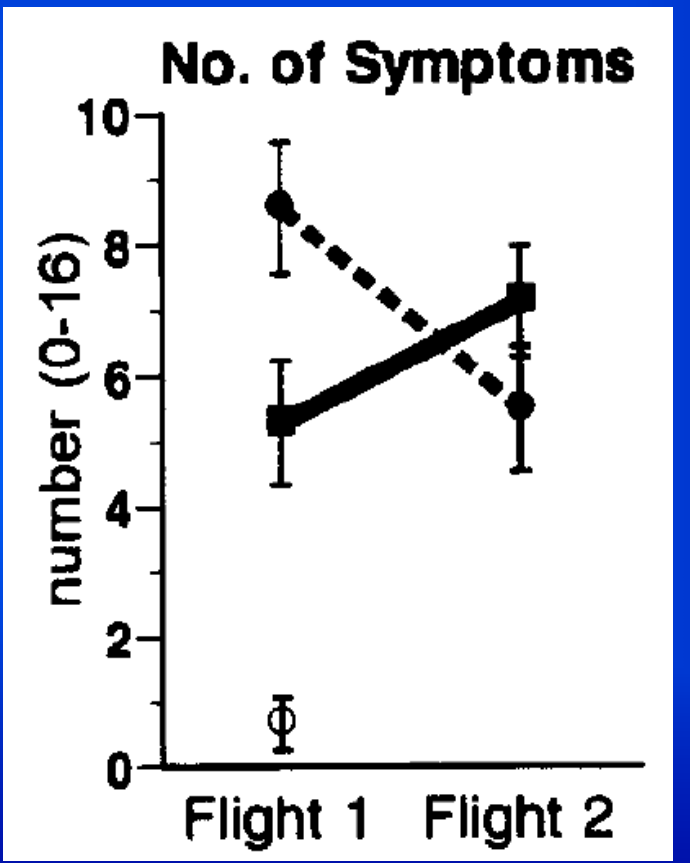
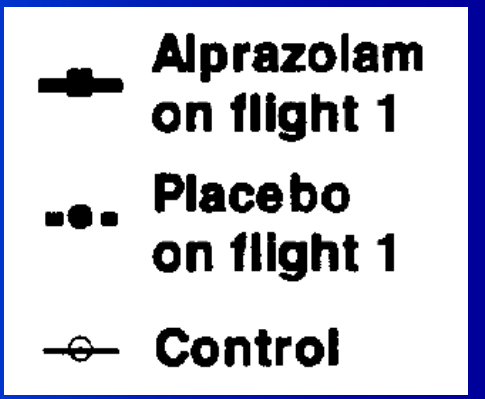
Benzodiazapines, Exposure, and Fear of Flying







Wilhelm & Roth (1997) *Behav. Res. Therapy*

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Erasing Fear Memories

- Is there any way to erase fear memories?
- During memory consolidation, a fear memory is labile and can be erased
- After memory consolidation, a fear memory is indelible and cannot be erased
  - EXCEPT at the time when it is retrieved, during which it becomes labile again and can be erased
- After memory reconsolidation, a fear memory is indelible and cannot be erased
  - EXCEPT at the time when it is next retrieved, during which it becomes labile again and can be erased

