Optimizing extinction learning for treating fear and anxiety

Michelle G. Craske, Ph.D.
October, 2017

Distinguished Professor of Psychology, Psychiatry and Biobehavioral Sciences
Director, Anxiety and Depression Research Center
Associate Director, Staglin Family Music Center for Behavioral and Brain Health
UCLA
<table>
<thead>
<tr>
<th>Refusal</th>
<th>Attrition</th>
<th>~50% Response Rate</th>
<th>Return of Fear</th>
</tr>
</thead>
</table>

Effective, but....
What are the mechanisms of exposure therapy?

How can mechanisms be optimized to enhance response rate and reduce return of fear?
Experimental Laboratory

Clinical

Analog
Extinction Learning

Fear Learning

CS → US
Extinction Learning

Fear Learning

CS → US

Extinction Learning

CS → US
Inhibitory extinction representations compete with excitatory fear learning representations that remain intact.
Extinction Learning
(Bouton, 1993, 2002)

Inhibitory extinction representations compete with excitatory fear learning representations that remain intact.
Extinguished cue in extinction context

Hippocampus $\rightarrow$ activates vmPFC $\rightarrow$
Inhibitory interneurons basolateral amygdala $\rightarrow$ inhibit output neurons central amygdala $\rightarrow$ inhibits CR

Extinguished cue in different context

Hippocampus $\rightarrow$ not activate vmPFC $\rightarrow$
CR returns
Excitatory Association (humiliated)

Audience

Inhibitory Association (not humiliated)
Excitatory Association (humiliated)

Audience

Inhibitory Association (not humiliated)

Rapid Reacquisition

Spontaneous Recovery

Context Renewal

Reinstatement

Fear Reduction During Exposure
How can inhibitory learning be maximized during exposure therapy?

How can inhibitory learning be maximally retrieved at a later point in time, after completion of exposure therapy?

Especially for anxious individuals who show deficits in inhibitory learning or regulation
Anxious Individuals: deficits in safety learning

Anxious individuals: deficits in safety learning


Effect size: anxiety patients vs healthy controls during acquisition
* p<.05
Duits et al. (2015) *Depression and Anxiety*
SAFE

NO SHOCK WILL BE GIVEN
DANGER
SHOCK MAY BE GIVEN
Anxious individuals: deficits in safety learning

Before Contraction

After Contraction

p<.05


Predicted by adolescent adversity
Anxious individuals: deficits in transfer of safety

Training phase: AX+, BX-
Test of inhibition phase: does B safety transfer to A (relative to novel C)


PTSD vmPFC? (Jovanovic et al., 2012)
Anxious individuals: deficits in extinction learning


![Graph showing mean SCR magnitude (uS/sqrt) for different conditions and stages: Conditioning, Extinction, Extinction Retest. CS+ and CS- conditions are compared.](image-url)
Anxious individuals: deficits in extinction learning


Deficits in vmPFC at extinction retest
(Milad et al., 2009; Milad et al., 2013; McLaughlin et al., 2015)
Anxious individuals: over-generalization of fear

Lissek et al., (2010). Am J of Psychiatry
Anxious individuals: over-generalization of fear

Lissek et al., (2010). *Am J of Psychiatry*

McGlade, Treanor, Zbozinek & Craske, (submitted)
Anxious individuals: over-generalization of fear

Deficits in hippocampal activation of vmPFC (Lissek et al., 2013)

McGlade, Treanor, Zbozinek & Craske, (submitted)

Lissek et al., (2010). *Am J of Psychiatry*
How can inhibitory learning be maximized during exposure therapy?

How can inhibitory learning be maximally retrieved at a later point in time, after completion of exposure therapy?

