Inhibitory models, fear extinction and application

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

How can mechanisms be optimized to enhance response rate and reduce return of fear?
STAY IN THE SITUATION UNTIL FEAR SUBSIDES

HABITUATION
Fear habituation does not predict follow-up behavioral avoidance test

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Fear habituation does not predict follow-up behavioral avoidance test
Fear habituation does not predict follow-up clinical severity: panic disorder

Meuret et al. (2012)
Journal of Consulting & Clinical Psychology

Greater within-session activation of anxiety inversely related to improvement in PDSS

Neither within-session or between-session reduction of anxiety predicted PDSS

Neither within-session or between-session reduction of physiology predicted PDSS
Extinction Learning

Fear 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.
Neural Mechanisms of Fear Extinction

Linmann et al., 2011; Milad et al., 2014; Shin & Liberzon, 2010

Am I in danger or am I safe?
- Is it a snake (or a twig)?
- Is it moving (towards me)?
- Where is it? Where am I?

Thalamus

vmPFC
sgACC
Amygdala
Hippocampus

aINS

plINS

Auditory cortex

Nature Reviews | Neuroscience
Neural Mechanisms of Fear Extinction

Linmann et al., 2011; Milad et al., 2014; Shin & Liberzon, 2010

Extinguished cue in extinction context
- hippocampus
- activates vmPFC
- activates inhibitory interneurons basolateral amygdala
- inhibit output neurons central amygdala
- inhibit CR
Neural Mechanisms of Fear Extinction

*Linmann et al., 2011; Milad et al., 2014; Shin & Liberzon, 2010*

Extinguished cue in extinction context
- hippocampus
- activates vmPFC
- activates inhibitory interneurons basolateral amygdala
- inhibit output neurons central amygdala
- inhibit CR

Extinguished cue in different context
- hippocampus not activated
- CR returns
Excitatory Association
CS=US
Excitatory Association
CS=US

Inhibitory Association
CS=noUS
Context Specific
Excitatory Association
CS=US

Inhibitory Association
CS=noUS
Context Specific

PRE-EXPOSURE -- EXPOSURE -- POST-EXPOSURE

?
Excitatory Association
CS=US

Inhibitory Association
CS=noUS
Context Specific
PRE-EXPOSURE

Excitatory Association
CS=US

Inhibitory Association
CS=noUS
Context Specific

Spontaneous Recovery:
Passage of time without exposure

EXPOSURE

POST-EXPOSURE

Spotted Face

EXPOSURE
Excitatory Association
CS=US

Inhibitory Association
CS=noUS
Context Specific

Context Renewal: Experience in a different context
Excitatory Association
CS=US

Inhibitory Association
CS=noUS
Context Specific

Reinstatement: CS in context of uncued adverse events
Excitatory Association
CS=US

Inhibitory Association
CS=noUS
Context Specific

Rapid Reacquisition: Adverse event with CS
Excitatory Association CS=US

Fear Reduction

Inhibitory Association CS=noUS Context Specific

PRE-EXPOSURE  EXPOSURE  POST-EXPOSURE

Context Specific Fear Reduction?
Excitatory Association
CS=US

Inhibitory Association
CS=noUS
Context
Specific

Inhibitory extinction memories sufficiently strong and retrievable to compete with excitatory fear memories
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: over-generalization of fear

Lissek et al., 2010, 2014

McGlade, Treanor & Craske, in prep
Anxious individuals: deficits in safety learning

Effect size:
anxiety patients vs healthy controls
during acquisition
(error bars= 95% CI)

Duits et al. (2015)
_Depression and Anxiety_
SAFE
NO SHOCK WILL BE GIVEN
DANGER
SHOCK MAY BE GIVEN
DANGER
SHOCK MAY BE GIVEN

0 Count down 55
Anxious individuals: deficits in safety learning

Anxious individuals: deficits in extinction learning


![Graph showing mean SIR SCR magnitude](image)
Anxious individuals: deficits in extinction learning


**Effect size:**

anxiety patients vs healthy controls during extinction (error bars=95% CI)

*p < .05, p = .057

Duits et al. (2015)

*Depression and Anxiety*
Deficits in vmPFC at extinction retest (Milad et al., 2009; Milad et al., 2013; McLaughlin et al., 2015)
Strength & Retrievability of Inhibitory Learning

- Violate Expectancies
- Offset Context Renewal Retrieval Cues, Multiple Contexts, Cholinergic Antagonist
- Consolidation Scheduling
- Variability of Stimulus & Emotion
- Wean Safety Signals & Behaviors
- Consolidation Pharmacologically
- Inhibitory Regulation Affect Labeling
- Positive Valence
- Erase Fear Memory: Disrupt Reconsolidation?

