Conditioned Fear Extinction and Fear Inhibition as Psychophysiological Indices of Trauma-related Psychopathology

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Brown Bag Series

Outline
- PTSD Symptom Overview
- Fear-potentiated Startle
- Establishment of Fear Extinction Paradigm
- Parametric Analysis of Fear Extinction
- Translation of Fear Extinction to Clinical PTSD Populations
- Genomics of Fear Processing in PTSD Populations

Human Psychophysiology of Emotion (HPOE) Laboratory

Effects of Combat Trauma
Atlanta VA Medical Center
Psychophysiology laboratory
PI: Seth D. Norrholm, PhD

Effects of Civilian Trauma
Grady Trauma Project
Psychophysiology laboratory
PI: Tanja Jovanovic, PhD

Co-investigators: Kerry Ressler, MD, PhD; Bekh Bradley, PhD; Barbara Rothbaum, PhD; Erica Duncan, MD; Boadie Dunlop, MD

The goals of this research program are to investigate fear-related neurobiological phenotypes associated with symptoms of trauma-related disorders. Such neurobiological phenotypes can provide investigative tools to increase our understanding of the bases of these disorders and develop better prevention or intervention programs.

Combat Involves Exposure to Multiple Types of Traumatic Events, Often Repeatedly
"I'm following the vehicles in front of me. This guy behind me is following too close. I can’t get off this road if something happens. I hate this feeling of being trapped. My heart races, my palms are sweating on the steering wheel. I have to get off this road."

37-yr old Operation Iraqi Freedom veteran discussing his physiological reactions to driving on Interstate 85 in Atlanta, Georgia

An almost universal experience of OIF/OEF veterans is traveling in humvee convoys. Designation between "combat" and "non-combat" has become meaningless since one of the most dangerous jobs in Iraq is driving a truck in a convoy where there is a great risk of lethal attack.

Many of the combat veterans we see at the Atlanta VAMC TRP present with humvee/IED-related index traumas as a result of fear conditioning and stimulus generalization. Posttraumatic Stress Disorder (PTSD)

- Onset determined by traumatic event, but low rates of illness relative to trauma exposure: Gene x Environment risk factors
- High rates of co-morbidity with depression, other anxiety disorders, substance abuse
- Heterogeneous: three major symptom clusters
  - Re-experiencing symptoms
  - Avoidance symptoms
  - Hyper-arousal symptoms

Re-experiencing symptoms as a result of fear conditioning and stimulus generalization
**PTSD Symptoms**

- Re-experiencing
  - Severe (repetitive) nightmares
  - Flashbacks or intrusive memories or mental images
- Avoidance and emotional numbing
  - Avoidance of reminders of the traumatic experience
  - Or of situations similar in any way to the traumatic experience
  - Feeling "cold", hard, distant
- Increased arousal or agitation
  - Can’t calm down or relax, can’t get to sleep or stay sleep
  - Anxiety (panic) attacks or anger (rage) outbursts

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**VA Combat Veteran Population**

<table>
<thead>
<tr>
<th></th>
<th>PTSD (PCL Score)</th>
<th>Depression</th>
<th>Suicidality</th>
<th>General Health</th>
<th>Quality of Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vietnam Era</td>
<td>64.2 ± 0.6</td>
<td>26.0 ± 0.3</td>
<td>5.19 ± 0.11</td>
<td>3.98 ± 0.05</td>
<td>3.31 ± 0.07</td>
</tr>
<tr>
<td>Global Conflicts (Somalia, Kosovo, etc.)</td>
<td>64.4 ± 3.4</td>
<td>26.1 ± 1.7</td>
<td>4.26 ± 0.49</td>
<td>3.83 ± 0.53</td>
<td>2.89 ± 0.30</td>
</tr>
<tr>
<td>1st Gulf War</td>
<td>66.9 ± 1.1</td>
<td>26.9 ± 0.5</td>
<td>4.88 ± 0.20</td>
<td>4.17 ± 0.10</td>
<td>3.00 ± 0.13</td>
</tr>
<tr>
<td>OIF</td>
<td>61.0 ± 2.3</td>
<td>25.5 ± 1.0</td>
<td>4.62 ± 0.51</td>
<td>3.57 ± 0.19</td>
<td>3.48 ± 0.22</td>
</tr>
<tr>
<td>OIF/OND</td>
<td>61.2 ± 0.6</td>
<td>23.7 ± 0.3</td>
<td>4.00 ± 0.08</td>
<td>3.71 ± 0.05</td>
<td>3.49 ± 0.06</td>
</tr>
</tbody>
</table>

Score Range: 17 - 85
9 - 36
3 - 11
1 - 6
1 - 7

Data obtained through administration of the Veterans Affairs Military Stress Treatment Assessment (VAMSTA)

