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

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Northern Illinois University
Brown Bag Series

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
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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.

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

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

Re-experiencing symptoms 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

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

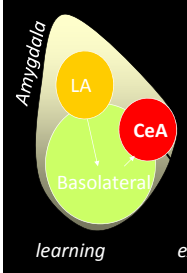
VA Combat Veteran Population

Symptom Presentations

	PTSD (PCL Score)	Depression	Suicidality	General Health	Quality of Life
Vietnam Era	64.2 ± 0.6	26.0 ± 0.3	5.19 ± 0.11	3.98 ± 0.05	3.31 ± 0.07
Global Conflicts (Somalia, Kosovo, etc.)	64.4 ± 3.4	26.1 ± 1.7	4.26 ± 0.49	3.83 ± 0.33	2.89 ± 0.30
1st Gulf War	66.9 ± 1.1	26.9 ± 0.5	4.88 ± 0.20	4.17 ± 0.10	3.00 ± 0.13
OEF	61.0 ± 2.3	25.5 ± 1.0	4.62 ± 0.31	3.97 ± 0.19	3.48 ± 0.22
OIF/OND	61.2 ± 0.6	23.7 ± 0.3	4.00 ± 0.08	3.71 ± 0.05	3.49 ± 0.06
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)

The Fear Response is a Hardwired Process involving the Amygdala



Fear / Panic Symptoms:

Lateral hypothalamus	heart rate, blood pressure
Dorsal vagal N.	bradycardia, ulcers
Parabrachial N.	panting, respiratory distress
Basal forebrain	arousal, vigilance, attention
Retic. Pontis Caudalis	increased *startle response*
Central Gray Area	*freezing*, social interaction
Paraventricular N.	corticosteroid release

Modified from Davis (1992) Ann Rev Neurosci 15: 353-

Neurobiology of Acoustic Startle

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

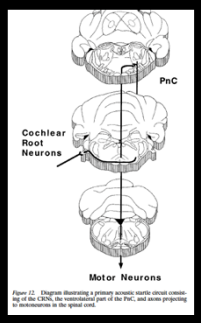
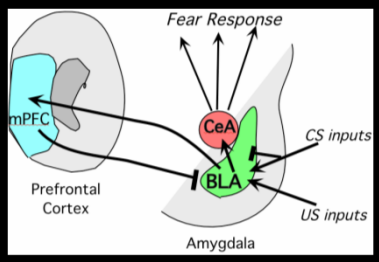


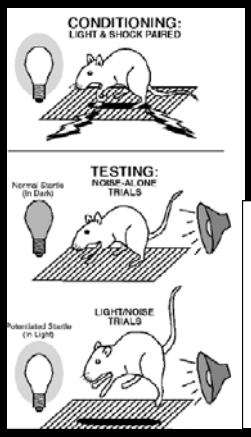
Figure 12. Diagram illustrating a primary acoustic startle circuit consisting of the CRN, the ventrolateral part of the PnC, and axons projecting to motoneurons in the spinal cord.

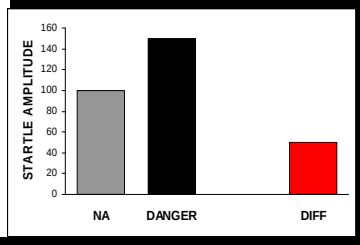
Neurobiology of Fear Responses

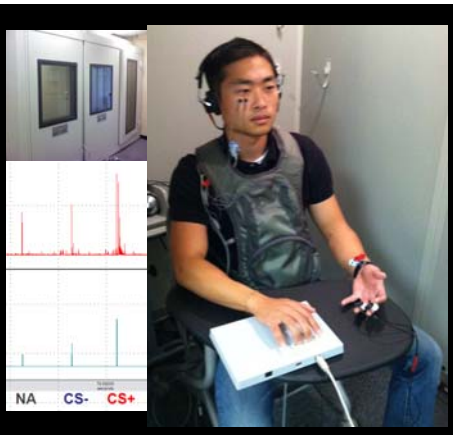


- **Amygdala involved in expression of fear responses—** **Fear Acquisition**
- **Prefrontal cortex involved in inhibiting amygdala activity—** **Fear Extinction**