Craske et al., 2008
Craske et al., 2012
Craske et al., 2014

Attend to Stimulus
Mismatch between US ‘expectancy’ and actual rate or frequency with which US occurs strengthens extinction learning (Rescorla & Wagner, 1972)
Design conditions of exposure to maximally violate expectancies (Craske et al., 2008, 2012, 2014)
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

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

Early Session Cues

• Learning curve asymptotes
  o prevents further learning from occurring (Rescorla & Wagner, 1972)
  o there is no more surprise!
• Add second CS at point of asymptote
  o inflate US expectancy and enhance learning on subsequent trials (Rescorla, 2006)
  o increase attentional salience of CS (Pearce & Hall, 1980)
LARGE SLOW MOVING RED 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></td>
<td>CSA (8)</td>
<td>CSA (8)</td>
</tr>
<tr>
<td>CSB (4)</td>
<td>CSB (4)</td>
<td>CSB + US (8)</td>
<td>Placebo</td>
<td>CSB (8)</td>
<td>CS- (8)</td>
</tr>
<tr>
<td>CS- (4)</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></td>
<td>CSA (8)</td>
<td>CSAB (8)</td>
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<tr>
<td>CSB (4)</td>
<td>CSB (4)</td>
<td>CSB + US (8)</td>
<td>Placebo</td>
<td>CSB (8)</td>
<td>CS- (8)</td>
</tr>
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<td>CS- (8)</td>
<td></td>
<td>CS- (8)</td>
<td></td>
</tr>
</tbody>
</table>


- SCR to CSA at Reinstatement:
  - $t(30) = 3.13, p < .005$

- US expectancy to CSA at Reinstatement:
  - $t(34) = 2.9, p < .01$
• Add US
  o inflate US expectancy and enhance learning on subsequent trials (Rescorla, 2006)
  o enhance attentional salience of CS (Pearce & Hall, 1980)
  o ambiguity of CS-US association slows reacquisition (Bouton et al., 2004)
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

Culver, Stephens, Fanselow & Craske (in submission)
Strength & Retrievability of Inhibitory Learning

ATTEND TO STIMULUS

OFFSET CONTEXT RENEWAL RETRIEVAL CUES, MULTIPLE CONTEXTS, CHOLINERGIC ANTAGONIST

CONSORTIUM SCHEDULING

VIOLATE EXPECTANCES

WEAN SAFETY SIGNALS & BEHAVIORS

CONSOLIDATION OF LEARNING DCS

INHIBITORY REGULATION AFFECT LABELING

ERASE FEAR MEMORY: RECONSOLIDATION?

Craske et al., 2008; Craske et al., 2012; Craske et al., 2014

VARIABILITY OF STIMULUS & EMOTION

POSITIVE VALENCE
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 to context via questions after each trial.

\[ F (1, 39) = 7.27, p < .05 \]

Treanor, Barry & Craske, in prep
Labeling

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

Reappraisal

E.g., “Sitting in front of the little spider is not dangerous for me.”

Distraction

E.g., “There is a table in front of the couch in my den.”

Exposure-Alone

### AFFECT LABELING: PUBLIC SPEAKING ANXIETY

<table>
<thead>
<tr>
<th>I feel</th>
<th>The audience will</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Anxious</td>
<td>1) Laugh at me</td>
</tr>
<tr>
<td>2) Angry</td>
<td>2) Judge me negatively</td>
</tr>
<tr>
<td>3) Sad</td>
<td>3) Think I’m weird</td>
</tr>
<tr>
<td>4) Other</td>
<td>4) Other</td>
</tr>
</tbody>
</table>

AFFECT LABELING: PTSD

6 sessions over 3 weeks, 20 mins per session
Compared to healthy controls, PTSD showed elevated amygdala activation when passively observing combat scenes.
67% of participants (8/12) showed decreased PTSD severity
42% (5/12) no longer clinically-significant PTSD
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
  o May attenuate “violation of expectancy – not surprised” before and during exposure
  o Consolidate learning after exposure
Strength & Retrievability of Inhibitory Learning

- Violate Expectancies
- Wean Safety Signals & Behaviors
- Offset Context Renewal Retrieval Cues, Multiple Contexts, Cholinergic Antagonist
- Consolidation Scheduling
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- Inhibitory Regulation Affect Labeling
- Positive Valence
- Erase Fear Memory: Reconsolidation?