Especially for anxious individuals who show deficits in inhibitory learning or regulation.
Formation of Inhibitory Learning

Disconfirm Expectancies
- Behavioral conditions
- Deepened extinction
- Reinforced extinction

Attention to Feared Stimuli
- Train attention
- Individual differences

Wean safety signals & behaviors

Variability
- Feared stimuli
- Trial timing

Inhibitory Regulation
Affect Labeling

Positive Affect
- Positive affect induction
- Positive valence to feared stimuli

Consolidation and Retrieval of Inhibitory Learning

Consolidation
- Mental rehearsal
- NMDA agonists
- Inhibitors of renin-angiotensin system

Context Attenuation
- Multiple contexts
- Retrieval cues
- Cholinergic receptor antagonists

Experimental Investigations
- animal
- healthy humans
- clinical analog
- clinical sample
Inhibitory Regulation

Affect Labeling

Disconfirm Expectancies
Behavioral conditions
Deepened extinction
Reinforced extinction

Attention to Feared Stimuli
Train attention
Individual differences

Wean safety signals & behaviors

Variability
Feared stimuli
Trial timing

Positive Affect
Positive affect induction
Positive valence to feared stimuli

Consolidation and Retrieval of Inhibitory Learning

Consolidation
Mental rehearsal
NMDA agonists
Inhibitors of renin-angiotensin system

Context Attenuation
Multiple contexts
Retrieval cues
Cholinergic receptor antagonists

Experimental Investigations
a=animal
b=healthy humans
c=clinical analog
d=clinical sample
Mismatch between US ‘expectancy’ and actual rate or frequency with which US occurs strengthens extinction learning (Rescorla & Wagner, 1972).

More variation in US expectancy during extinction, lower US expectancy at follow-up test, above and beyond other indices ($\beta=-.28$, $t(58)=-2.26$, $p<.05$) (Brown, LeBeau, Chat & Craske, 2016, Cognition and Emotion).
Acrophobia
Pre
BAT

NDC
Repeated trials
Duration = uncertainty
10 min ITI (2 days)

DC
One trial
Duration = certainty +
(2 days)

Post
BAT

4-week Follow-Up
BAT

Acrophobia Questionnaire – Anxiety Subscale:
One trial as effective as multiple trials

Early Session Cues

Learning curve asymptotes → no new learning
(Rescorla & Wagner, 1972)
Second CS at asymptote:
- inflate US expectancy & enhance subsequent learning (Rescorla, 2006)
  - increase CS attentional salience (Pearce & Hall, 1980)
LARGE SLOW MOVING RED AND BLACK SPIDER
LARGE SLOW MOVING RED AND BLACK SPIDER

SMALL FAST MOVING BROWN AND BLACK SPIDER
### PREDICTION ERROR: COMPOUND EXTINCTION


<table>
<thead>
<tr>
<th>GROUP</th>
<th>HABITUATION</th>
<th>CONDITIONING</th>
<th>DRUG</th>
<th>EXTINCTION PHASE 1</th>
<th>EXTINCTION PHASE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td>CSA (4)</td>
<td>CSA + US (8)</td>
<td>CSA (8)</td>
<td>CSA (8)</td>
<td>CS- (8)</td>
</tr>
<tr>
<td></td>
<td>CSB (4)</td>
<td>CSB + US (8)</td>
<td>Placebo</td>
<td>CSB (8)</td>
<td>CS- (8)</td>
</tr>
<tr>
<td></td>
<td>CS- (4)</td>
<td>CS- (8)</td>
<td></td>
<td>CS- (8)</td>
<td></td>
</tr>
<tr>
<td>Compound</td>
<td>CSA (4)</td>
<td>CSA + US (8)</td>
<td>CSA (8)</td>
<td>CSAB (8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CSB (4)</td>
<td>CSB + US (8)</td>
<td>Placebo</td>
<td>CSB (8)</td>
<td>CS- (8)</td>
</tr>
<tr>
<td></td>
<td>CS- (4)</td>
<td>CS- (8)</td>
<td></td>
<td>CS- (8)</td>
<td></td>
</tr>
</tbody>
</table>
Add US:
- inflate US expectancy & enhance subsequent learning (Rescorla, 2006)
  - enhance CS attentional salience (Pearce & Hall, 1980)
  - CS-US ambiguity slows reacquisition (Bouton et al., 2004)
Culver, Stephens, Fanselow & Craske (2017). Building physiological toughness: Some aversive events during extinction may attenuate return of fear

*J. Beh Ther & Exp Psychiatry*

Group X Time: $b = 0.02$, $t(895) = 5.04$, $p < 0.001$

Group X Time: $b = 0.33$, $t(895) = 6.01$, $p < 0.001$
Group x Slope, $b = -0.15$, $t(115) = -2.70$, $p = 0.01$.