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**Neurobiology of Acoustic Startle**

- Translational tool: observed in all mammals
- Non-invasive measurement
- Simple 3 neuron subcortical circuit
- Modulated by emotion via amygdala
Neurobiology of Fear Responses

- Amygdala involved in expression of fear responses—Fear Acquisition
- Prefrontal cortex involved in inhibiting amygdala activity—Fear Extinction


FEAR-POTENTIATED STARTLE: A MEASURE OF FEAR

PHASES OF FEAR LEARNING

EXPERIMENTAL

- Conditioned Fear Response

CLINICAL

- Fear-related Symptoms
- Traumatic Event
- Extinction-based Exposure Therapy
- Symptom Relapse:
  - Subsequent Stressors
  - Change in Context
  - Time

ESTABLISHMENT OF FEAR EXTINCTION PARADIGM

Fear Extinction: Simple Discrimination (A+/B-)

- Employed paradigm previously validated in our previously published work (Norrholm et al., 2006; Norrholm et al., 2008; Norrholm et al., 2010)
- CS’s – illuminated colored squares
- US: 140 p.s.i. airblast to the throat
- Startle probe: 40 ms, 108 dB white noise burst

Differential Fear Conditioning:

Acquisition: 3 blocks of 4 trials
PARAMETRIC ANALYSIS OF HUMAN FEAR EXTINCTION
HUMAN FEAR EXTINCTION: CS MODALITY

Norrholm et al., 2011, Frontiers in Beh Neuroscience
Fear Acquisition: Fear-potentiated Startle

FEAR EXTINCTION
PARADIGM: COMBAT PTSD
Methods

Participants:
25 PTSD patients referred to the study from the Trauma Recovery Program and related medical clinics at the Atlanta VAMC and 18 healthy volunteers recruited from the Emory University community.

Data Acquisition
BIOPAC MP150 Psychophysiological Recording System
BIOPAC electromyography (EMG) electrodes and In Vivo Metric leads

US Expectancy
CEDRUS Button Box response keypad
Participants pressed a button marked "+" if they expected the US on a trial, "-" if they did not expect the US, and "0" if they did not know

Data analysis
MindWare (Gahanna, Oh)

Participant Demographics

<table>
<thead>
<tr>
<th></th>
<th>No PTSD</th>
<th>PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>35.9 ± 3.2</td>
<td>32.8 ± 1.7</td>
</tr>
<tr>
<td>Sex</td>
<td>10 M, 9 F</td>
<td>20 M, 5 F</td>
</tr>
<tr>
<td>CAPS</td>
<td>N/A</td>
<td>123 ± 42</td>
</tr>
<tr>
<td>BDI</td>
<td>8.15 ± 2.08</td>
<td>30.71 ± 2.98*</td>
</tr>
<tr>
<td>CTQ</td>
<td>49.25 ± 4.62</td>
<td>57.79 ± 6.82</td>
</tr>
<tr>
<td>ASI</td>
<td>22.69 ± 2.10</td>
<td>34.21 ± 3.92*</td>
</tr>
<tr>
<td>CDRS</td>
<td>77.20 ± 4.34</td>
<td>55.71 ± 1.64*</td>
</tr>
</tbody>
</table>

Demographic data for participants with and without PTSD.
Means ± Standard Error
M - Male, F - Female, AA - African American, C - Caucasian, A - Asian

Combat Veterans
Fear Acquisition: Fear-potentiated Startle

Fear Acquisition: CS+/CS- Discrimination

Fear Acquisition: US Expectancy

Combat Veterans

Fear Extinction: Fear-potentiated Startle

Combat Veterans

Fear Extinction: US Expectancy

FEAR EXTINCTION PARADIGM:

SYMPTOM SEVERITY
Fear Acquisition: Fear-potentiated Startle

(A) Low Sxs PTSD

(B) High Sxs PTSD

Fear Acquisition: CS+/CS− Discrimination

Fear Extinction:

(A) Fear-potentiated Startle

(B) Cognitive Awareness

FEAR EXTINCTION PARADIGM: CIVILIAN PTSD
Civilian Trauma
Fear Acquisition: Fear-potentiated Startle


Civilian Trauma
Fear Acquisition: CS+/CS- Discrimination


Civilian Trauma
Fear Extinction: Fear-potentiated Startle and US-Expectancy

Extinction is predicted by startle to CS-

Table: Outcome Variable

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Δ R²</th>
<th>Δ F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Depression</td>
<td>0.01</td>
<td>0.38</td>
<td>0.540</td>
</tr>
<tr>
<td>2. Trauma History</td>
<td>0.02</td>
<td>0.32</td>
<td>0.732</td>
</tr>
<tr>
<td>3. Danger cue (CS- Late Acq)</td>
<td>0.003</td>
<td>0.12</td>
<td>0.720</td>
</tr>
<tr>
<td>4. Safety cue (CS- Late Acq)</td>
<td>0.22</td>
<td>9.89</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

