Theoretical Basis of Memory
Reconsolidation
In Trauma-Focused Therapy
Cortex:

- Main site of **permanent** memory, which is very compactly coded.
- New memories must be filed near similar experiences.
- Permanent storehouse of **semantic** memories – general time and context-independent (facts), (i.e. as opposed to **episodic memory** – individual experiences).
Hypothalamus:

- Central control center in the brain, including emotions
- Regulates visceral functions - fighting, fleeing, feeding, and reproducing
- Two different autonomic nervous systems (ANS)
  - Sympathetic: “fight or flight”
  - Parasympathetic: “rest and digest”
- **PTSD results in imbalanced ANS**
**Hippocampus:**

- Parsing and recording of momentary experiences
- Temporarily saves current experiences until they can be stored more permanently in the cortex
- Encoding of memories by hippocampus cannot be completely done (consolidated) without sleep
- Transference from short-to-long term memory
Amygdala:

- Major role in processing and memory of emotional reactions and especially important events
- Bypasses the cortico-hippocampal route
- Coding of life-threatening events are “burned” into neural circuitry (e.g. life insurance policy for future survival)
- Direct encoding preserves all details (sights, sounds, smell, etc...)
**Routine Experience:**
- Hypothalamus – evaluates incoming stimuli and circumstances
- Hippocampus – initial parsing and recording
- Memory consolidated via sleep (REM)
- Transference to the cortex
- Cortex – permanent storage near similar experience

**Life or Death Experience:**
- Hypothalamus – evaluates incoming stimuli and circumstances
- Bypassing of cortico-hippocampal route by amygdala
- Events and sensation “burned” into neural circuitry
- No integration into semantic memory -- PTSD
Functional neural systems are thought to have a prominent role in pathophysiology of PTSD (Shalev, Liberzon, & Marmar, 2017)

**Fear Learning:**

Abnormal fear learning is one explanation for the pathophysiology of PTSD.

Fear-related memory formation is *localized to the amygdala*, including interplay between various nuclei and cell types in basolateral complex of the amygdala (Fanselow & LeDoux, 1999)
Threat Detection:

Dysfunctional threat detection manifests as symptoms of PTSD including: hypervigilance, heightened threat anticipation, and exaggerated reactivity to salient stimuli.

PTSD is associated with over-reactivity in the insula (Lanius et al., 2007), amygdala, and dorsal anterior cingulate cortex (Milad et al., 2007), and with hyper-connectivity of brain networks that detect salient stimuli in the environment (Sripada et al., 2012)

Shalev, Liberzon, & Marmar, 2017
Emotion Regulation and Executive Function:

Impaired executive function and emotion regulation may underlie memory and concentration deficits, poorly controlled emotional responses, irritability, and impulsivity (i.e. symptoms of PTSD).

Impaired connectivity in the fronto-parietal regions, within and between executive function networks, has been observed in patients with PTSD (Spirada et al., 2012).
Contextual Processing:

PTSD is characterized by hypervigilance that is inappropriate to the situation and misreading of cues as threatening despite a safe context.

Appropriate contextual processing depends on good signaling in the medial prefrontal cortex and hippocampus (Lang et al., 2009)

Hippocampal changes have been reported in patients with PTSD (Pitman et al., 2012; Shin & Liberzon, 2010)
Anxiety disorders, PTSD, and substance use disorders are characterized by maladaptive memory processes (Treanor, Brown, Rissman, & Craske, 2017).

Lay public generally believes that memories are permanent and cannot be edited or erased (Simons & Chabris, 2011).

However, memories when recalled can be altered, sometimes profoundly.

Under certain conditions, original memory can return to a labile state in which new information can be woven into the memory and old information can be weakened or lost (Treanor, Brown, Rissman, & Craske, 2017).

