Fear and Reward Processing in PTSD: Diagnostic and Treatment Implications

Yuval Neria, PhD
Professor of Clinical Medical Psychology, Columbia Psychiatry, CUMC
Director, PTSD Research and Treatment Program, NYSPI

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Outline

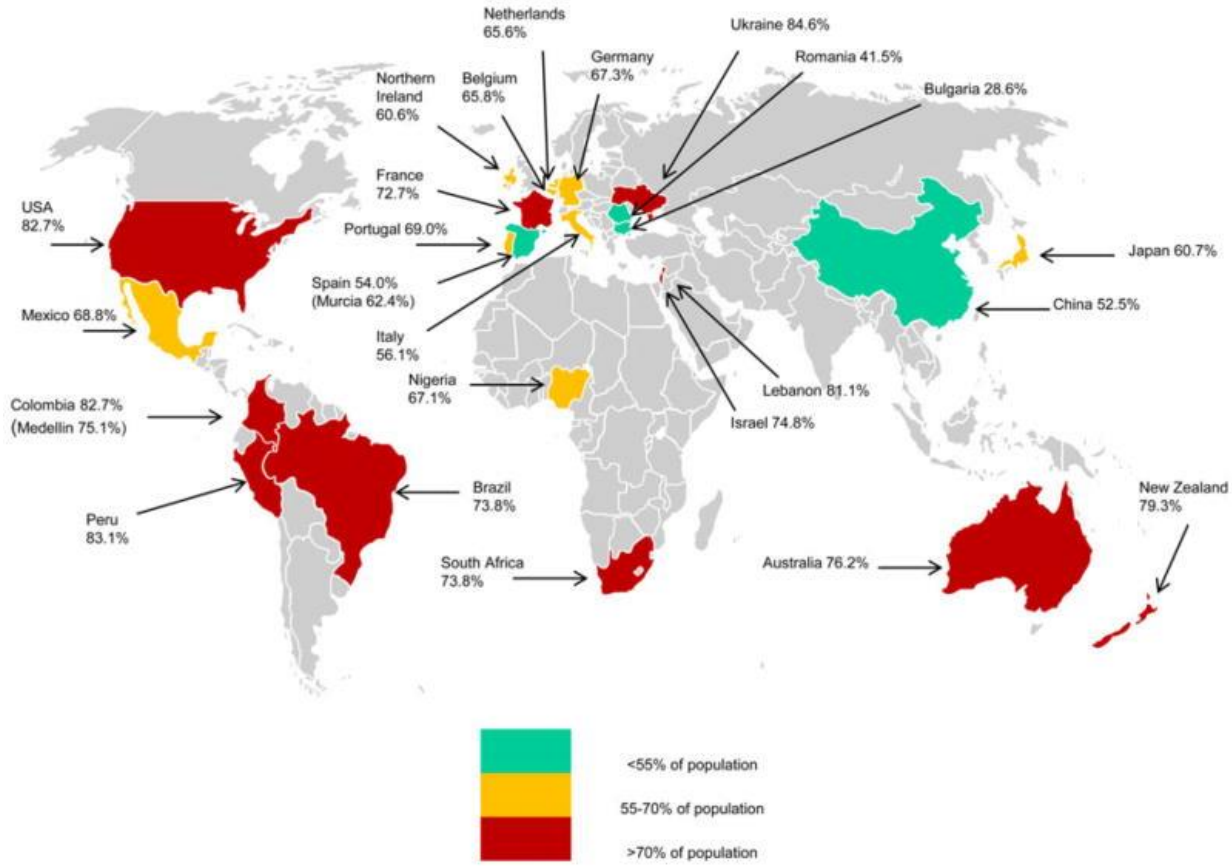
Part 1: What can be learned from epidemiological studies on the neurobiology of PTSD?

Part 2: What are the neural markers of PTSD, and can they be targeted in treatment?

Part 3: Reflections on PTSD diagnosis and research

Part 1: What Can We Learn from Epidemiological Studies on the Neurobiology of PTSD?

Trauma is Global



World Health Organization (Benjet et al., 2016)

The Impact of Trauma: Not Limited to PTSD

Consequences of exposure to trauma commonly include:

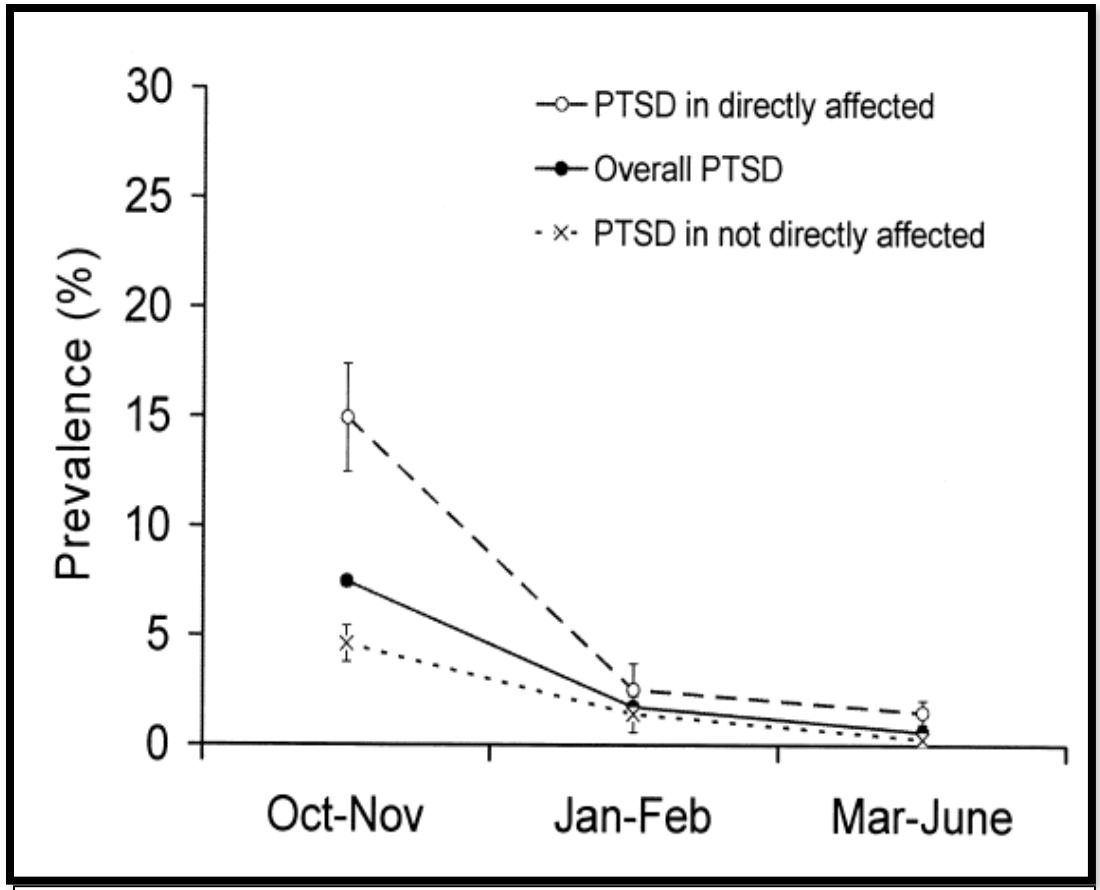
- Depression (e.g., Galea et al., 2002)
- Generalized Anxiety Disorder (e.g., Neria et al., 2006)
- Physical Illness
- Bipolar Illness (e.g., Neria et al., 2008)

Neria, Gross, Marshall, & Susser (Eds.), 9/11: Mental Health in the Wake of Terrorist Attacks. Cambridge University Press. 2006
Neria, Galea & Norris (Eds.), Mental Health of Disasters. Cambridge University Press. 2009

Why Focus on PTSD?