Norrholm et al (2011) Biol Psychiatry
PTSD Symptom Clusters:

Exaggerated Startle Response


Genomics of Fear Processing in PTSD

- a dopamine catabolic enzyme primarily expressed in the prefrontal cortex and hippocampus, regions which are critically associated with inhibition of fear responses.
- the COMT gene is located on chromosome 22q11 and possesses several common single nucleotide polymorphisms (SNPs), including a G/A substitution (rs4680) at codon 158.
- This SNP results in a valine (Val) to methionine (Met) substitution that affects the thermostability and activity of COMT.
- From a psychiatric perspective, Met allele carriers, and especially Met/Met homozygote individuals, may be more susceptible to anxiety disorders

Demographics, Trauma History, and PTSD Symptom Severity

<table>
<thead>
<tr>
<th>Demographics</th>
<th>PTSD+ (n=28)</th>
<th>PTSD− (n=72)</th>
<th>Genotype</th>
<th>Val/Val (n=241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (% female)</td>
<td>67.3</td>
<td>69.7</td>
<td>73.5</td>
<td>71.9</td>
</tr>
<tr>
<td>Race (% AA)</td>
<td>90.0</td>
<td>87.9</td>
<td>86.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Age (M, SD)</td>
<td>37.6 (13.1)</td>
<td>37.6 (13.9)</td>
<td>38.1 (12.2)</td>
<td>38.4 (12.4)</td>
</tr>
</tbody>
</table>

| Trauma exposure | | |
|-----------------|---|---|---|---|
| Visit (M, SD) | 4.6 (2.5)** | 2.4 (2.2) | 2.7 (2.3) | 3.3 (2.6) |

| PTSD symptoms | | |
|----------------|---|---|---|---|
| PSS total (M, SD) | 27.4 (9.5)** | 7.1 (7.8) | 14.8 (12.1) | 15.1 (12.8) |
| PSS-re-experiencing | 7.0 (3.0)** | 1.7 (2.3) | 5.5 (3.8) | 3.8 (4.5) |
| PSS-avoidance | 12.2 (4.1)** | 2.8 (2.6) | 6.5 (2.9) | 6.4 (5.1) |
| PSS-hyper-arousal | 9.2 (3.6)** | 2.8 (3.1) | 4.4 (4.2) | 5.4 (4.6) |
**COMT genotype, PTSD diagnosis, and Fear Responses**

**Design:** Interaction of COMT genotype and PTSD diagnosis on fear-potentiated startle, COMT DNA methylation status, and COMT mRNA expression.

**Setting:** Medical and gynecological clinics of an urban hospital in Atlanta, Georgia.

**Participants:** The study included 270 unrelated participants with varying degrees of trauma exposure, of which 98 met criteria for PTSD, and 172 did not meet criteria for PTSD. Thirty participants had the COMT Met/Met genotype, and 240 were Val-allele carriers.

Significant interaction of genotype, PTSD diagnosis, and fear conditioning trial type.

Focusing on the CS- (safety signal), main effects of genotype, and PTSD diagnosis, and an interaction of genotype and diagnosis, with highest fear to the safety signal in Met/Met carrier with PTSD

**DNA methylation of the COMT gene**

Seven sites were significantly associated with PTSD.

4 of these sites were associated with fear-potentiated startle to the CS-.

The strongest association was with cg23601416.

DNA methylation of the COMT gene

The Met/Met genotype associated with DNA methylation at 7 CpG sites, 4 of which associated with fear-potentiated startle to the CS.
These results suggest that multiple differential mechanisms for regulating COMT function are associated with impaired fear inhibition in PTSD:

1. at the level of protein structure via the Val^{158}Met genotype and
2. at the level of gene regulation via differential methylation.

Conclusions

1. Veteran PTSD patients displayed impaired within-session extinction of fear; an effect that is strongly associated with PTSD symptom severity
2. Civilian PTSD patients show greater “fear load” at the time of Extinction; a level of fear that must be overcome to achieve successful extinction
3. COMT genotype and methylation status are associated with impaired fear inhibition in PTSD

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Ongoing/Future Directions

• Gene x Environment, epigenetic, and genomic analyses of combat and civilian PTSD populations
• Neuroimaging of fear expression, safety signal, and extinction learning in the latter populations
• Eye-tracking, attention bias towards/away from threat to index additional PTSD symptom clusters (e.g., hypervigilance, avoidance)
  - Recent results demonstrate a positive correlation between fear load during extinction and threat bias (Fani et al., 2011)
Disclosures

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- Drs. Ressler is a co-founder of Extinction Pharmaceuticals for the development of NMDA-based therapeutics to enhance extinction.