Emerging Treatments of Anxiety Informed by Scientific Knowledge about the Brain
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 or 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
  - Threat-related activation that is maladaptive, which can be affected by therapeutic change
Neural Circuitry of Psychotherapeutic Change

- Neural pathways that support dysfunctional thinking and behavior patterns
  - Anxiety, panic, worries, phobias, obsessions
  - 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
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
“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
Pharmacotherapy and Psychotherapy

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


The graph shows the reduction in fear levels at midtreatment, 1 week posttreatment, and 3 months posttreatment for two groups: Placebo (light gray) and D-cycloserine (dark gray). At each time point, the D-cycloserine group shows a larger reduction in fear compared to the Placebo group.
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D-cycloserine, Exposure Therapy, and Social Anxiety Disorder

Hofmann et al. (2006) *Arch. Gen. Psychiatry*
Pharmacotherapy and Psychotherapy

SSRIs and Extinction

Karpova et al. (2011) Science
Pharmacotherapy and Psychotherapy
SSRIs and Extinction

Karpova et al. (2011) Science
Pharmacotherapy and Psychotherapy
Benzodiazepines, 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

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
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<tbody>
<tr>
<td>Group 1:</td>
<td>Reminder 10 min</td>
<td>Extinction</td>
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<tr>
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<tr>
<td>Group 2:</td>
<td>No reminder</td>
<td>Extinction</td>
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<td>Extinction</td>
<td>Re-extinction</td>
</tr>
</tbody>
</table>

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

Schiller et al. (2010) *Nature*
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Using Extinction to Erase Fear Memories in Humans

Schiller et al. (2010) *Nature*