- Signature outcome of trauma exposure
- Prevalence rates are high (lifetime 7-35%, depending on the trauma type)
- Massive economic burden ($232 billion in 2018)
- Diagnostic challenges are yet to be (systematically) addressed
- Treatment efficacy is moderate at best
- Evidence for brain plasticity can be traced after exposure to trauma, in recovery, or in persistence of symptomatology

PTSD Among New York City Residents One, Three, and Six Months After 9/11 Attacks



N=1,008	N=2,001	N=2,752

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Galea et al., AJE, 2003

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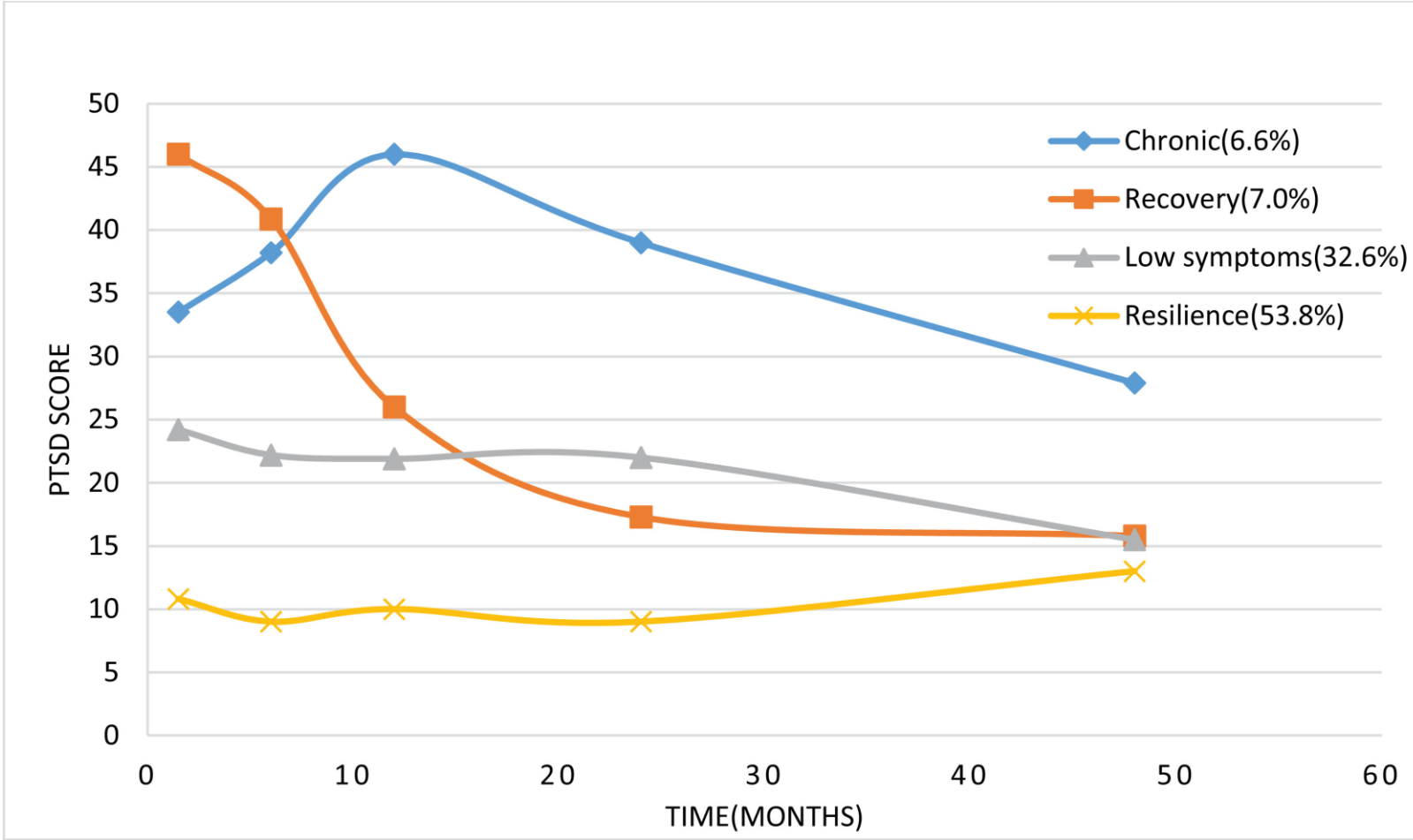
Trajectories of PTSD Symptoms Among Children Who Survived the Lushan Earthquake: A Four-Year Longitudinal Study



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Cheng et al., Journal of Affective Disorders, 2019

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Part 1: Conclusions and Questions

- Trauma is common and most people demonstrate resilience, even in the most severe circumstances
- Many PTSD cases recover over time (demonstrating brain plasticity)
- Significant minority will develop chronic, unremitted PTSD symptomatology

Key questions:

- What are the neural markers of yet-to-be remitted PTSD?
- Can neural deficiencies be addressed in treatment?

Part 2: What Are the Neural Markers of Unremitted PTSD?

- PTSD is conceptualized as a "fear disorder"
- Illness course is developed after exposure to a terrifying event
- Multiple fear-related symptoms are specifically linked to the trauma:
  - Re-experiencing (flashbacks, nightmares, frightening thoughts)
  - Avoidance (staying away from places, events, or objects that are reminders of the trauma)
  - Arousal and reactivity (easily startled, tense or "on edge," difficulty sleeping, angry outbursts)

- Goal: studying the underlying circuits of fear processing

Question 1: Which Capacity is Deficient in PTSD?

1. Fear learning (or fear conditioning): Association between aversive unconditioned stimulus (US; e.g., electrical shock) and a neutral context (e.g., a room) or neutral stimulus (e.g., light) is formed, resulting in the expression of fear responses to the originally neutral stimulus or context
2. Extinction learning: gradual decrements of conditioned fear responses in the lack of exposure to the original aversive stimulus
3. Extinction recall: retrieval and expression of the learned extinction memory after a delay

Question 2: Should We Expect Sex Differences in Fear Processing?