Figure 2: Skin Conductance Response (SCR) during Reacquisition

- Control: $b = 0.09^*$
- Partial Reinforced: $b = -0.06$
Inhibitory Regulation

Affect Labeling\textsuperscript{b,c,d}

Disconfirm Expectancies
Behavioral conditions\textsuperscript{c,d}
Deepened extinction\textsuperscript{a,b}
Reinforced extinction\textsuperscript{a,b}

Attention to Feared Stimuli
Train attention\textsuperscript{b}
Individual differences\textsuperscript{d}

Wean safety signals & behaviors\textsuperscript{a,b,c}

Variability
Feared stimuli\textsuperscript{a,c,d}
Trial timing\textsuperscript{a,b,c}

Formation of Inhibitory Learning

Consolidation and Retrieval of Inhibitory Learning

Positive Affect
Positive affect induction\textsuperscript{b,c}
Positive valence to feared stimuli\textsuperscript{c}

Context Attenuation
Multiple contexts\textsuperscript{a,b,c}
Retrieval cues\textsuperscript{a,c,d}
Cholinergic receptor antagonists\textsuperscript{a}

Experimental Investigations
\textsuperscript{a}=animal
\textsuperscript{b}=healthy humans
\textsuperscript{c}=clinical analog
\textsuperscript{d}=clinical sample
Attention is critical to learning.

CS salience (prominent, conspicuous, attention-grabbing) enhances extinction learning (Mackintosh, 1975; Pearce & Hall, 1980).
Context renewal (ABC) decreased as function of training attention to CS+/CS- versus context.

\[ F(2, 108) = 7.16, p < .05 \]

Treanor, Barry & Craske (in prep)
Replicated:

(a) MR image showing activation cluster in left amygdala during Rejection vs. Neutral that predicted CBT response (p<.005); and (b) parameter estimates extracted from this region and plotted vs. LSAS difference scores (controlling for baseline LSAS scores), indicating that greater activity in this region during Rejection vs. Neutral was associated with better CBT outcomes.

VIOLATION OF EXPECTANCIES: CLINICAL APPLICATION

- Design exposures to violate expectancies from outset
- Add fear stimuli within exposure trial
  - driving exposure.....add interoceptive exposure
  - contaminant exposure....add another contaminant
- Occasional negative outcomes within exposure trial
  - social rejections
  - panic attacks (e.g., yohimbine)
- Attend in order to learn
- Role of cognitive restructuring
  - May attenuate “violation of expectancy – not surprised” before and during exposure
  - Consolidate learning after exposure
Inhibitory Regulation

- Affect Labeling^{b,c,d}

Disconfirm Expectancies
- Behavioral conditions^{c,d}
- Deepened extinction^{a,b}
- Reinforced extinction^{a,b}

Attention to Feared Stimuli
- Train attention^{b}
- Individual differences^{d}

Wean safety signals & behaviors^{a,b,c}

Variability
- Feared stimuli^{a,c,d}
- Trial timing^{a,b,c}

Formation of Inhibitory Learning

Consolidation and Retrieval of Inhibitory Learning

Positive Affect
- Positive affect induction^{b,c}
- Positive valence to feared stimuli^{c}

Consolidation
- Mental rehearsal
- NMDA agonists^{a,b,c,d}
- Inhibitors of renin-angiotensin system^{a}

Context Attenuation
- Multiple contexts^{a,b,c}
- Retrieval cues^{a,c,d}
- Cholinergic receptor antagonists^{a}

Experimental Investigations
- =animal
- =healthy humans
- =clinical analog
- =clinical sample
Extinction context specific → context renewal in different context

CONTEXT SPECIFICITY

Extinction context specific → context renewal in different context

Replicated


F(1,30) = 5.79, p < 0.05, n² = 0.16
F(1,30) = 11.81, p < 0.005, n² = 0.28

• Mental reinstatement in spider fears (Mystkowski, Echiverri, Labus & Craske, 2006)

  “Remember what happened and what you learned last time, and where all of that took place.”
OFFSET CONTEXT RENEWAL

• Mental reinstatement in spider fears (Mystkowski, Echiverri, Labus & Craske, 2006)
  “Remember what happened and what you learned last time, and where all of that took place.”

