Fear and Threat Processing: Behavioral Models for Investigating the Neurobiology of PTSD

Rajendra Morey, M.D.
Associate Professor of Psychiatry
Duke University School of Medicine
Duke-UNC Brain Imaging and Analysis Center
Durham VA Medical Center
Disclosures

• No financial disclosures or competing interests
Symptoms of PTSD (DSM-5)

A. extremely traumatic events such as interpersonal violence (rape), combat, life-threatening accidents, or natural disasters. 

exposure can be direct, witnessing, or learning that a close friend of relative experienced trauma

B. distressing and intrusive memories, thoughts or feelings, flashbacks, nightmares, emotional distress and physical reactivity with reminders

C. avoid places, activities or thoughts that could remind of the trauma

D. difficulty recalling key feature of the trauma, overly negative thoughts and assumptions, negative affect, blame of self or others (guilt/shame), isolation, difficulty experiencing positive affect.

E. Irritability or aggression, hypervigilance (enhanced state of threat sensitivity or preoccupation with the potential for danger), difficulty sleeping, poor concentration, heightened startle
Comorbidities

• Psychiatric – substance abuse, mood disorders (particularly depression), anxiety disorders (particularly panic disorder), impulsive or dangerous behavior or self-harm

• Medical – chronic pain and inflammation, cardiometabolic disorders and heightened risk of dementia (accelerated brain aging)
Risk factors and Environment

• Socioeconomically disadvantaged
• Racial/Ethnic or religious minority
• People in conflict zones
• Mentally ill
• LGBT community
• Cognitive and Personality Styles
• Low IQ
Epidemiology and Prevalence

Yehuda et al 2015; Nature Reviews
Themes - Neuroscience of PTSD.

- Fear conditioning and extinction
- Emotion regulation and response to threat
- Memory reconsolidation
Trauma Cues – Reliving and Re-experiencing Symptoms

Trauma Memory (association)

Trauma cue / Trigger

Trauma Reliving (renewal)
An experimental model for PTSD

• Survivors of PTSD may learn to:
  • exhibit anxiety-related behaviors based on previous traumatic experiences and reminders of their trauma
  • generalize fear to a variety of triggers that resemble the initial trauma
  • experience difficulty extinguishing fear associations
  • more readily reawaken these fear associations

• The fear conditioning and extinction is a widely used model for studying PTSD
Fear Conditioning Model

Day 1 Training: tone + shock
- US (Shock) → CS (Tone) → Rat learns to fear tone

Day 2 Test 1: tone only
- CS (Tone) → CR (Freeze) → Rat freezes in response to tone

Day 3 Test 2: tone only
- CS (Tone) → Rat does not freeze
What is the fear neurocircuitry that generates these behavioral responses?

Parsons and Ressler
Adapting fear conditioning model

• However, we know that trauma cues that trigger symptoms may only vaguely resemble the initial trauma.

• DSM-5 criteria B specifies symptoms of “intense psychological distress and physiological reactivity may symbolize or resemble the traumatic events.”

• Similarity between cue or reminder and initial trauma experience might vary along a variety of dimensions that include shape, context, smell, emotional valence, semantic associations, and others parameters.

• How can we make the conventional fear conditioning model better suited to test this reality?
Fear generalization paradigm

• Pavlov (1927) observed that the CR generalized to graded stimuli that closely resembled the original CS, and diminished as perceptual similarity decreased.

• Gradients that track perceptual similarity have been consistently observed in animal conditioning experiments (Honig and Urcuioli, 1981).

• Animals trained with a single CS show more widespread generalization than animals trained to discriminate between different stimuli along the same sensory dimension (Jenkins and Harrison, 1960).

• Generalization as a function of intensity — from a medium volume tone that predicts the US to a loud volume tone that has never predicted the US (Ghirlanda and Enquist, 2003).
Where does generalization interfere along this pathway?
Fear circuits in the brain

Fear Extinction: Acquisition of contingencies between CS+ and US

Fear memory:
- Association with CS+
- Context Modulation of fear extinction

Fear learning (association)

Fear expression

Integrates limbic responses with goals and actions

Fear learning (association)
Overall Design of Fear Generalization

- Fear conditioning with CS- (safety) and CS+ that is paired with shock.

- Generalization test with additional morphs. S2 is midway between CS- and CS+. S4 and S5 are higher intensity (express greater fear) than CS+

- Preceded by pre-conditioning to get baseline activation to each of the facial morphs.