- Many epidemiological studies (though not all of them) show that women are more likely to develop PTSD following exposure to trauma
- Should we expect women to differ from men on fear processing?

Brief Methods

- Comparing patients with PTSD to trauma-exposed healthy controls
- Utilizing fear learning/extinction task in the scanner
- Multimodal assessments:
  - fMRI
  - Skin Conductance Response (SCR)
  - Clinical assessments

Experimental Fear Learning/Extinction fMRI Task

Day 1

Conditioning

8 CS+E

Shock

8 CS+NE

Shock

16 CS-

Extinction

16 CS+E

16 CS-

Day 2

Recall

8 CS+E

8 CS+NE

16 CS-

Milad et al., Biol Psychiatry 2009

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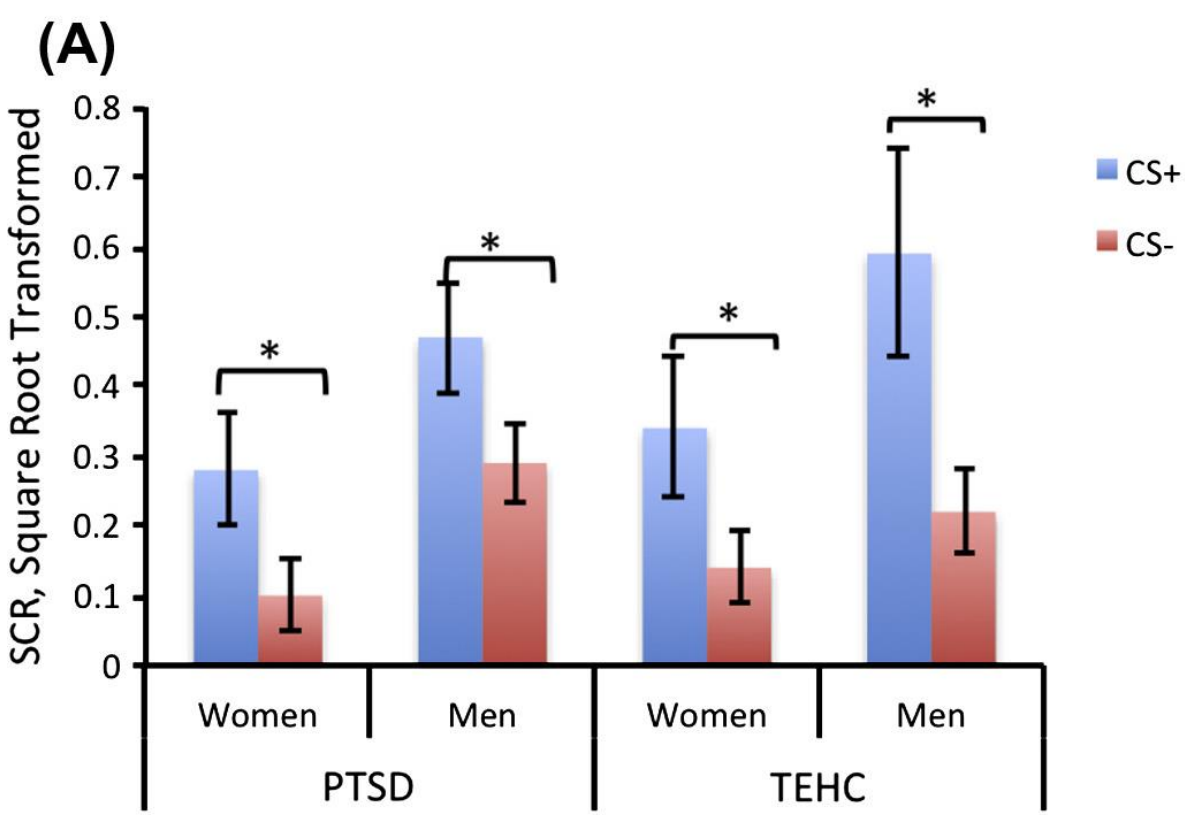
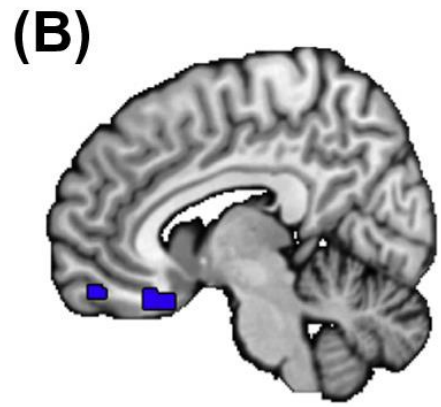
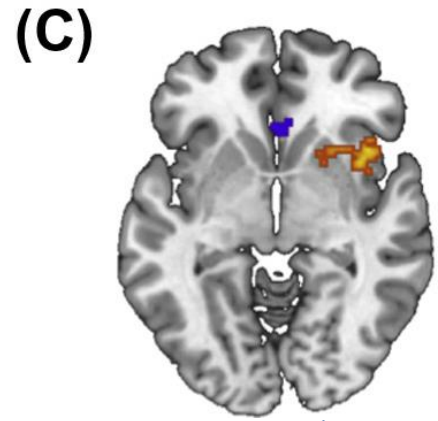
Fear Conditioning

Erel Shvil







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Shvil et al., Neurobiology of Learning and Memory, 2014