FEAR-POTENTIATED STARTLE: A MEASURE OF FEAR

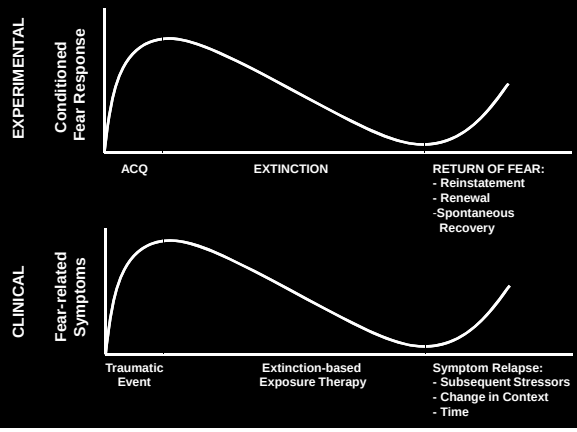






http://cdmrp.army.mil/pubs/video/prm/norrholm_video.shtml

PHASES OF FEAR LEARNING



ESTABLISHMENT OF FEAR EXTINCTION PARADIGM

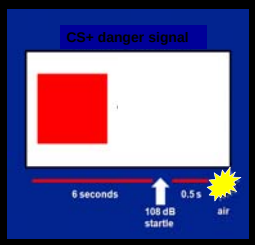
Fear Extinction: Simple Discrimination (A+/B-)

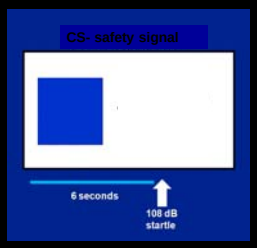
- Employed paradigm previously validated in our previously published work (Norrholm et al., 2006; Norrholm et al., 2008; Norrholm et al., 2010)
- CS's – illuminated colored squares
- US: 140 p.s.i. airblast to the throat
- Startle probe: 40 ms, 108 dB white noise burst

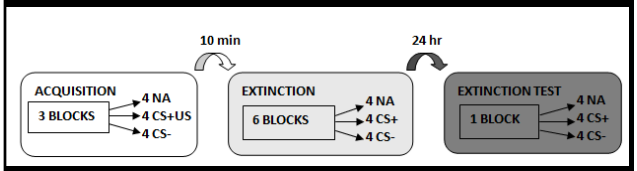
CS+ (DANGER) CS- (SAFETY)

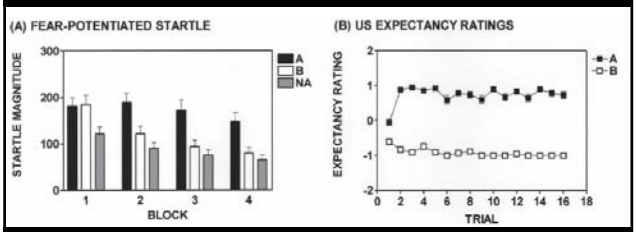
Differential Fear Conditioning:

Acquisition: 3 blocks of 4 trials

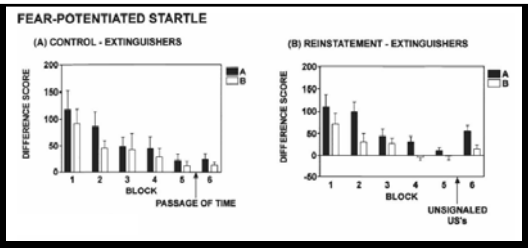








Norrholm et al., 2006, Learning & Memory



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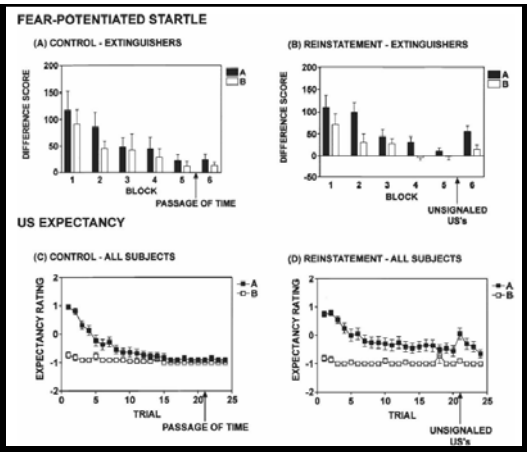
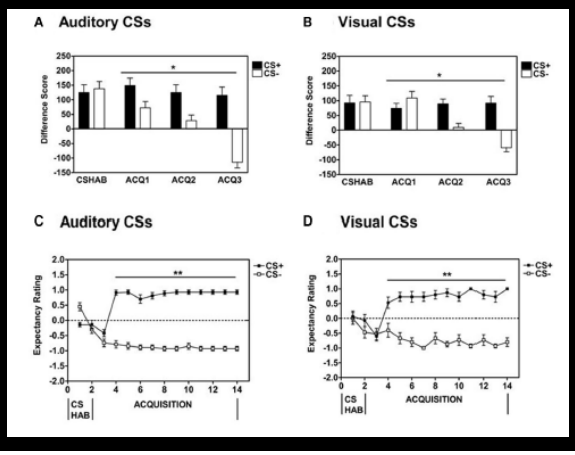
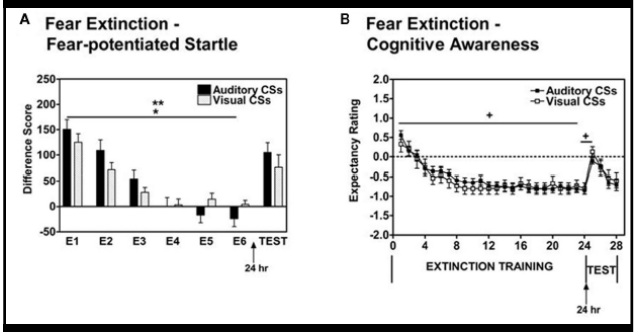


Norrholm et al., 2006, Learning & Memory

PARAMETRIC ANALYSIS OF HUMAN FEAR EXTINCTION

HUMAN FEAR EXTINCTION: CS MODALITY

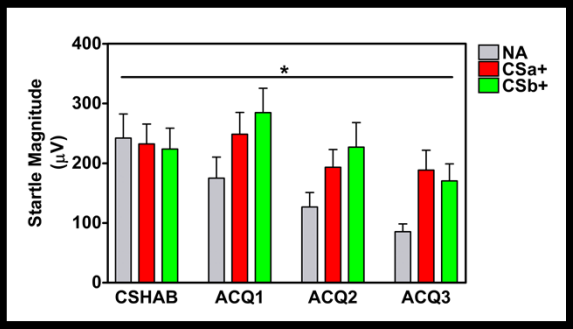


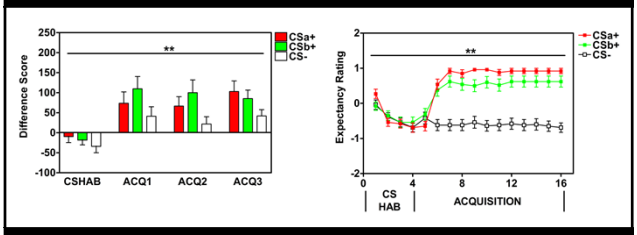


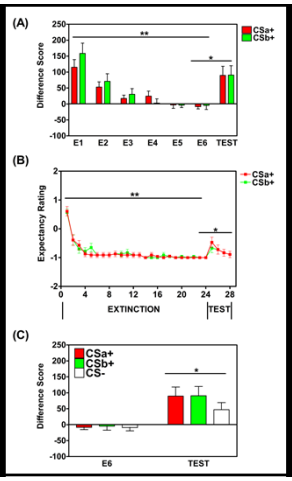
Norrholm et al., 2011, Frontiers in Beh Neuroscience

HUMAN FEAR EXTINCTION: MULTIPLE CSs

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 "+" of they expected the US on a trial, "-" if they did not expect the US, and "0" if they did not know