- Subjects are NOT told the rules.

Morey et al. 2015, Translational Psychiatry
Locus coeruleus is the site of noradrenergic neurotransmitter synthesis that act at alpha and beta adrenergic sites for fight-or-flight.

Morey et al 2015; Translational Psychiatry
The IFG integrates limbic responses with goal-directed actions, including holding affective material in working memory, directing attention to affectively-salient information, and integrating it with decision-making processes.

*Morey et al 2015; Translational Psychiatry*
The role of the amygdala in generalization may be through the thalamus – the amygdala may initiate a rapid generalized response by way of direct connections with the sensory thalamus.

No generalization effect; PTSD > trauma-exposed controls (main effect)

Amygdala in PTSD responds indiscriminately to less and more threat-salient stimuli but more than in trauma-exposed controls.

Morey et al 2015; Translational Psychiatry
Summary and Conclusions

Fear neurocircuitry in PTSD are biased toward stimuli that possess greater emotional intensity than the original conditioned fear stimulus.

Greater fear generalization in PTSD was demonstrated in the locus coeruleus, thalamus, insula, and inferior frontal gyrus, compared to trauma exposed control subjects.

This study contributes to a growing appreciation that fear conditioning processes in PTSD are subject to modifications that take place beyond the initial fear learning episode to make fear memories more resistant to extinction, less contextually specific, and overgeneralized.

These functional brain changes may contribute to symptoms of PTSD, which are frequently triggered by trauma cues that may resemble, but are not identical to cues in the index trauma.
Clinical observations of generalization

• Patients with PTSD generalize to vast array of stimuli in their environment

• Generalization often occurs in an incremental fashion that is progressive - color blue or hotdogs.

• Examine generalization where the relationship between stimulus and the CS+ is more distant than the fear faces.
Generalization to unique exemplars in a semantic category

Fear Acquisition (training)

Dunsmoor et al 2013; Cerebral Cortex
Hypothesis

• If we observe greater CS+ (tools) than CS- activity, it means subjects are generalizing fear associations across the entire semantic category since each exemplar is displayed only once.

• We hypothesize the PTSD would show greater CS+ vs. CS- activation than controls in key fear learning brain regions (e.g. amygdala, striatum, etc.)
PTSD group shows greater CS+ vs. CS- activation than trauma-exposed controls

- Contrast shows PTSD > Control for the CS+ vs. CS- contrast ($p < .05$; whole-brain corrected)

- The amygdala in the PTSD group generalizes fear associations for the entire semantic category (tools/animals) more than in trauma-exposed controls
PTSD group shows greater CS+ vs. CS- activation than trauma-exposed controls

- Contrast shows PTSD > Control for the CS+ vs. CS- contrast ($p < .05$; whole-brain corrected)

- The accumbens (related to reinforcing stimuli) in the PTSD group generalizes fear associations for the entire semantic category (tools/animals) more than in trauma-exposed controls

Morey et al., In Preparation
PTSD group shows greater CS+ vs. CS- activation than trauma-exposed controls

- Contrast shows PTSD > Control for the CS+ vs. CS- contrast ($p < .05$; whole-brain corrected)

- The caudate (related to goal directed action) in the PTSD group generalizes fear associations for the entire semantic category (tools/animals) more than in trauma-exposed controls

Morey et al., In Preparation
PTSD group shows greater CS+ vs. CS- activation than trauma-exposed controls

• Contrast shows PTSD > Control for the CS+ vs. CS- contrast ($p < .05$; whole-brain corrected)

• The anterior cingulate in the PTSD group generalizes fear associations for the entire semantic category (tools/animals) more than in trauma-exposed controls

Morey et al., In Preparation
Conclusions – Part II

• Generalization occurs not only with perceptual features and emotional intensity but also occurs in PTSD with neutral conceptual level (semantic) categories.

• Subjects had no conscious awareness of the CS-US association (e.g. tool = shock) but nevertheless “learned” it, which may explain the accumbens and caudate engagement and generalization response.

• Generalization effect occurs despite the use of a different exemplar from the category on every trial.

• Stronger amygdala and ventral striatal response associated with category generalization in the PTSD group despite remarkably different perceptual features (clam vs. giraffe).
• PTSD is characterized by symptoms of hyperarousal and hypervigilance that produce considerable functional impairment.

