Can traumatic memories be erased?

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- No corporate relationships or interests
- I am a basic scientist, not a clinician
Fear...Terror...Trauma
Learning to fear

• Forming fear memories is adaptive
  • Survival depends on detecting and avoiding both new and past threats

• …but traumatic memories can lead to psychopathology
  • post-traumatic stress disorder (PTSD)

• Anxiety disorders are most prevalent mental health disorder in world
Prevalence of anxiety disorders

Post-traumatic stress disorder (PTSD)

- PTSD is anchored to a traumatic event (i.e., a memory)
- Direct or perceived threat to life:
  - Natural disaster
  - Combat trauma or terrorist attack
  - Domestic or sexual abuse
  - Death of a loved one
  - Motor vehicle accident
  - Physical or sexual assault
  - Emergency medical crisis
Post-traumatic stress disorder (PTSD)

- PTSD symptoms involve memories of the trauma (re-experiencing)
  - Flashbacks (“being there again”)
  - Nightmares
- Other symptoms include:
  - Numbing and social withdrawal
  - Avoidance of trauma reminders (either thoughts or situations)
  - Hypervigilance (scanning)
  - Physiological reactivity (startle, light/noise sensitivity)
PTSD can co-occur with many disorders

PTSD

- Major Depression
- Substance Addiction
- Traumatic Brain Injury
- Obsessive-Compulsive Disorder
- Social Phobia, Panic
- Generalized Anxiety Disorder
- Suicidality
Learning to fear: Pavlovian fear conditioning

- Fundamental form of associative learning modeling aspects of PTSD
- High level of experimental and parametric control
- Characterized in both animals and humans
PTSD, fear conditioning, and extinction

- **Fear conditioning** (*learning*)
  - Trauma-associated stimuli evoke learned fear (*fear memory*)

- **Extinction** (*new learning*)
  - Experiencing trauma-associated cues in a safe setting reduces fear (*extinction memory*)

- **Relapse**
  - Time, stress, or context change cause fear to return
How do you treat PTSD?

- Cognitive-behavioral therapies (CBT) generally more effective than medications

- *Prolonged exposure (PE) therapy* is an effective form of CBT
  - Repeatedly confront fears in a safe setting (*extinction procedure*)
  - Often accompanied with relaxation techniques
  - Goal is to reduce fear and other PTSD symptoms
Extinction memories are *labile*

- Extinction *suppresses* fear memories, but....
- Fear *relapses* under a variety of conditions
- Extinction *does not erase* the fear memory...
Extinction is not erasure!

- Extinction fosters new inhibitory learning

- Konorski (1967): “in the course of extinction the inhibitory connections are being formed side by side with the totally preserved excitatory connections”

Konorski (1967). Integrative Activity of the Brain.
Brain circuits for fear, extinction, and relapse

- Fear conditioning
  - Trauma memories formed in amygdala

- Extinction
  - Prefrontal cortex inhibits fear memories in the amygdala

- Context (who, what, where, when)
  - Hippocampus places memories in context and drives relapse

Can traumatic memories be erased?
Memory erasure as science fiction?

- Men in Black (1997)
  - “Neuralyzer” used to wipe memories of alien encounters
Memory erasure as science fiction?

  - Couple in a soured relationship has memories of each other erased
Memory editing from science fiction to clinical practice

Elizabeth A. Phelps1,2* & Stefan G. Hofmann3

Science fiction notions of altering problematic memories are starting to become reality as techniques emerge through which unique memories can be edited. Here we review memory-editing research with a focus on improving the treatment of psychopathology. Studies highlight two windows of memory vulnerability: initial storage, or consolidation; and re-storage after retrieval, or reconsolidation. Techniques have been identified that can modify memories at each stage, but translating these methods from animal models to humans has been challenging and implementation into clinical therapies has produced inconsistent benefits. The science of memory editing is more complicated and nuanced than fiction, but its rapid development holds promise for future applications.
Windows to edit (erase?) memory

Memory over time

- Encoding
- Labile
  - Head trauma (TBI)
  - Electroconvulsive therapy (ECT)
  - Protein synthesis inhibition (PSI)
- Consolidation
- Stable
- Reactivation
- More reactivations
  - ECT
  - PSI
  - Propranolol
- Reconsolidation

Phelps and Hofman (2019)
Disrupting reconsolidation in humans

- Patients underwent ECT for monopolar depression
- ECT delivered after reactivation of an emotional story learned 1 week earlier

Kroes et al. (2014). Nature Neuroscience
Selectively targeting memories in brain
Erasing a memory trace

- Josselyn & Frankland target fear memories in mouse amygdala

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Han et al. (2009). Science
Erasing a memory trace

Capture memory neurons during learning

After learning, inject toxin to kill memory neurons

Fear memory erased

△ Memory neuron

△ Targeted with toxin

Memory neurons deleted

Han et al. (2009). Science
Reactivating memories

- Tonegawa lab captures memory neurons during fear conditioning

Liu, Ramirez…Tonegawa (2012). Nature
Reactivating memories

- Liu and Tonegawa capture memory neurons during fear conditioning
- Optical reactivation of neurons produces fear

Liu, Ramirez…Tonegawa (2012). Nature
Capturing engrams

- Activity-dependent tagging typically performed during learning

- Includes both sensory representations of context and shock and associations between the two

- *Can memories be captured during retrieval?*
Capturing memories during retrieval

- Normal memory recollection driven by retrieval cues
- Clinical therapies use retrieval cues ("imaginal exposure") to reactivate remote traumatic memories
- Can fear memories be retrieved and captured with "imaginal" cues?
“Covert capture” of a fear memory

- Capture hippocampal neurons activated by “imaginal” fear memory retrieval
- Re-activate neurons with a systemic drug (CNO)
- Does activating captured neurons cause fear?

Viral plasmids provided by D. Roy and S. Tonegawa

Ressler and Maren, unpub.
Backward fear conditioning

Fear to CS without CS->US association
Backward fear conditioning: mediation by context
Context extinction reduces freezing to a backward CS

Goode, Ressler and Maren, unpub.
Capture and reactivation of a fear memory

Ressler and Maren, unpub.
Rapamycin impairs reconsolidation
Cautions, caveats, and questions

• Manipulations that cause amnesia often induce retrieval failure, not true erasure
  • “Forgotten, but not gone”
  • Prior work has not demonstrated that memory loss is complete or permanent (savings?)

• Memory is highly associative, can a memory truly be “selectively” erased?

• Is memory erasure ethical?
  • What are we (as individuals or as a culture) without memories of the past, good or bad?
Conclusions

• Exposure therapy does not erase traumatic memories (relapse)
• Retrieved/reactivated memories are susceptible to disruption
• Modern tools allow selective targeting and manipulation of engrams (neural representations of memory)
• Translation to clinic must proceed with cautions and caveats in mind
Thanks!

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