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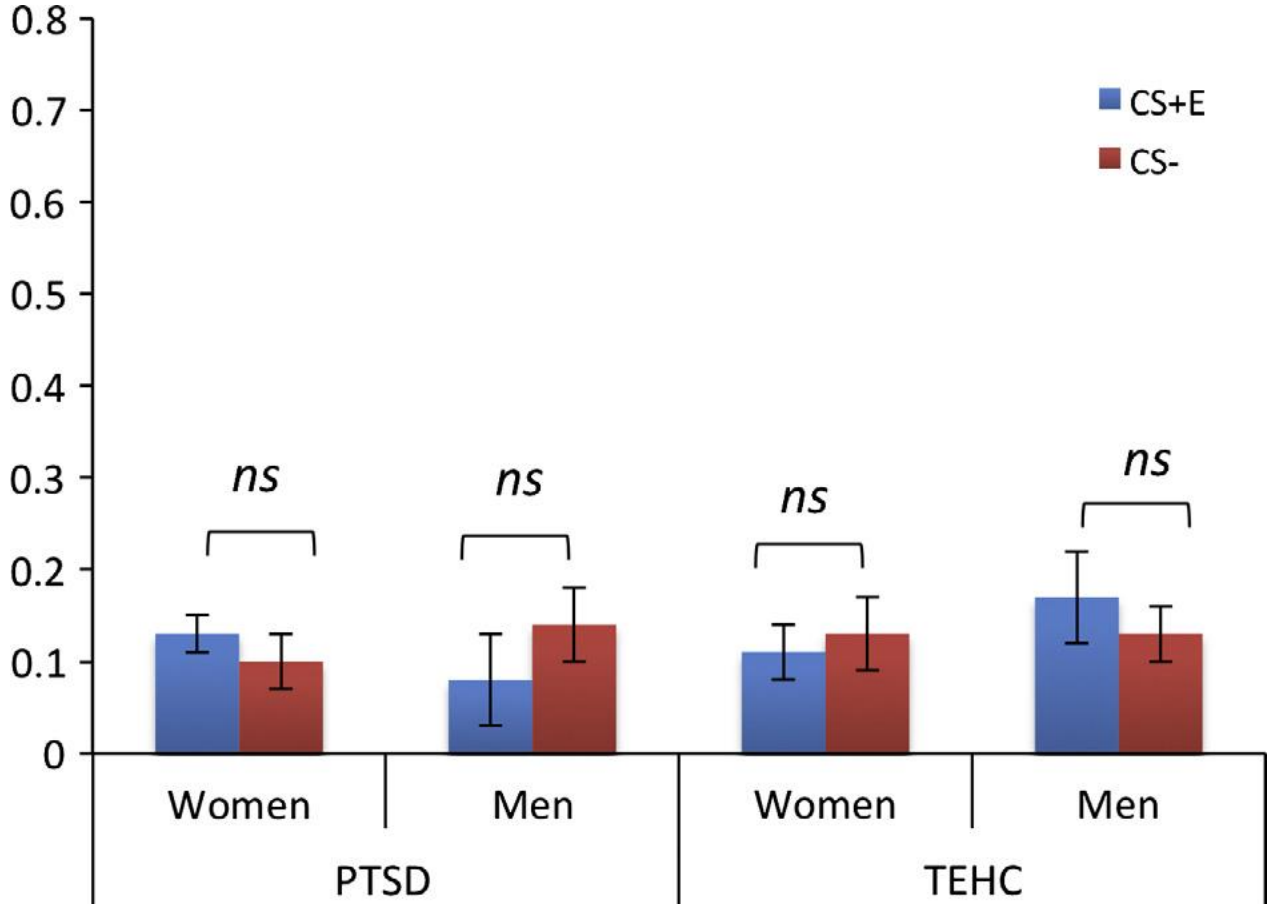
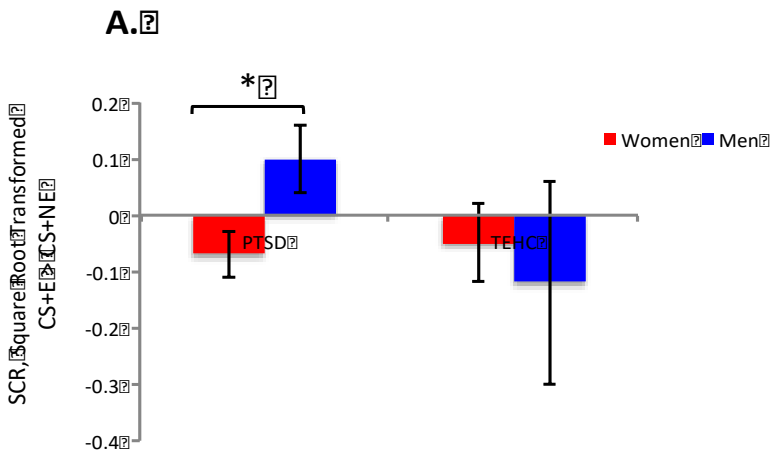
Extinction Learning

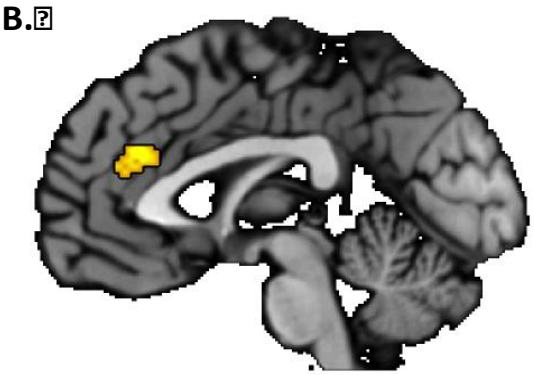
Erel Shvil



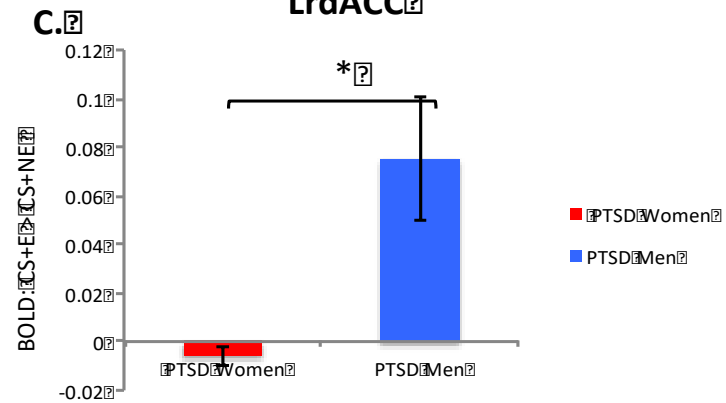
Extinction Recall

Erel Shvil

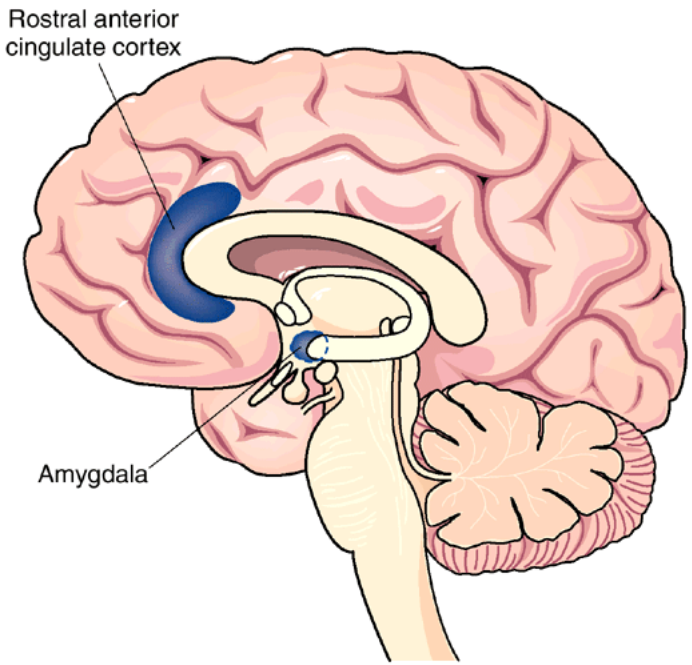




LrdACC

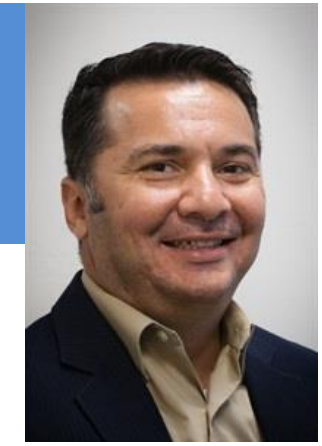


Anterior Cingulate Cortex (ACC)