• Models of threat processing have been largely overlooked

• Successful planning and execution of complex tasks in environmental conditions where an array of threats or perceived threats.

• A key behavioral feature of PTSD is enhanced perception of threat in ostensibly safe environments.

• Many individuals with combat PTSD continue in combat zones or other dangerous environments (law enforcement, corrections officers, EMS) that requires attending to multiple competing demands.

• **Goal** – How do are the neural systems needed for goal-directed processing modulated by PTSD when unpredictable threat is present in the environment
Emotional undermodulation and overmodulation in PTSD

AMYGDALA

vmPFC

Hyperarousal
- Re-experiencing

Hypoarousal
- Depersonalization, derealization, emotional numbing, and analgesia
Perceived threat predicts the neural sequelae of combat stress

GA van Wingen¹,²,³, E Geuze⁴,⁵, E Vermetten⁴,⁵ and G Fernández¹,⁶

¹Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, Nijmegen, The Netherlands; ²Department of Neurology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; ³Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; ⁴Research Centre, Military Mental Health, Ministry of Defense, Utrecht, The Netherlands; ⁵Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, Utrecht University Medical Center, Utrecht, The Netherlands and ⁶Department for Cognitive Neuroscience, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
Perceived threat predicts the neural sequelae of combat stress

• Prospective design to investigate the consequences of severe combat stress in soldiers before and after deployment to a combat zone.

• Control group not deployed to combat zone.

• None of the included subjects developed PTSD.

• fMRI task was to match the cue with angry face or fearful face in a block design – decision about angry or fearful and respond accordingly.

Van Wingen et al 2011; *Molecular Psychiatry*
Perceived threat predicts the neural sequelae of combat stress

Severe stress from combat exposure increases amygdala and insula reactivity to biologically salient stimuli, but not in controls

Van Wingen et al 2011; Molecular Psychiatry
Amygdala-dorsal ACC coupling under threat

Individual differences in perceived threat during military deployment affects functional coupling of the amygdala with the dorsal anterior cingulate cortex (dACC)

Van Wingen et al 2011; *Molecular Psychiatry*
Amygdala-insula coupling under threat

Individual differences in perceived threat during military deployment affects functional coupling of the amygdala with the insula

Van Wingen et al 2011; Molecular Psychiatry
unpredictable threat with competing demands /priorities
Unpredictable threat study in non-clinical subjects

• First study in trauma unexposed non-clinical subjects
• N=16 young adults performed the task during fMRI scanning.

Archival Report

Amygdala–Prefrontal Cortex Functional Connectivity During Threat-Induced Anxiety and Goal Distraction

Andrea L. Gold, Rajendra A. Morey, and Gregory McCarthy

ABSTRACT

Gold, Morey, McCarthy 2014; Biological Psychiatry
Threat response

Gold et al 2014; Biological Psychiatry
Unpredictable threat modulates the functional connectivity between amygdala and vmPFC

Gold et al 2014; Biological Psychiatry
Brain behavior correlations

Gold et al 2014; Biological Psychiatry
Amygdala and vmPFC relationship
So what?

• van Wingen and colleagues showed connectivity changed with stress of combat, specifically perceived stress during deployment.

• This is a real-life stressor.

• Gold et al showed et al that a laboratory manipulation of stress induced by unpredictable threat also produced connectivity changes.

• Both led to cortico-limbic changes in functional connectivity.

• Perhaps our laboratory manipulation can give us valid information about unpredictable threat in PTSD.
Study in veterans with PTSD – same paradigm

- US military veterans with PTSD from recent conflicts (n=25)
- Trauma-exposed veterans without PTSD (n=25)
- Recruited at the Durham VA Medical Center in NC
- PTSD diagnosis with CAPS-4
- **Goal**: Investigate functional alterations of neural systems in PTSD during unpredictable threat while performing complex goal directed tasks, which involve balancing competing demands and priorities.

Sun et al; in preparation
Table 1. Demographic and clinical information (n= 50).