• Retrieval cues in public speaking fears (Culver, Stoyanova & Craske, 2011)
Context specificity of extinction mediated by hippocampus; encoding of spatial-temporal contextual configurations (Fanselow, 2000)

“Downregulation” of hippocampus during extinction eliminates context specificity in rodents
  - Lesion
  - Pharmacological: Scopolamine - blocks acetylcholine at cholinergic receptors

Zelikowsky, Pham & Fanselow (2012)
Context A
Acquisition?

Placebo
.4mg SCOP
.5mg SCOP
.6mg SCOP

Context B
Extinction
Virtual Reality

Seven Sessions
Biweekly:
7 speeches per
session

Day 1 to Day 28--------------------------Day 32

SCOPOLAMINE TO DECONTEXTUALIZE EXPOSURE
Context A
Acquisition?

Context B
Extinction
Virtual Reality

Placebo
.4mg SCOP
.5mg SCOP
.6mg SCOP

Day 1 to Day 28-----------------------------Day 32

Seven Sessions
Biweekly:
7 speeches per session

SCOPOLAMINE TO DECONTEXTUALIZE EXPOSURE
SCOPOLAMINE TO DECONTEXTUALIZE EXPOSURE

Context A
Acquisition
?

Day 1 to Day 28-----------------------------Day 32

Placebo
.4mg SCOP
.5mg SCOP
.6mg SCOP

Seven Sessions
Biweekly:
7 speeches per session
SCOPOLAMINE TO DECONTEXTUALIZE EXPOSURE

Day 1 to Day 28-----------------------------Day 32

Context A Acquisition ?

Placebo
.4mg SCOP
.5mg SCOP
.6mg SCOP

Context B Extinction Virtual Reality

Seven Sessions Biweekly: 7 speeches per session

Context B Virtual Reality (Same)
Day 1 to Day 28------------------------Day 32

Placebo
.4mg SCOP
.5mg SCOP
.6mg SCOP

Context A Acquisition ?

Seven Sessions Biweekly: 7 speeches per session

SCOPOLAMINE TO DECONTEXTUALIZE EXPOSURE
SCOPOLAMINE TO DECONTEXTUALIZE EXPOSURE

Day 1 to Day 28-----------------------------------Day 32

Placebo
.4mg SCOP
.5mg SCOP
.6mg SCOP

Context B Extinction
Virtual Reality

Seven Sessions
Biweekly:
7 speeches per session

Context B Virtual Reality
(Same)

Context C Virtual Reality
(Different)

Context A Acquisition


Context A

Acquisition?

Day 1 to Day 28-------------------------------Day 32

Placebo
.4mg SCOP
.5mg SCOP
.6mg SCOP

Seven Sessions
Biweekly:
7 speeches per session

Context B

Extinction

Virtual Reality

Context C

Virtual Reality

(Same)

(Different)
SCOPOLAMINE TO DECONTEXTUALIZE EXPOSURE

- Double-blinded administration
- 60 Ps completed VR exposure and post-assessment (6 dropout/removal)
  - 21 placebo
  - 19 .5mg scopolamine
  - 20 .6mg scopolamine
- 22 male, 35 female, 1 other
- Mean age 24.93 yrs (range 18-53)
- All DSM-IV/5 Social Anxiety Disorder
- Baseline severity
  - Mean Social Anxiety Disorder SCID-CSR = 4.25 (0-8)
  - Mean SUDS BAT = 72.05 (0-100)
Mnemonic Similarity Task

Separation Task - Objects

Encoding Phase
Indoor/Outdoor?

Test Phase
Old/Similar/New?