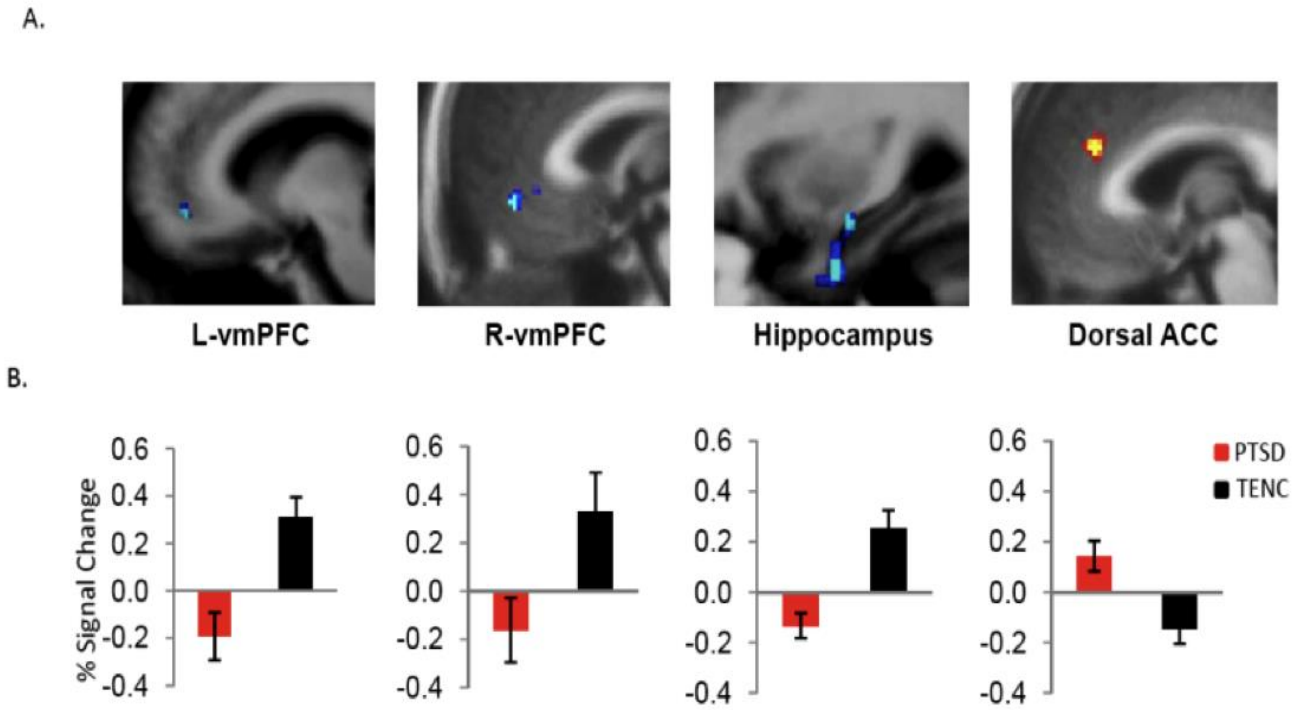


- Crucially involved in normal and abnormal fear processing
- Connection to both the “emotional” limbic system and the “cognitive” prefrontal cortex
- Modulating amygdala-dependent fear processing

Extinction Recall in PTSD



Mohammed Milad



1. Hypoactive hippocampus
2. Hypoactive vmPFC
3. Hyperactive dACC

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Milad et al, Biological Psychiatry, 2009

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Main Conclusions, So Far

- **Clinically,** patients with PTSD are reminded of the trauma while awake and asleep in multiple ways
- **Neurobiologically,** PTSD patients (particularly men) show aberrant capacity to recall extinction of fear memories, coupled with poor top-down neural control
- **Taken together**: PTSD patients manifest little to no capacity to forget the trauma
- **Question**: should we see PTSD as a "memory disorder"?

Question 3: Can We Normalize Deficient Fear Processing in Patients with PTSD?

- **To test this, we chose to study the effects of Prolonged Exposure treatment on the brain of patients with PTSD**
  - Prolonged Exposure (PE), a first-line treatment for PTSD, was guided by learning theory
  - PE Approach: repeated imaginal and in vivo exposures to the trauma memories, aiming to facilitate extinction by processing the memories in safe conditions (in the absence of the threat)

Question 3: Can We Normalize Deficient Fear Processing in Patients with PTSD (Cont.)?

1. Can PE treatment:

– Reverse extinction recall impairments?

– Alter functional connectivity of key fear processing pathways?

2. Does hippocampus volume have a role in PE treatment outcome?

Study design: Two scans, before and after PE. Comparison to trauma exposed healthy controls

Fear Extinction fMRI Task

Day 1

Conditioning

8 CS+E

Shock

8 CS+NE

Shock

16 CS-

Extinction

16 CS+E

16 CS-

Day 2

Recall

8 CS+E

vs.

8 CS+NE

16 CS-

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Milad et al., Biol Psychiatry 2009