<table>
<thead>
<tr>
<th>TEST</th>
<th>CONT (n=25)</th>
<th>PTSD (n = 25)</th>
<th>PTSD vs. CONT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>t (p)</td>
</tr>
<tr>
<td>Age</td>
<td>38.2(7.8)</td>
<td>43.7(10.1)</td>
<td>2.143(0.037)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>22/3</td>
<td>22/3</td>
<td>NS</td>
</tr>
<tr>
<td>CAPS</td>
<td>6.3(6.6)</td>
<td>46.9(14.7)</td>
<td>12.633(&lt;0.001)</td>
</tr>
<tr>
<td>BDI</td>
<td>4.9(6.9)</td>
<td>18.2(13.2)</td>
<td>4.438(&lt;0.001)</td>
</tr>
<tr>
<td>CTQ</td>
<td>46.0(24.2)</td>
<td>54.2(24.5)</td>
<td>1.197(0.237)</td>
</tr>
<tr>
<td>CES</td>
<td>3.5(5.2)</td>
<td>14.2(12.0)</td>
<td>3.793(&lt;0.001)</td>
</tr>
<tr>
<td>TLEQ</td>
<td>12.7(13.3)</td>
<td>22.1(11.8)</td>
<td>2.437(0.019)</td>
</tr>
<tr>
<td>AUDIT</td>
<td>4.0(4.3)</td>
<td>3.7(3.1)</td>
<td>-0.228(0.775)</td>
</tr>
<tr>
<td>DAST</td>
<td>0.2(0.7)</td>
<td>0.8(1.2)</td>
<td>1.817(0.075)</td>
</tr>
<tr>
<td>STAI_state</td>
<td>27.7(8.4)</td>
<td>40.8(11.5)</td>
<td>4.578(&lt;0.001)</td>
</tr>
<tr>
<td>STAI_trait</td>
<td>29.7(7.9)</td>
<td>44.5(11.8)</td>
<td>5.197(&lt;0.001)</td>
</tr>
</tbody>
</table>
unpredictable threat with competing demands /priorities

Time Line of a Block

2 sec  30 sec  12 sec

SAFE: NO SHOCK

THREAT: SHOCK

No Threat

Threat From 0, 1, or 2 Unpredictable Shocks

Avatar  Prey  Predator
reduced discrimination of the amygdala response in PTSD patients who exhibited high activation regardless of threat

amygdala response of the trauma-exposed control group successfully discriminated between low and high threat salience
Brain Behavior Correlations – prey captures vs. activation

Threat-related activation of vmPFC was correlated with successful goal-directed behavior in trauma-exposed controls but not in PTSD.

PTSD patients are unsuccessful at engaging vmPFC resources to effect increased task performance.

Trauma-exposed controls can engage the vmPFC to effect improved task performance.

Sun et al; in preparation
Brain Behavior Correlations – avatar captures vs. activation

PTSD: vmPFC activation to threat decreased as performance worsened.

Controls: vmPFC activation to threat increased as performance worsened.

PTSD patients are unsuccessful at engaging vmPFC resources as stress/demands of task increases but can manage at low demands.

Trauma-exposed controls can engage the vmPFC when task gets more stressful/demanding.
Unpredictable threat modulates the connection between amygdala and vmPFC more strongly in trauma-exposed controls than PTSD.
Weaker functional connectivity between amygdala and vmPFC is correlated with successful goal-directed behavior in trauma-exposed controls but not in PTSD.
Discussion

• A generalized response of the amygdala that limits discrimination between threatening and non-threatening stimuli may explain hypervigilance symptoms of PTSD.

• Reduced threat discrimination of the amygdala, and weaker amygdala-vmPFC functional connectivity to unpredictable threats, may explain the impaired performance of PTSD patients engaged a goal-directed tasks.

• trauma survivors (non-PTSD) who performed goal-directed task successfully rely on the vmPFC function more than on amygdala-vmPFC connectivity, which may reflect post-trauma adaptations that promote resilience to PTSD
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1 Danger       | Life Threat to Self—Personal: Exposure to the threat of death or actual threatened serious injury  
Life Threat to Other—Personal: Exposure to the actual or threatened death of others |
| 2 Non-Danger   | Aftermath of Violence—Personal: Exposure to grotesque or haunting images, sounds, or smells of dead or severely injured humans or animals  
Traumatic Loss—Witnessed or Learned About: e.g. death of a family member, friend, or unit member  
Moral Injury by Self: Committing an act that is perceived to be a gross violation of moral or ethical standards (e.g. killing or injuring others, rape, atrocities). A service member who nearly committed these acts could also experience moral injury  
Moral Injury by Others: Witnessing or being the victim of an act that is perceived to be a gross violation of moral or ethical standards (e.g. killing or injuring others, rape, atrocities, betrayal). Events can also be indirectly experienced (i.e. learned about) if they are directly relevant to the individual |
Brain regions engaged in PTSD by danger vs. non-danger trauma