Craske et al., 2008; Craske et al., 2012; Craske et. al., 2014

Attend to Stimulus
VARIABILITY

• Random and variable practice enhances retrievability of newly learned information (Magill & Hall, 1990)
  • Increases storage strength (Soderstrom & Bjork, 2015)
  • Increases retrieval cues (Estes, 1966)
• Traditional exposure is blocked and massed
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![Graph showing mean SUDS levels](image)

**Autonomic arousal and subjective distress did NOT habituate in Varied Group**
VARIABILITY

- Random and variable practice enhances retrievability of newly learned information (Magill & Hall, 1990)
  - Increases storage strength (Soderstrom & Bjork, 2015)
  - Increases retrieval cues (Estes, 1966)
- Traditional exposure is blocked and massed

Methods of variability

- stimuli
- approach to stimuli
- time between exposures
Craske et al., 2008; Craske et al., 2012; Craske et al., 2014

Strength & Retrievability of Inhibitory Learning

- Consolidation Scheduling
- Violate Expectancies
- Wean Safety Signals & Behaviors
- Consolidation of Learning DCS
- Offset Context Renewal Retrieval Cues, Multiple Contexts, Cholinergic Antagonist
- Inhibitory Regulation Affect Labeling
- Positive Valence
- Variability of Stimulus & Emotion
- Erase Fear Memory: Reconsolidation?

Attend to Stimulus
Extinction is context specific → context renewal in a context different from extinction context; new context reactivates the excitatory CS=US association

Extinction is context specific → context renewal when tested in a context that differs from extinction context; new context reactivates the excitatory CS=US association.

Replicated


• Multiple contexts (Vansteenswegen et al., 2007; Balooch, Neumann, & Boschen, 2012; Bandarian-Balooch, Neumann & Boschen, 2015)
  o situations
  o internal states
  o initial acquisition context
OFFSET CONTEXT RENEWAL

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

• Retrieval cues (Culver, Stoyanova & Craske, 2011): mild effects and risk of safety signal properties
CONTEXTUAL LEARNING AND HIPPOCAMPUS

• 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

Context B Extinction
Virtual Reality

Placebo
.2mg SCOP
.4mg SCOP
.6mg SCOP

Seven Sessions
Biweekly: 7 speeches per session

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

SCOPOLAMINE TO DECONTEXTUALIZE EXPOSURE
Context A Acquisition?

Acquisition?

Extinction

Virtual Reality

Seven Sessions

Biweekly: 7 speeches per session

Placebo: 0.2mg SCOP, 0.4mg SCOP, 0.6mg SCOP

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

SCOPOLAMINE TO DECONTEXTUALIZE EXPOSURE
Day 1 to Day 28------------------------Day 32

Context A
Acquisition

Placebo
.2mg SCOP
.4mg 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
.2mg SCOP
.4mg SCOP
.6mg SCOP

Seven Sessions
Biweekly:
7 speeches per session

Context A Acquisition

Virtual Reality (Same)
SCOPOLAMINE TO DECONTEXTUALIZE EXPOSURE

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

Context A Acquisition?

Context B Extinction Virtual Reality

Placebo
.2mg SCOP
.4mg SCOP
.6mg SCOP

Seven Sessions Biweekly:
7 speeches per session

Context B Virtual Reality (Same)

Context C Virtual Reality (Different)
Seven Sessions Biweekly: 7 speeches per session

Placebo 2mg SCOP 4mg SCOP 6mg SCOP

Day 1 to Day 28

Day 32

Context A Acquisition

Context B Extinction

Virtual Reality (Same)

Virtual Reality (Different)

SCOPOLAMINE TO DECONTEXTUALIZE EXPOSURE
Primary CS (e.g., feared physical sensation, social situation):