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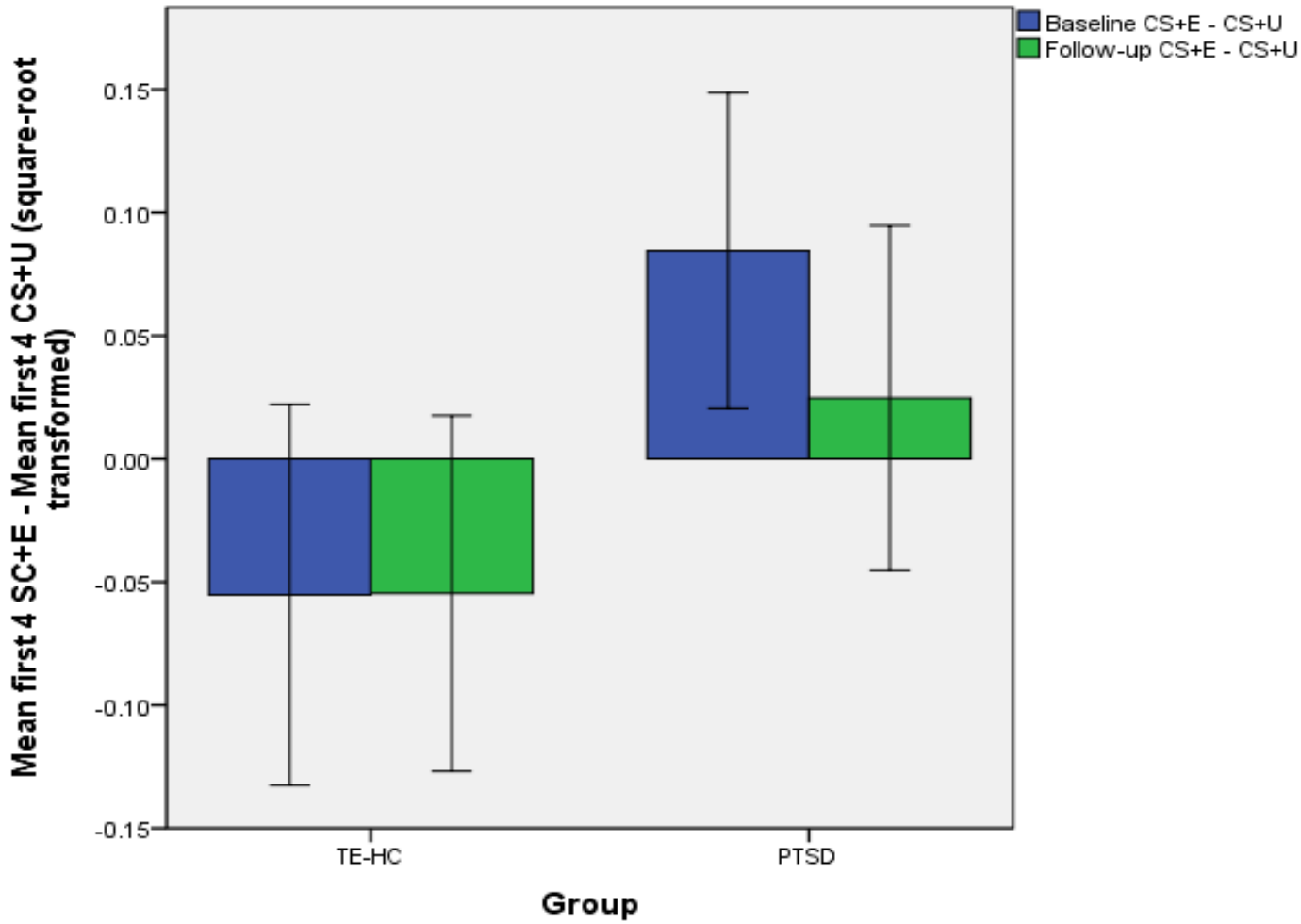
Normalizing Extinction Recall?

Liat Helpman



Helpman et al., Neuroimage, 2016

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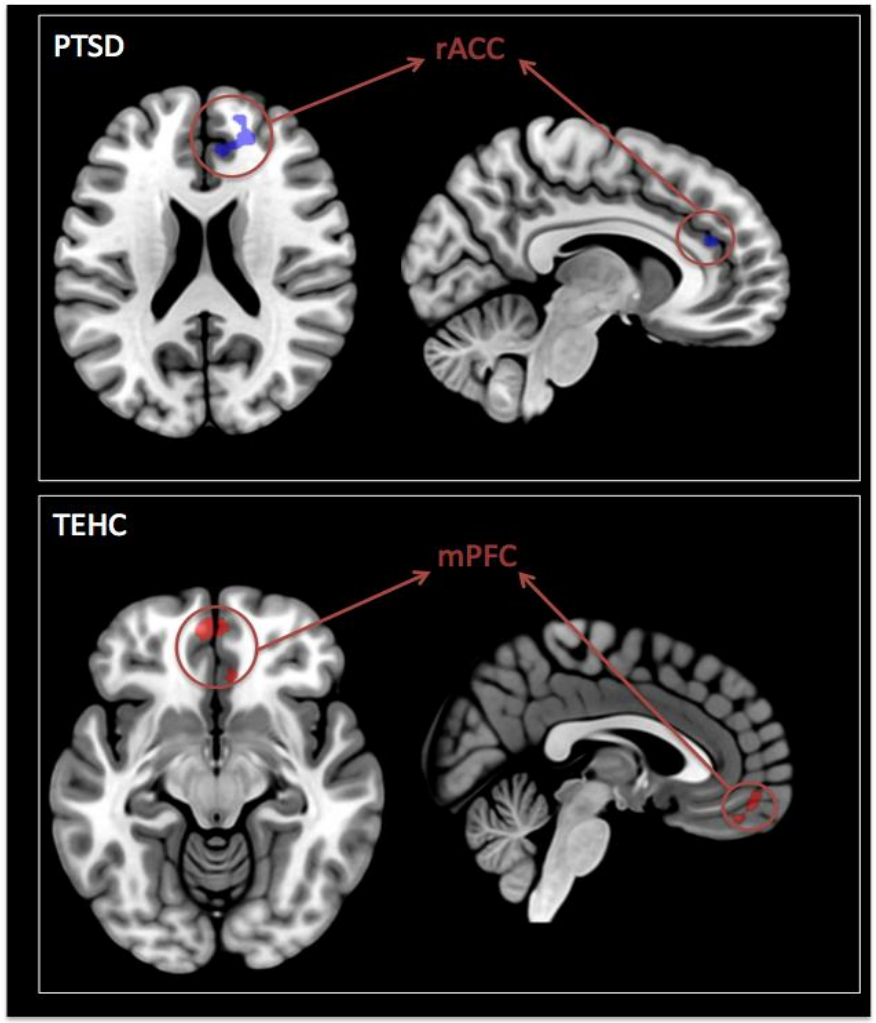
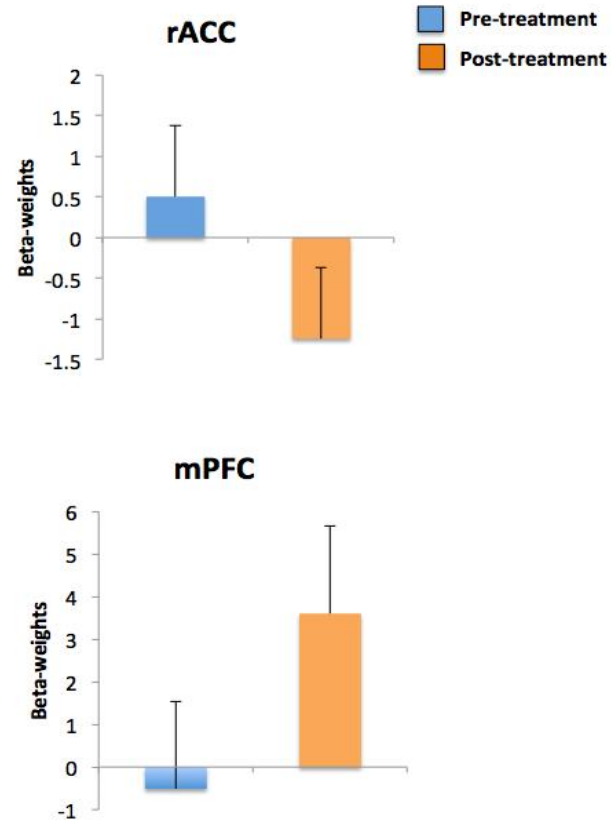
Normalizing Extinction Recall?