Ramage et al 2015; SCAN
Danger and non-danger can be intertwined
Moral Injury Event Scale

<table>
<thead>
<tr>
<th>(1) I saw things that were morally wrong</th>
<th>Strongly Agree</th>
<th>Moderately Agree</th>
<th>Slightly Agree</th>
<th>Slightly Disagree</th>
<th>Moderately Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2) I am troubled by having witnessed others’ immoral acts</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>(3) I acted in ways that violated my own moral code or values</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>(4) I am troubled by having acted in ways that violated my own morals or values</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>(5) I violated my own morals by failing to do something that I felt I should have done</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>(6) I am troubled because I violated my morals by failing to do something that I felt I should have done</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>(7) I feel betrayed by leaders who I once trusted</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>(8) I feel betrayed by fellow service members who I once trusted</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>(9) I feel betrayed by others outside the U.S. military who I once trusted</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>10. I trust my leaders and fellow service members to always live up to their core values</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>(11) I trust myself to always live up to my own moral code</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

- 51% of post-9/11 veterans who served in a warzone report “witnessing morally wrongs acts,” 30% report “not stopping morally wrong acts even when possible,” and 24% report “doing something morally wrong.”

- Moral injury correlated with symptom frequency of PTSD ($r = .49; p < .001$), greater PTSD symptom severity ($r = .50; p < .001$), higher levels of depression ($r = .59; p < .001$), and greater alcohol use ($r = .38; p = .003$).
Associations of Perceived Betrayal with Structural Measures of Cortical Gray Matter

R Superior parietal lobule
(Area No. 27)

L Orbital Sulci
(Area No. 64)

Temporo-parietal and parietal activation associated with guilt (Michl et al 2014; SCAN) and supramarginal associated with guilt (Morey et al 2012; NeuroImage)

Sun, Nieuwsma and Morey; in preparation
3rd Theme: Memory Reconsolidation

- experiences are encoded in working and short-term memory and then consolidated into long-term memory.

- memory reconsolidation: every time a memory is recalled it is momentarily made labile and then needs to be reconsolidated.

- the memory may be updated or changed based on new experience and a particular memory may be thought of as being only as old as the last time it was recalled.

- each time a traumatic experience is recalled, the patient’s memory may be updated.

- there is a high potential that the reconsolidation process may reinforce prior beliefs and interpretations (likely including cognitive distortions around guilt, responsibility, and self-blame).

Ross et al, 2017; JAMA Psychiatry
Telephone game

Broken telephone game
Predictions for Memory of CS+

• Negative events and emotions that do not satisfy the PTSD diagnostic criteria for a trauma may lead to symptoms that would otherwise qualify as PTSD (Rubin et al., 2008).

• PTSD includes a vivid central memory of the trauma that is strongly colored by emotional and sensory impressions (Bernsten et al 2003).

• PTSD includes an inability to recall key features of the traumatic event while clinical evidence often describes delayed recall (Elliot 1997).
Overall Design of Fear Generalization

- Fear conditioning with CS- (safety) and CS+ that is paired with shock.

- Generalization test with additional morphs. S2 is midway between CS- and CS+. S4 and S5 are higher intensity (express greater fear) than CS+

- Preceded by pre-conditioning to get baseline activation to each of the facial morphs.

- Subjects are NOT told the rules.

Morey et al. 2015, Translational Psychiatry
generalization of fear memory

**S5 vs. CS+

$p = .002$

S4 vs. CS+

$p > .8$

Morey et al 2015; Translational Psychiatry
Memory distortions and reduced hippocampal activity in PTSD

- Patients with PTSD relied on gist-based representations in lieu of encoding contextual details (greater false alarms to novel trauma lures).

- Also PTSD patients show reduced hippocampal activation than controls during successful encoding of trauma stimuli.

Hayes et al., 2011; Journal of Psychiatric Research
Collaborators

- Kevin LaBar
- Mike Hauser
- Joseph Dunsmoor
- Gregory McCarthy
- Ryan Wagner
- Alison Adcock
- Andrea Gold
- Ahmad Hariri
- Jonathan Weiner
- Jason Nieuwsma
- Allison Ashley-Koch
- Christine Marx
- Michael De Bellis