Data analysis

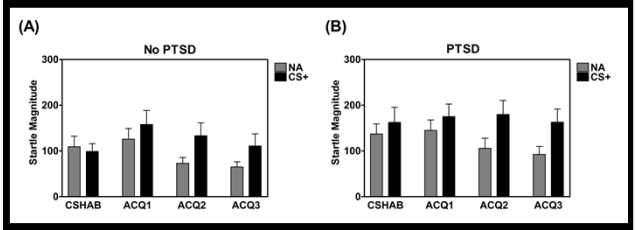
MindWare (Gahanna, OH)

Participant Demographics

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

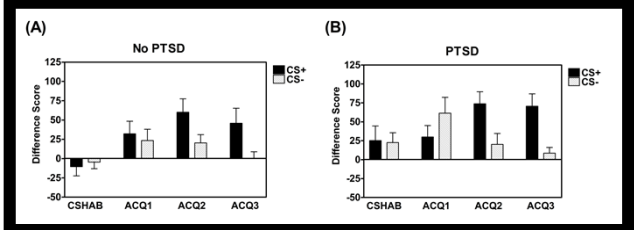
Demographic data for participants with and without PTSD.
Means ± Standard Error
M - Male, F- Female, AA – African American, C – Caucasian, A - Asian

Combat Veterans
Fear Acquisition: Fear-potentiated Startle



Norrholm, S.D., & Jovanovic, T. (2011).
Current Psychiatry Reviews, 7(3): 194-204.

Combat Veterans
Fear Acquisition: CS+/CS- Discrimination



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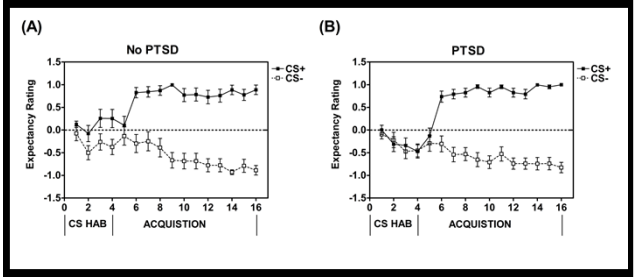
Combat Veterans
Fear Acquisition: US Expectancy



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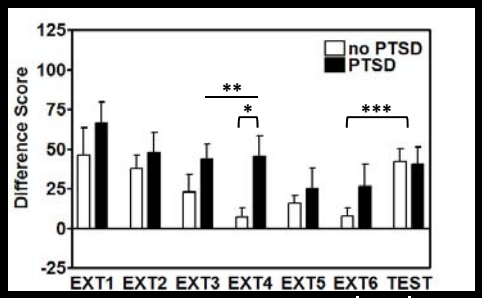
Combat Veterans
Fear Extinction: Fear-potentiated Startle



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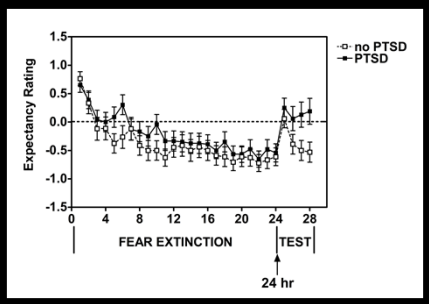

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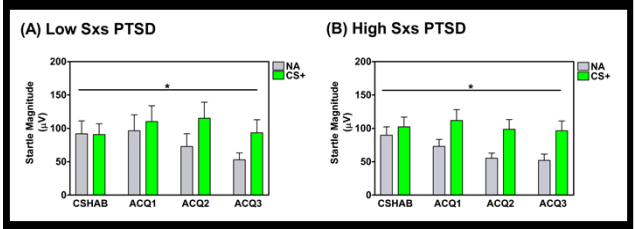
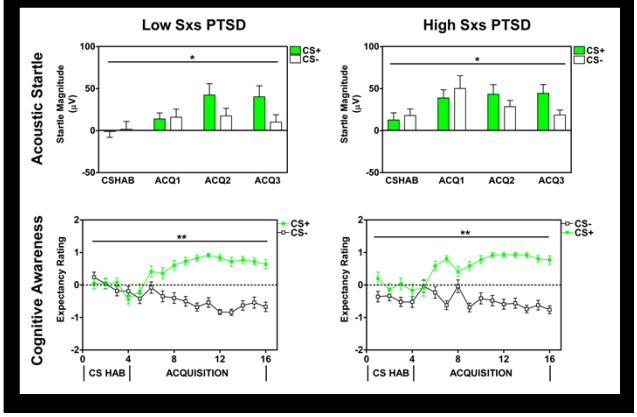
FEAR EXTINCTION PARADIGM:

SYMPTOM SEVERITY

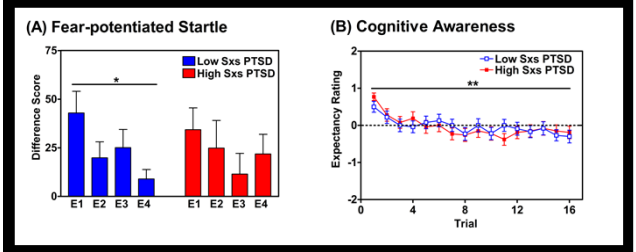
Fear Acquisition: Fear-potentiated Startle



Fear Acquisition: CS+/CS- Discrimination



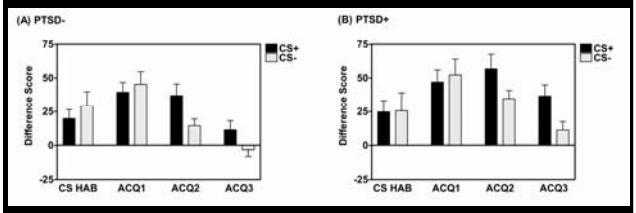
Fear Extinction:



FEAR EXTINCTION PARADIGM: CIVILIAN PTSD

Civilian Trauma

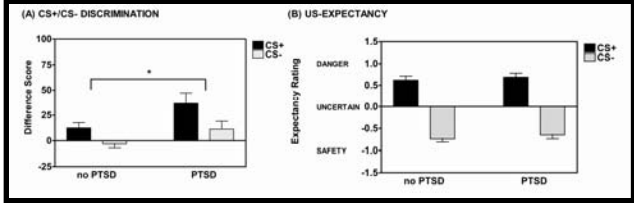
Fear Acquisition: Fear-potentiated Startle



Norrholm,S.D., Jovanovic, T., Olin, I.W., Sands, L.A., Karapanou, I., Bradley, B., & Ressler, K.J. Biol Psychiatry. 2011 Mar 15;69(6):556-63.

Civilian Trauma

Fear Acquisition: CS+/CS- Discrimination



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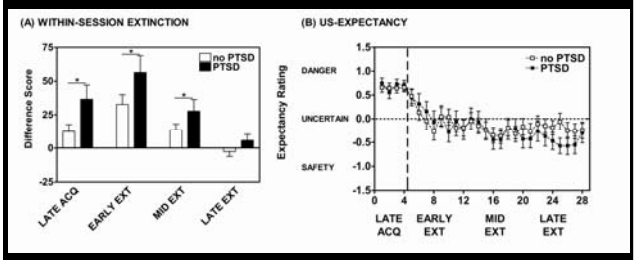
Civilian Trauma

Fear Extinction: Fear-potentiated Startle and US-Expectancy



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Extinction is predicted by startle to CS-

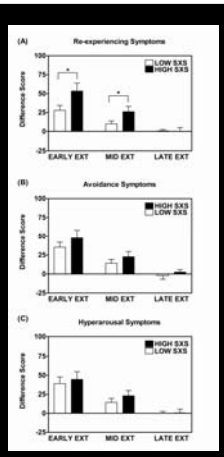
	Outcome Variable		
	Extinction		
Predictors	**Δ R^2**	**Δ F**	**p**
1. Depression	0.01	0.38	0.540
2. Trauma History	0.02	0.32	0.732
3. Danger cue (CS+ Late Acq)	0.003	0.12	0.720
4.Safety cue (CS- Late Acq)	**0.22**	**9.89**	**0.003***

Norrholm et al (2011) *Biol Psychiatry*

Civilian Trauma

PTSD Symptom Clusters:

Exaggerated Startle Response



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GENOMICS OF FEAR PROCESSING IN PTSD

catechol-O-methyl-transferase (*COMT*)

-a dopamine catabolic enzyme primarily expressed in the prefrontal cortex and hippocampus, regions which are critically associated with inhibition of fear responses.