This process is referred to as memory reconsolidation (K. Nader & Hardt, 2009; K. Nader, Schafe, G. E., & LeDoux, J. E., 2000).
Background on Memory

PTSD Paradox in Military Environment:
Symptoms are adaptive reflexes and skills

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
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<tbody>
<tr>
<td>Hyperalert, hypervigilant (e.g. crowds, traffic)</td>
<td>Sharply tuned threat perception, rapid reflexes</td>
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<tr>
<td>Reliving combat events, guilt, second-guessing</td>
<td>Intense mission preparation, rigorous training</td>
</tr>
<tr>
<td>Intolerance of mistakes</td>
<td>Attention to details, minimize mistakes</td>
</tr>
<tr>
<td>Anger</td>
<td>Adrenaline / intensity for accomplishing the mission</td>
</tr>
<tr>
<td>Detached, numb</td>
<td>Emotional control in combat</td>
</tr>
<tr>
<td>Social withdrawal</td>
<td>Unit cohesion, unit is family</td>
</tr>
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Adapted from Hoge, C. (personal communications)
- **Reconsolidation Hypothesis**: Memories are labile after being retrieved, and are consolidated each time they are retrieved. (Monfils, Cowansage, Klann, & LeDoux, 2009; Schiller et al., 2010)

- Reconsolidation is an evolutionary, *adaptive* mechanism – new information is incorporated into old memories. (Hardt, Einarsson, & Nader, 2010)

- The reconsolidation effect is specific to the targeted memory, and not others.

- Once a memory is labile, it requires molecular processes (e.g. protein synthesis) to reconsolidate (Tronson & Taylor, 2007)

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**The “Reconsolidation” Window**
Disrupting reconsolidation of original memory trace may:

- "Erase" the fear memory (e.g. in PTSD and anxiety) (Agren et al., 2012)
- "Erase" the reward-based memory (e.g. substance abuse) (Dennis & Perrotti, 2015)

Note: "Extinction" involves formation of a new memory trace (i.e. to override the existing memory), instead of reconsolidation of the original memory trace (remains intact).
Factors may influence reconsolidation: (Monfils, Cowansage, Klann, & LeDoux, 2009)

- **Length of time engaged in the memory recall trial** (too long results in extinction rather than reconsolidation, too short does not result in reconsolidation). (Treanor, Brown, Rissman, & Craske, 2017)

- **Strength of the memory** (stronger memories are harder, such as those in PTSD and substance use disorders) (Suzuki et al., 2004)

- **Age of memory** (uncertainty of susceptibility to reconsolidation)

- **Similarity (greater)** between environmental context that memory was initially acquired and is being retrieved. (Besnard, 2012)
Propranolol HCI:

- Noradrenergic β-blocker
- Passes the blood-brain barrier and is presumed to block the β-adrenergic receptors in the amygdala
- Interferes with the PKA-CREB pathway involved in the neuroplasticity of memory (Johansen et al. 2011)
- Disrupts memory reconsolidation (Kindt, Soeter, & Vervliet, 2009; Soeter & Kindt, 2011)
Propranolol Decreases PTSD Symptoms

Immediate Treatment with Propranolol Decreases Posttraumatic Stress Disorder Two Months after Trauma

Guillaume Vaiva, François Ducrocq, Karine Jezequel, Benoit Averland, Philippe Lestavel, Alain Brunet, and Charles R. Marmar

- Trauma victims ($n=19$) ages 21-30 recruited at Emergency Departments (France) shortly after admission for motor vehicle accidents or physical assault.
- 11 patients received monotherapy propranolol (40 mg) 3x/day for 7 days, followed by tapering (days 8-12)
- 8 patients refused propranolol (groups similar on presenting characteristics)
- Two months after trauma exposure, psychiatrist, blind to treatment status of participants, assessed PTSD symptoms and diagnosis.
Propranolol Decreases PTSD Symptoms

**Mean PTSD Score**

- Propranolol: 6.18
- No Propranolol: 11.75

*p = 0.04*

**Diagnosis of PTSD**

- Propranolol: 9.1
- No Propranolol: 37.5

*p = 0.01*
Short report

Reactivating addiction-related memories under propranolol to reduce craving: A pilot randomized controlled trial