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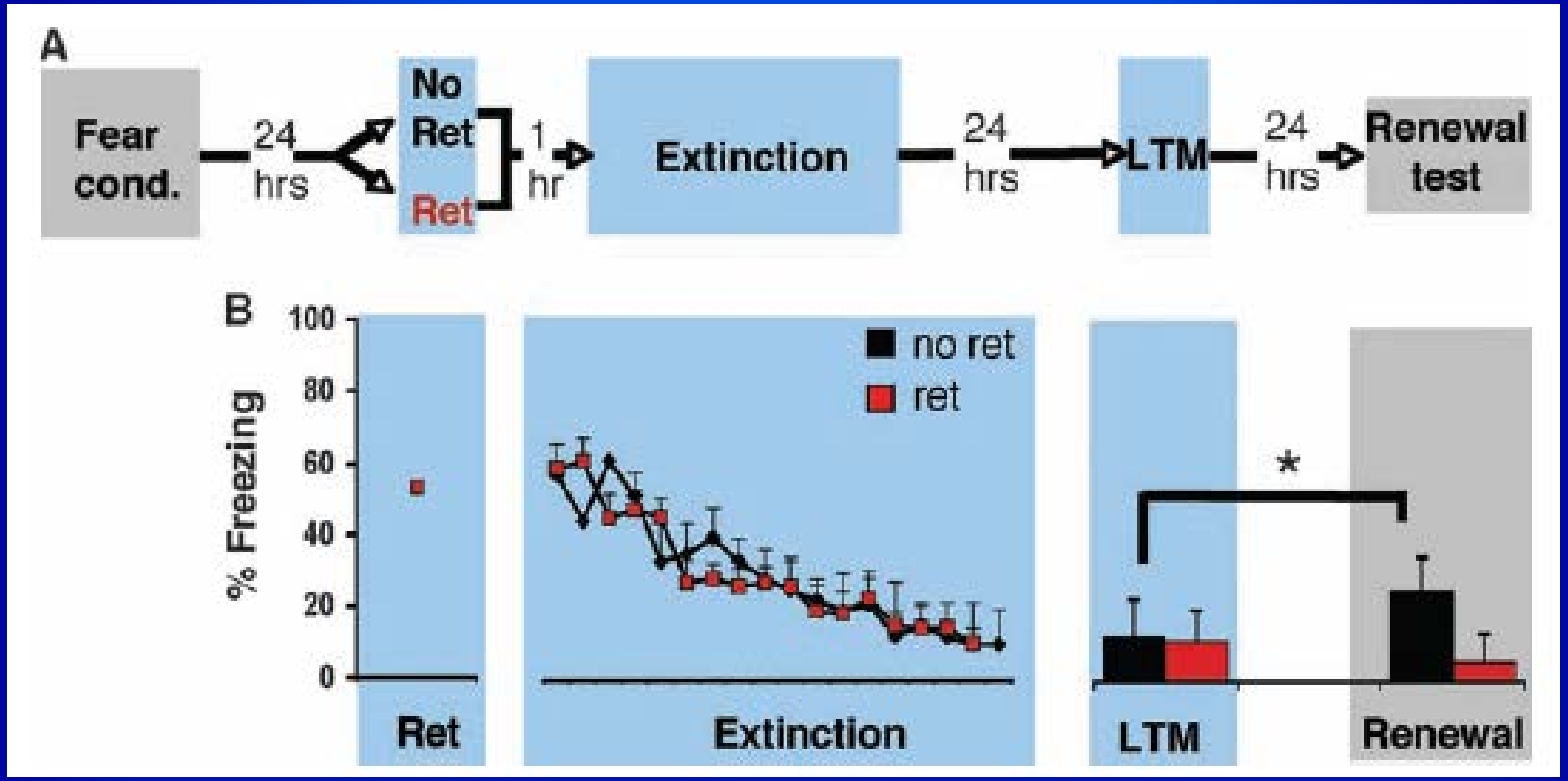
Using Extinction to Erase Fear Memories in Rats



Monfils et al. (2009) *Science*

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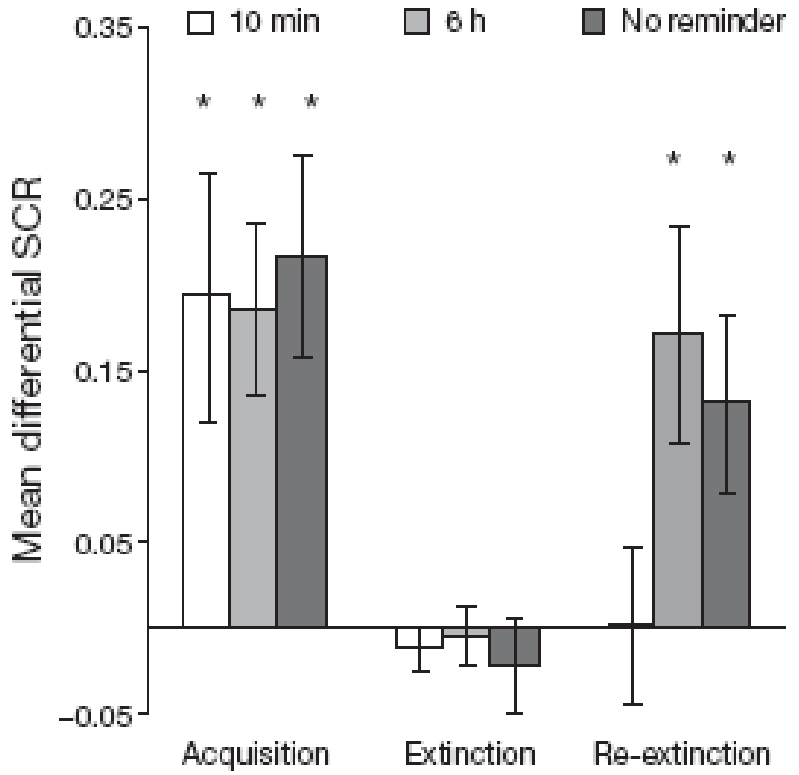
Using Extinction to Erase Fear Memories in Humans

a

	Day 1	Day 2		Day 3
Group 1:	Acquisition	Reminder	10 min →	Extinction	Re-extinction
Group 2:	Acquisition	Reminder	6 h →	Extinction	Re-extinction
Group 2:	Acquisition	No reminder	→	Extinction	Re-extinction

Spontaneous recovery: (1st trial of re-extinction) – (last trial of extinction)

b



Schiller et al. (2010) *Nature*