Liat Helpman





Helpman et al., Neuroimage, 2016

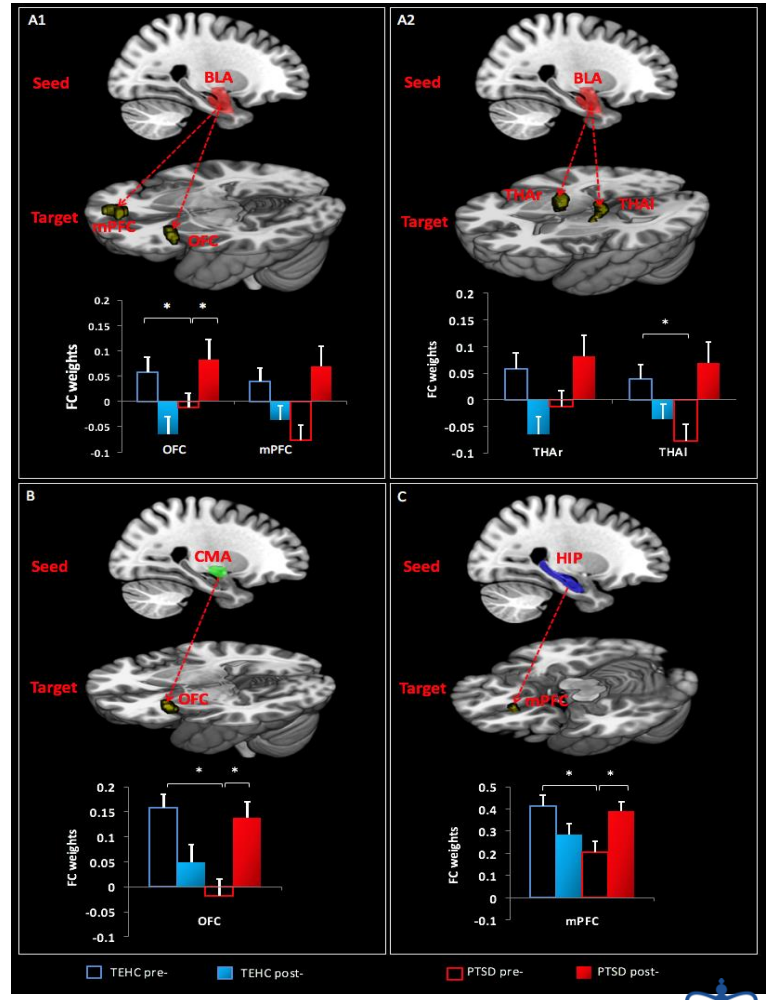
Exposure-Based Therapy Changes Amygdala and Hippocampus Resting-State Functional Connectivity in Patients with PTSD

Xi Zhu

Pre-post rsFC increases in:

- BLA-orbitofrontal cortex (OFC)
- BLA-THA
- CMA-OFC
- Hippocampus-mPFC

Increase in CMA-OFC connectivity was associated with reduction in PTSD



Zhu et al., Depression and Anxiety, 2018

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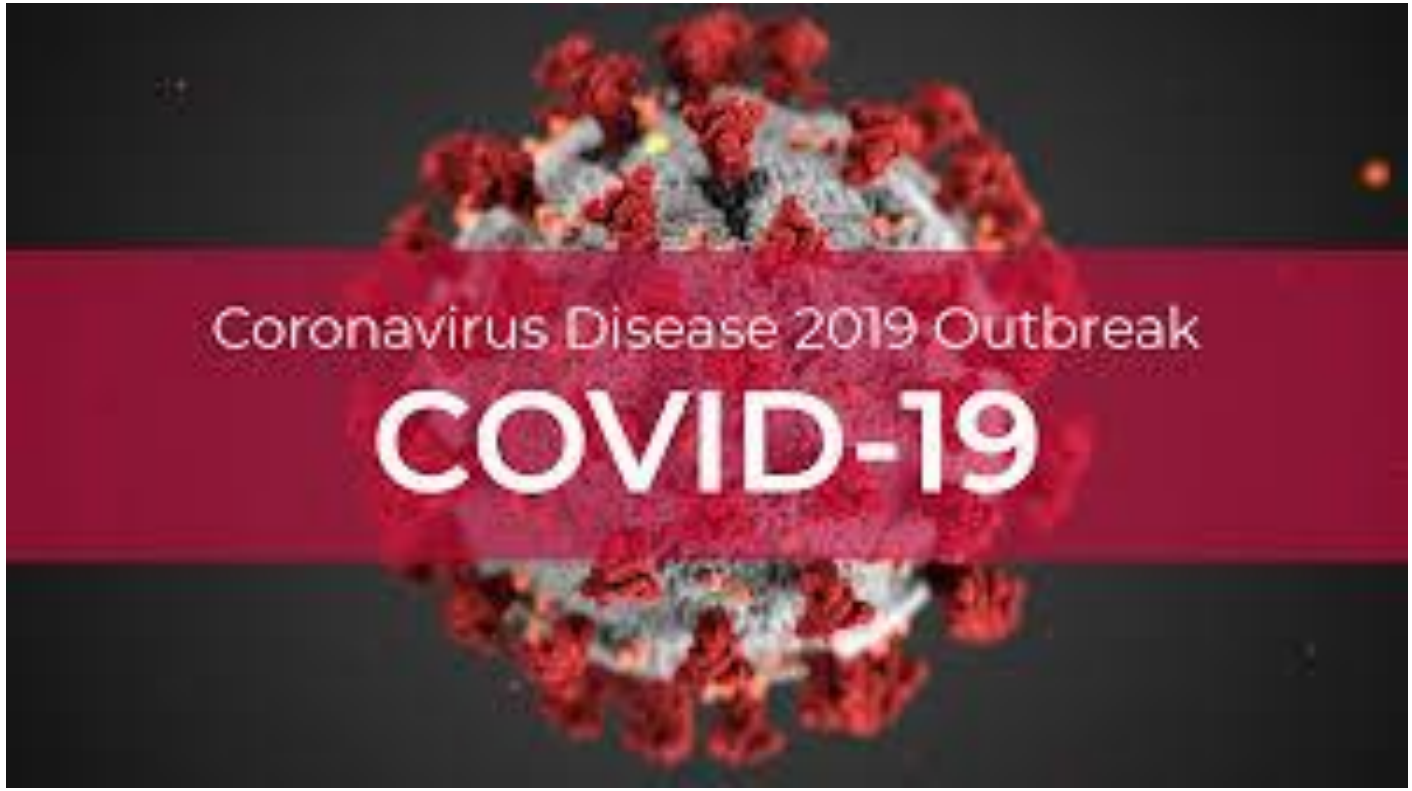
Part 2: Summary