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Example of Memory Reconsolidation - Propranolol

- Double-blind, randomized controlled trial of propranolol vs. placebo
- \( N = 17 \) adults (18-65) with substance dependence enrolled in addiction rehabilitation program
- Participants prepared narrative detailing personal drug-using experience, including people, places, environmental cues, withdrawal stages, etc.
- Pre-session rating of severity of alcohol/drug cravings, followed by receipt of study drug (or placebo)
- After 1-hr, participants read aloud their personalized craving script to interviewer to insure being emotionally engaged in script-reading
- Total of six bi-weekly sessions (separated by no less than 48 h) over 3 weeks
Example of Memory Reconsolidation - Propranolol

Fig. 2. Subjective Craving Scores Over Time in an Intent-to-treat Analysis. Treatment session 1 (baseline) is controlled. Propranolol group (n = 9): M session 2 = 2.53, SE = 0.57, M session 6 = 1.97, SE = 0.49, p = .005, paired effect size of d = 1.40. Placebo group (n = 8): M session 2 = 2.64, SE = 0.45; M session 6 = 2.60, SE = 0.37, p = .89, paired effect size of d = 0.06.
Example of Memory Reconsolidation - Propranolol

Archival Report

An Abrupt Transformation of Phobic Behavior After a Post-Retrieval Amnesic Agent

Marieke Soeter and Merel Kindt

Biological Psychiatry December 15, 2015; 78:880–886

- $N = 45$ (41 women) age 18-32 years who scored $>17$ on Spider Phobia Questionnaire
- Baby tarantula placed in closed jar on a table at far end of room.
- Random assignment to propranolol, placebo, or propranolol w/o memory reactivation
- Subjects performed series of behavioral tests (3 minutes) with tarantula and rated their level of anxiety

[Link to video]
<table>
<thead>
<tr>
<th>Step</th>
<th>Instructions BAT</th>
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<tbody>
<tr>
<td>1</td>
<td>Sit in front of a spider that is in a closed jar at a distance of 20 cm.</td>
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<tr>
<td>2</td>
<td>Hold the palm of your hand on either side of the closed jar for at least 10 seconds.</td>
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<tr>
<td>3</td>
<td>Open the jar with the spider.</td>
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<tr>
<td>4</td>
<td>Pick up the open jar with the spider for at least 10 seconds.</td>
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<tr>
<td>5</td>
<td>Direct the spider’s movement in the jar with a pencil for at least 10 seconds.</td>
</tr>
<tr>
<td>6</td>
<td>Put the spider in a tummy-tub.</td>
</tr>
<tr>
<td>7</td>
<td>Follow the spider with a bare finger as it crawls around the tummy tub for at least 10 seconds.</td>
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<tr>
<td>8</td>
<td>Let the spider walk on your bare hands.</td>
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</tbody>
</table>

BAT, behavioral approach task.
Figure 1. Schematic representation of the experimental design for (A) the MR_propranolol and MR_placebo group and (B) the propranolol group. BAT, behavioral approach task; FU, follow-up; MR, memory reactivation; SPQ, Spider Phobia Questionnaire.
Example of Memory Reconsolidation - Propranolol

https://youtu.be/mIsIPqYvwUM?t=1848

30:55 to 37:05
Figure 2. Behavioral approach toward the baby tarantula at t0: pretreatment and t3: posttreatment, as well as t4: 3-month follow-up and t5: 1-year follow-up for the three experimental groups. MR, memory reactivation.
Example of Memory Reconsolidation - Propranolol

Figure 3. Self-declared spider fear on the Spider Phobia Questionnaire at t0: pretreatment and t3: posttreatment as well as t4: 3-month follow-up and t5: 1-year follow-up for the three experimental groups. MR, memory reactivation; SPQ, Spider Phobia Questionnaire.
References