2.5 s
0.5 s ISI

64 repetitions
64 novel foils
64 similar lures
Expect scopolamine to increase errors in ‘similar lures’ or even ‘novel foils’ due to impaired pattern separation.
Mnemonic Similarity Task

- Lure incorrectly judged as being seen before
- Lure is correctly judged as being a lure (similar but not seen before)
- New item incorrectly judged as being seen before

- Placebo
- .5mg
- .6mg
Continuous Paired Associate Learning Task

- A set of boxes appear on screen.
- The boxes open consecutively to reveal an object inside.
- Instruction to remember which object in which box.
- Subsequently, objects displayed in the center of screen.
- Instructed to click on box that contained that object.
Visual Paired Associate Learning Task

- A set of boxes appear on screen.
- The boxes open consecutively to reveal an object inside.
- Instruction to remember which object in which box.
- Subsequently, objects displayed in the center of screen.
- Instructed to click on box that contained that object.

Expect Scopolamine to disrupt location memory
Continuous Paired Associate Learning Task

Accuracy

- Placebo
- .5mg
- .6mg

* denotes significant difference.
Extinction Generalization Paradigm:
Acquisition CS+ with Scopolamine
Extinction Generalization Paradigm:
Extinction GSa (some features of CS+) with Scopolamine
Extinction Generalization Paradigm:
Test GSb (some features of GSa and some features of CS that never underwent extinction) without Scopolamine
Extinction Generalization Paradigm: Test GSb (some features of GSa and some features of CS that never underwent extinction) without Scopolamine

Expect Scopolamine to improve generalization to GSb due to impaired discrimination of GSa from CS and therefore more generalization to GSb.
Subjective Units of Distress during BAT Speech

Baseline

Post
Subjective Units of Distress during VR Speech
Eye Blink Startle during VR Speech Anticipation

![Graph showing eye blink startle responses during Ctx Renewal and Ext Retest with placebo, .5mg, and .6mg conditions. The graph indicates significant differences with an asterisk (*) for certain conditions.](image-url)
SCR Orienting During VR Speech

![Graph showing SCR orienting during VR speech with Placebo, .5mg, and .6mg conditions.](image)
SCR Omission During VR Speech

![Graph showing SCR Omission During VR Speech](image.png)
Incorrectly classifying a similar lure as “old” (i.e., impaired pattern separation) predicts lower eye blink startle during speech in renewal context.
Mnemonic Similarity Task Predicting Eye Blink Startle During CTX Renewal

Lower accuracy in recognizing a previously seen item predicts lower eye blink startle during speech in renewal context.
Mnemonic Similarity Task Predicting SCR Omission During CTX Renewal

Incorrectly classifying a similar lure as “old” (i.e., impaired pattern separation) relates to lower SCR omission response during speech in renewal context.

\[ \text{Beta} = -1.74, \quad R^2 = 0.09 \]
Formation of Inhibitory Learning

Disconfirm Expectancies
Behavioral conditions\(^c,d\)  
Deepened extinction\(^a,b\)  
Reinforced extinction\(^a,b\)

Attention to Feared Stimuli
Train attention\(^b\)  
Individual differences\(^d\)

Wean safety signals & behaviors\(^a,b,c\)

Variability
Feared stimuli\(^a,c,d\)  
Trial timing\(^a,b,c\)

Consolidation and Retrieval of Inhibitory Learning

Consolidation
Mental rehearsal  
NMDA agonists\(^a,b,c,d\)  
Inhibitors of renin-angiotensin system\(^a\)

Positive Affect
Positive affect induction\(^b,c\)  
Positive valence to feared stimuli\(^c\)

Context Attenuation
Multiple contexts\(^a,b,c\)  
Retrieval cues\(^a,c,d\)  
Cholinergic receptor antagonists\(^a\)

Experimental Investigations
\(^a\)=animal  
\(^b\)=healthy humans  
\(^c\)=clinical analog  
\(^d\)=clinical sample
VARIABILITY

- Random and variable practice enhances retrieval of newly learned information (Magill & Hall, 1990)
  - storage strength (Soderstrom & Bjork, 2015)
  - retrieval cues (Estes, 1966)
- Random and variable practice enhances:
  - prediction error (Rescorla & Wagner, 1972)
  - CS salience (Pearce & Hall, 1980)
- Traditional exposure is blocked and massed

\[ F(1,26)=12.72, \ p<0.01 \]
VARIABILITY


Beck Anxiety Inventory

(F(1, 31)=5.6, p<0.05)