Optimal Exposure:
**Primary CS (e.g., feared physical sensation, social situation):**

**Optimal Exposure:**

_________________________________________________________________
Primary CS (e.g., feared physical sensation, social situation):

Optimal Exposure:
Primary CS (e.g., feared physical sensation, social situation):

Optimal Exposure:
**Physical Sensations**
- Increased heart rate
- Dizziness
- Shortness of breath

**Situations and Settings**
- Construction work
- Exercise
- Playing with children
- Breathing dusty air

**Feared Objects**
- None

**Feared Outcome**
- Heart attack

**Feared Thoughts / Images**
- Image of having a heart attack or stroke
- Image of my funeral
- Thinking “I’m going to die”

**Safe Places**
- Home
- Near hospital or doctor

**Safety Objects**
- Anxiety pills
- Having my wife nearby
- Cell phone

**Safety Behaviors**
- Going to see the doctor
- Avoid exercise or other activities that increase arousal
- Relaxing breathing
- Distraction

**Duration**
- Physical sensations – approximately 10 minutes

**Principal CS (e.g., feared physical sensation, social situation):**
- Increased heart rate

**Optimal Exposure:**
- Having increased heart rate, dizziness, shortness of breath while breathing dusty air without
- my anxiety pills, wife, or phone. I am concentrating on my physical feelings and am imagining
- having a heart attack. I do this for at least 15 minutes.
Exposure Plan
What am I testing out (What feared outcome am I most worried about? or What am I worried I will not be able to tolerate)?
If my heartbeat goes above 150 BPM, I’ll have a heart attack and die.

How am I testing it out?
I will exercise to elevate my heart rate above 150 BPM. I will keep my heart rate above 150 for fifteen minutes. I will repeat this exercise five times.

Strategies for this Session (Check All That Apply):

□ What am I throwing out? I will not bring my anxiety medication with me

□ How will I stay with it? I will focus on my racing heart beat throughout the exposure and describe my emotions

□ How will I combine it? N/A

□ How will I face it? N/A

Put it all together: What is my “exposure”?
I will exercise to elevate my heart rate above 150 BPM. I will keep my heart rate above 150 for fifteen minutes. I will repeat this exercise five times. During the exposure, I will not have my anxiety medication available. I will focus on my rapid heartbeat and describe my emotions.
Exposure Plan

What am I testing out (What feared outcome am I most worried about? or What am I worried I will not be able to tolerate)?

If my heartbeat goes above 150 BPM, I’ll have a heart attack and die.

How am I testing it out?
I will exercise to elevate my heart rate above 150 BPM. I will keep my heart rate above 150 for fifteen minutes. I will repeat this exercise five times.

Strategies for this Session (Check All That Apply):

☐ What am I throwing out? I will not bring my anxiety medication with me

☐ How will I stay with it? I will focus on my racing heart beat throughout the exposure and describe my emotions

☐ How will I combine it? I will drink coffee before I exercise

☐ How will I face it? N/A

Put it all together: What is my “exposure”?  
I will drink coffee and then exercise to keep my heart rate above 150 for fifteen minutes. I will repeat this exercise five times. During the exposure, I will not have my anxiety medication available. I will focus on my rapid heartbeat and describe my emotions.
Exposure Plan

What am I testing out (What feared outcome am I most worried about? or What am I worried I will not be able to tolerate)?

If my heartbeat goes above 150 BPM, I’ll have a heart attack and die.

How am I testing it out? And how am I changing it up?

I will use five different exercises to elevate my heart rate above 125 BPM. I will keep my heart rate above 150 for fifteen minutes. I will repeat this in five different places.

Strategies for this Session (Check All That Apply):

☐ What am I throwing out? I will not bring my anxiety medication with me

☐ How will I stay with it? I will focus on my racing heart beat throughout the exposure and describe my emotions

☐ How will I combine it? I will drink coffee before I exercise

☐ How will I face it? N/A

Put it all together: What is my “exposure”?