- principal synaptic dopamine clearing mechanism in these brain regions that are largely devoid of dopamine transporter expression

- 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

	PTSD DIAGNOSIS		COMT rs4680 GENOTYPE	
Demographics	PTSD+ (n=98)	PTSD- (n=172)	Met/Met (n=30)	Val allele (n=240)
Sex (% female)	67.3	60.7	73.3	61.8
Race (% AA)	90.8	87.9	80.0	90.0
Age (M, SD)	40.3 (11.4)	37.6 (12.9)	38.2 (12.1)	38.6 (12.4)
Trauma exposure				
TEI (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 (7.0)	14.8 (12.1)	15.1 (12.8)
PSS re-experiencing	7.0 (3.8)**	1.7 (2.5)	3.5 (3.8)	3.8 (4.0)
PSS avoidance	11.3 (4.3)**	2.8 (3.4)	6.8 (5.9)	6.0 (5.6)
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

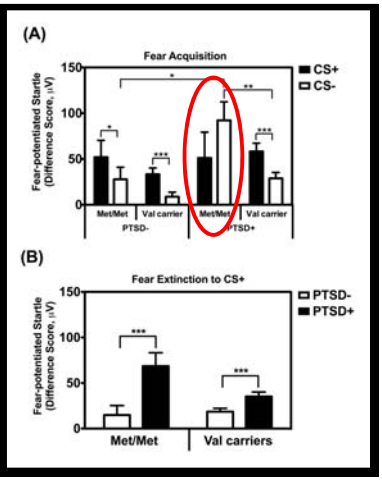
Design: Interaction of *COMT* genotype and PTSD diagnosis on fear-potentiated startle, *COMT* DNA methylation status, and *COMT* mRNA expression.

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

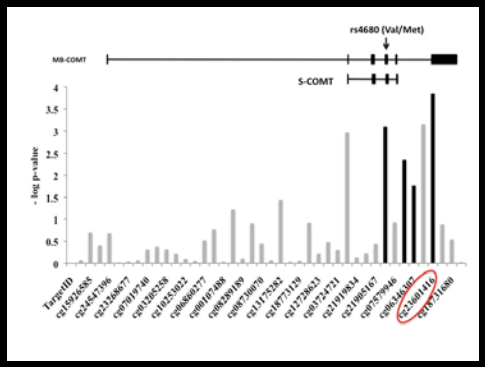
Participants: The study included 270 unrelated participants with varying degrees of trauma exposure, of which 98 met criteria for PTSD, and 172 did not meet criteria for PTSD. Thirty participants had the *COMT* Met/Met genotype, and 240 were Val-allele carriers.

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



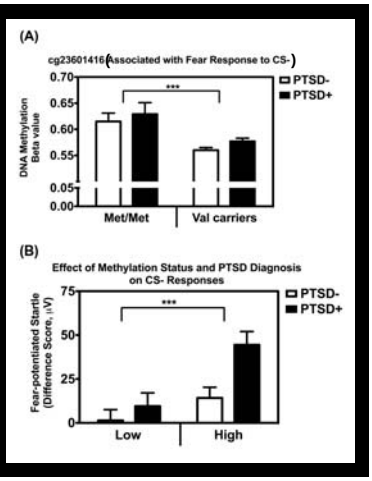
The Met/Met genotype associated with DNA methylation at 7 CpG sites, 4 of which associated with fear-potentiated startle to the CS-

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.



Genomics of Fear Processing

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

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

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)

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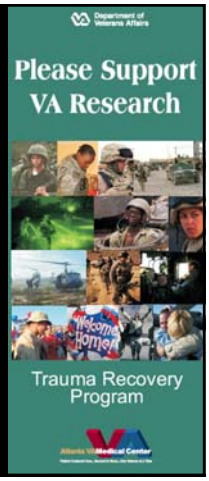

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