<table>
<thead>
<tr>
<th></th>
<th>Pre-treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>BlockedMassed</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>RandomVariable</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

- BlockedMassed: Yellow
- RandomVariable: Blue
Inhibitory Regulation

Affect Labeling\(^{b,c,d}\)

Disconfirm Expectancies

Behavioral conditions\(^{c,d}\)
Deepened extinction\(^{a,b}\)
Reinforced extinction\(^{a,b}\)

Attention to Feared Stimuli

Train attention\(^{b}\)
Individual differences\(^{d}\)

Wean safety signals & behaviors\(^{a,b,c}\)

Variability

Feared stimuli\(^{a,c,d}\)
Trial timing\(^{a,b,c}\)

Formation of Inhibitory Learning

Consolidation and Retrieval of Inhibitory Learning

Positive Affect

Positive affect induction\(^{b,c}\)
Positive valence to feared stimuli\(^{c}\)

Consolidation

Mental rehearsal
NMDA agonists\(^{a,b,c,d}\)
Inhibitors of renin-angiotensin system\(^{a}\)

Context Attenuation

Multiple contexts\(^{a,b,c}\)
Retrieval cues\(^{a,c,d}\)
Cholinergic receptor antagonists\(^{a}\)

Experimental Investigations

\(^{a}\)=animal
\(^{b}\)=healthy humans
\(^{c}\)=clinical analog
\(^{d}\)=clinical sample
• CS+ acquires negative valence during fear acquisition (Hermans et al., 2005; Zbozinek, Hermans, Prenoveau, Liao & Craske, 2014)
  o Relatively resistant to extinction
  o Predicts fear reinstatement
• Induction of positive affect reduces reinstatement (Zbozinek, Holmes & Craske, 2015) and rapid reacquisition (Zbozinek & Craske, 2016)

• Induction of positive affect during exposure decreases fear and increases approach behavior following exposure (Dour, Brown & Craske, 2016)
Inhibitory Regulation

Affect Labeling$^{b,c,d}$

Disconfirm Expectancies
Behavioral conditions$^{c,d}$
Deepened extinction$^{a,b}$
Reinforced extinction$^{a,b}$

Attention to Feared Stimuli
Train attention$^b$
Individual differences$^d$

Wean safety signals & behaviors$^{a,b,c}$

Variability
Feared stimuli$^{a,c,d}$
Trial timing$^{a,b,c}$

Formation of Inhibitory Learning

Consolidation and Retrieval of Inhibitory Learning

Positive Affect
Positive affect induction$^{b,c}$
Positive valence to feared stimuli$^c$

Context Attenuation
Multiple contexts$^{a,b,c}$
Retrieval cues$^{a,c,d}$
Cholinergic receptor antagonists$^a$

Experimental Investigations
$^a$=animal
$^b$=healthy humans
$^c$=clinical analog
$^d$=clinical sample

Mental rehearsal
NMDA agonists$^{a,b,c,d}$
Inhibitors of renin-angiotensin system$^a$
Extinction: vmPFC inhibits amygdala at extinction test (Milad et al., 2014)

Affect Labeling (implicit emotion regulation): (Lieberman, 2007)
AFFECT LABELING: SOCIAL ANXIETY DISORDER

Affect Label vs Gender Label: (A) Magnetic resonance image showing significant amygdala activation from the omnibus F-test examining differences across all four groups of participants and (B) parameter estimates extracted from this cluster. Error bars represent standard errors within each group. Group differences between $SP_{Depr}$ and HCs were significant at $P < 0.005$.