I will drink caffeine and then exercise to keep my heart rate above 150 for fifteen minutes. I will repeat this using five different exercises in five different places. During the exposure, I will not have my anxiety medication available. I will focus on my rapid heartbeat and describe my emotions.
Rehearsal and Consolidation

• Repeatedly rehearse the CS-noUS relationship facilitates long-term extinction memory consolidation (Joos, 2011; Meeter & Murre, 2004)

• “Exposure rehearsal”: discuss non-occurrence of US following exposure

• Use open-ended questions
  – “What did you expect prior to the exposure?” “What actually happened?”
  – “Was that different from what you expected?”
  – “What did you learn?”
Craske et al., 2008; Craske et al., 2012; Craske et al., 2014

- Strength & Retrievability of Inhibitory Learning
  - Offset Context Renewal Retrieval Cues, Multiple Contexts, Cholinergic Antagonist
  - Consolidation Scheduling
  - Violate Expectancies
  - Consolidation of Learning DCS
  - Wean Safety Signals & Behaviors
  - Inhibitory Regulation Affect Labeling
  - Positively Valenced
  - Erase Fear Memory: Reconsolidation?
  - Attend to Stimulus
  - Variability of Stimulus & Emotion
• CS+ acquires negative valence during fear acquisition

• Compared to fear arousal, CS+ negative valence more resistant to extinction

• Negative valence CS+ predicts more fear reinstatement (Hermans et al., 2005; Zbozinek, Hermans, Prenoveau, Liao & Craske, 2014)
Zbozinek, Holmes & Craske (2015)
*Behaviour Research and Therapy*
“It’s your birthday, and your partner reaches over to you with a present. You open it and feel incredibly happy.” Imagine the scenario and rate vividness of the image.
“It’s your birthday, and your partner reaches over to you with a present. You open it and feel incredibly happy.”

Concentrate on words and rate difficulty in understanding
Increased positive affect

CS-US acquisition

Positive Imagery Training Scenarios

Positive Verbal Training Scenarios

CS-US extinction

Reinstatement
CS-US acquisition

Positive Imagery Training Scenarios

Positive Verbal Training Scenarios

CS-US extinction

Reinstatement

Increased positive affect

Increased positive valence to CS+
VALENCE

Zbozinek, Holmes & Craske (2015) *Behaviour Research and Therapy*
Replicated with Rapid Reacquisition
Zbozinek & Craske, in press
*Cognition and Emotion*

Replicated with extinction generalization
Zbozinek & Craske, in prep

Zbozinek, Holmes & Craske (2015) *Behaviour Research and Therapy*
Exposure to Live Spider

Positive Valence Training Video

Neutral Valence Training Video

Exposure to Live Spider

Test

Reinstatement

Test

Dour, Brown & Craske (2016)

*J of Beh Ther & Exp Psych*
Exposure to Live Spider

Neutral Valence Training Video

Dour, Brown & Craske (2016)

J of Beh Ther & Exp Psych
Exposure to Live Spider

Neutral Valence Training Video

Exposure to Live Spider

Test

Reinstatement

Test
Less fear of spiders at retest
(B=-1.14, SE=.42, p=.01)

Percent who took one more step after Reinstatement,
($\chi^2$(1)=3.94, p=0.047)
Positive affect enhances encoding, rehearsal, and retrieval (Craik, 2002; Craik & Lockhart, 1972)

Positive mood increases relational processing, or relating incoming information to already-known information (Clore & Huntsinger, 2007)

Propose that positive mood enhances extinction processes (Zbozinek & Craske, 2016)
Strength & Retrievability of Inhibitory Learning

- ATTEND TO STIMULUS
- OFFSET CONTEXT RENEWAL RETRIEVAL CUES, MULTIPLE CONTEXTS, CHOLINERGIC ANTAGONIST
- CONSOLIDATION SCHEDULING
- WEAN SAFETY SIGNALS & BEHAVIORS
- CONSOLIDATION OF LEARNING DCS
- VIOLATE EXPECTANCIES
- INHIBITORY REGULATION AFFECT LABELING
- POSITIVE VALENCE
- ERASE FEAR MEMORY: RECONSOLIDATION?

Craske et al., 2008
Craske et al., 2012
Craske et al., 2014
CONCLUSIONS

• Exposure outcomes enhanced by:
  • design exposure to violate explicit expectancies
  • addition of fear cues
  • occasional negative outcomes
  • attend to fear cues (+ affect labeling)
  • variability of fear cues
  • multiple contexts, retrieval cues, mental reinstatement, and scopolamine (?)
  • positive valence or positive affect training

Overlaps with behavioral testing model