Fig. 2. Treatment-related changes were observed in amygdala-prefrontal functional connectivity during affect labeling. Using the right amygdala as a seed region, greater symptom reduction was associated with more negative functional connectivity with right vIPFC from pre- to post-treatment (A). Similarly, using the left amygdala as a seed region, greater symptom reduction was associated with more negative functional connectivity with vmPFC from pre-to-post treatment (B). Together, results indicate that larger reductions in anxiety were associated with stronger negative amygdala-prefrontal connectivity at post- relative to pre-treatment. [Blue indicates changes in right amygdala functional connectivity; Red indicates changes in left amygdala functional connectivity; correlations are significant based on whole brain analyses, $p < .005$, clusters thresholded at $k > 40$].

### AFFECT LABELING TRAINING: SPIDER PHOBIA

<table>
<thead>
<tr>
<th>Labeling</th>
<th>Reappraisal</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Spider" /></td>
<td><img src="image2.png" alt="Spider" /></td>
</tr>
<tr>
<td>E.g., “Sitting in front of the <em>ugly</em> spider makes me very nervous.”</td>
<td>E.g., “Sitting in front of the <em>little</em> spider is <em>not dangerous</em> for me.”</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distraction</th>
<th>Exposure-Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3.png" alt="Spider" /></td>
<td><img src="image4.png" alt="Spider" /></td>
</tr>
<tr>
<td>E.g., “There is a <em>table</em> in front of the couch in my <em>den</em>.”</td>
<td></td>
</tr>
</tbody>
</table>

Labeling

E.g., “Sitting in front of the ugly spider makes me very nervous.”

AFFECT LABELING TRAINING: SPIDER PHOBIA

Attention to CS

Disconfirm Expectancy

Wean safety signals & behaviors
I feel: Nervous Afraid Scared Panicked

More Anxiety Words used During Exposure

Less Fear Responding at Re-Test

AFFECT LABELING: PUBLIC SPEAKING ANXIETY

I feel _______________
1) Anxious
2) Angry
3) Sad
4) Other

The audience will ___________
1) Laugh at me
2) Judge me negatively
3) Think I’m weird
4) Other

AFFECT LABELING: PTSD

6 sessions over 3 weeks, 20 mins per session

Sad    Angry    Other

How do you feel when viewing this image?
Compared to healthy controls, PTSD showed elevated amygdala activation when passively observing combat scenes.

Lisa J. Burklund, Carolyn D. Davies, Andrea Niles, Jared B. Torre, Lily Brown, Matthew D. Lieberman & Michelle G. Craske. (In preparation.) Affect labeling: A promising new approach to treating combat-related PTSD. This research was supported by the Defense Advanced Research Projects Agency (DARPA), an agency of the U.S. Department of Defense, through the Army Research Laboratory.
67% of participants (8/12) showed decreased PTSD severity
42% (5/12) no longer clinically-significant PTSD

Lisa J. Burklund, Carolyn D. Davies, Andrea Niles, Jared B. Torre, Lily Brown, Matthew D. Lieberman & Michelle G. Craske. (In preparation.) Affect labeling: A promising new approach to treating combat-related PTSD. This research was supported by the Defense Advanced Research Projects Agency (DARPA), an agency of the U.S. Department of Defense, through the Army Research Laboratory.
Should some memories be forgotten?
Interfering with reconsolidation of a fear memory changes original fear memory (vs extinction, which leaves original memory intact but in competition with competing inhibitory memories) (Bouton, 2002).
Disruption of memory reconsolidation

- Pharmacological disruption of protein synthesis during reconsolidation window
  - Anisomycin (Nader, Schafe & Le Doux, 2000)
  - Propranolol (humans) (Kindt et al., 2013)
- Behavioral disruption during reconsolidation window: reconsolidation updates memory with new information about safety through extinction learning
  - Animals (Monfils et al., 2009)
  - Humans (Schiller et al., 2010; Agren et al., 2012)
Disruption of memory reconsolidation

• Term “erasure” is not accurate
  • Declarative knowledge remains while emotional expressions (fear or craving) are mitigated
    o individuals remain aware that certain stimuli paired with shock following disruption of reconsolidation (Soeter & Kindt, 2011)
Boundary conditions on Disruption of Reconsolidation: Duration
Treanor, Brown, Rissman & Craske, 2017

• Brief reminder trial (usually CS presentation): in Pavlovian fear conditioning, typical reminder trial is a few seconds (Soeter & Kindt, 2011; Suzuke et al., 2004)

• Optimal duration of reminder may depend on temporal parameters of initial learning
  - reminder trials considerably shorter than CS during acquisition failed to disrupt reconsolidation (Alfei, Monti et al., 2015)
• Clinical barrier:
  • Retroactively determine duration of initial conditioning in clinical samples?
  • Tendency to mentally retrieve the CS (e.g., worry) limits control over duration of reminder trial: mental retrieval of initial learning sufficient to induce memory lability (Hupbach et al., 2007)
  • In advance of exposure, patients anticipate & mentally retrieve the CS for hours → extinction rather than reconsolidation
Boundary conditions on Disruption of Reconsolidation: 
Cue Specificity 
Treanor, Brown, Rissman & Craske, 2017

- Majority of studies use the same CS for initial acquisition and memory reactivation
- Disruption in reconsolidation may not generalize to other CS
  - Two CSs each paired separately with US: disrupting consolidation of one does not alter responding to the other, with either behavioral (Schiller et al., 2009) or pharmacological disruptions (Doyere, Debiec et al., 2007; Soeter & Kindt, 2011)
  - Second order conditioning (CS1 + US, CS1 + CS2, CS2 predicts US) and other generalization stimuli
• Clinical Barrier:
  • Associative networks often composed of multiple complex CSs:

  Multiple CSs associated with trauma: a sexual assault survivor may fear people resembling the perpetrator, physical intimacy, and specific social situations
  • multiple second order stimuli (e.g., friend of perpetrator)
  • Exposure usually to generalization CSs rather than original CS
Boundary conditions on Disruption of Reconsolidation: Memory Strength
Treanor, Brown, Rissman & Craske, 2017

• Stronger memories less susceptible to reconsolidation than weaker memories (Suzuki et al., 2004; Kwak, Choi et al., 2012)

• Repeated labilization and reconsolidation of declarative memory limits impact of behavioral strategies upon disruption of reconsolidation (Forcato, Fernandez & Pedreira, 2013)

• Clinical Barrier: Most clinical fears involve strong memories that are repeatedly reconsolidated
  • Re-traumatization (PTSD, military, social rejection): repeated aversive events strengthen fear memories
  • Repeated mental rehearsal of CS-US association strengthens fear memory
Boundary conditions on Disruption of Reconsolidation: Age of Memory
Treanor, Brown, Rissman & Craske, 2017

• Disruption of reconsolidation is time-dependent and may be less successful with older memories -- data are not fully robust

• Protein synthesis inhibitors disrupt reconsolidation in rodents 2-8 days after acquisition of memory but not 2-4 weeks later (Inda, Muravieva & Alberini, 2011; Milekic & Alberini, 2002; Frankland et al., 2006; Boccia et al., 2006)

• Unknown if purely behavioral methods for disruption of reconsolidation (i.e., extinction) effective with older memories in humans

• Clinical Barrier: Most do not seek treatment till many years after fear onset
• Some (not all) evidence for context specificity: when acquisition trials and reminder trials presented in different contexts, fail to induce memory labilization and disruption of reconsolidation (Chan et al., 2010)

• Clinical Barrier: Exposure treatment almost always occurs in a context very different than the original acquisition context (clinic setting vs natural environment)
• Majority of studies with animals or healthy samples
• Chronically stressed rats show resistance to disruption of reconsolidation (Hoffman et al., 2015)
• High trait anxiety predicted less disruptive effects of propranolol on reconsolidation (Soeter & Kindt, 2013)
• Clinical barrier: anxiety
Boundary conditions on Disruption of Reconsolidation: Conclusion
Treanor, Brown, Rissman & Craske, 2017

• Reconsolidation offers mnemonic advantages, allowing integration of new information into an established memory

• Capacity of memory to be strengthened or updated offers evolutionary advantages, such as stronger memories for biologically significant events or adaptation to changing environmental demands

• To extent that Pavlovian memories of threat are essential to survival, there may be additional evolutionary advantages to protect those memories from constant updating unless under very specific circumstances, such as exact replication of the original learning