- Multimodal brain imaging can assist in identification and targeting of fear-related markers
- Aberrant fear circuitry is a major mechanism underlying chronic unremitted PTSD
- Dysfunctional fear processing may interfere with recovery
- PE proved efficacious in engaging fear circuitry:
  - Extinction deficits were partially reversed
  - Changes in ACC function were demonstrated
  - Amygdala and hippocampal rsFC pathways were altered

Part 3: Reflections on PTSD Diagnosis and Research



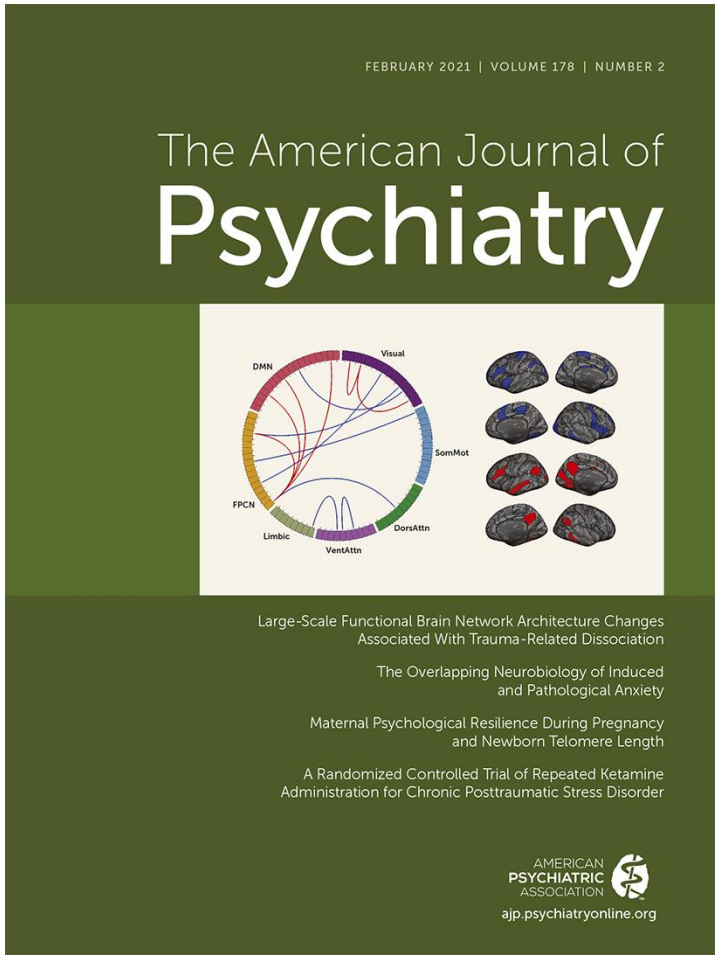
Common Problems in the Field

- Difficulty in replicating fMRI findings
- Small to moderate effect sizes in RCTs
- Prolonged Exposure (gold standard treatment): nonresponse rates range from 25% to 60%, with dropout rates reaching 50%
- Few medications found to ameliorate PTSD, with small effect sizes

Questions:

Do we have a problem with fMRI tasks? Are PTSD treatments inherently weak? Or do we have a problem with the diagnosis of PTSD?

The Problem with PTSD

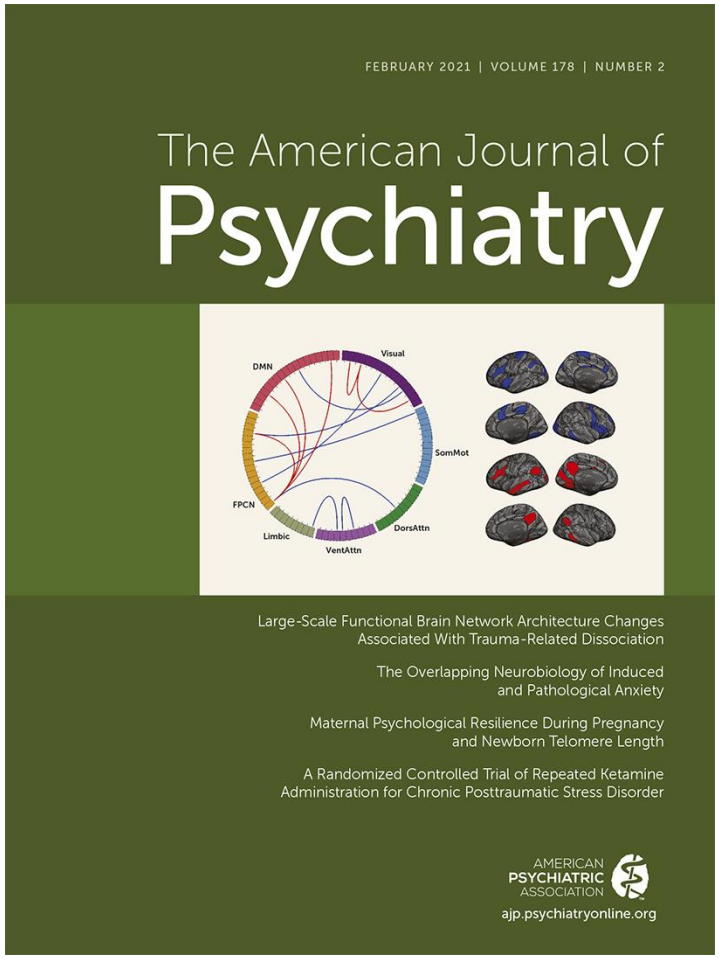


- PTSD diagnosis is a broad constellation of physical, affective, behavioral, and cognitive symptoms
- PTSD overlaps with MDD, GAD, and more
- Galatzer-Levy and Bryant (2013) identified 636,120 ways to meet criteria for DSM-5 PTSD

Consequences:

1. PTSD is (too) heterogeneous, potentially including multiple phenotypes
2. Different PTSD studies=different combinations of patient populations

The Problem with PTSD



- Lack of clear biological margins between PTSD, MDD, and other disorders result in a <u>lack of diagnostic specificity</u>

Urgent need to:

- improve diagnostic specificity
- identify clinically meaningful neurobiological markers of diagnosis, which can serve as objective measurable targets for treatments

The Case of Comorbid PTSD-MDD

- ~50% of PTSD cases exhibit comorbid MDD
- PTSD-MDD vs. PTSD alone:
  - Greater severity and worse clinical outcomes
  - Greater distress, higher suicide risk, and poorer treatment response
  - Difficulties engaging in treatments (anhedonia; emotion dysregulation), particularly in PE

Altered rsFC of Fear and Reward Circuitry in PTSD-MDD

Xi Zhu

RESEARCH ARTICLE

Altered resting state functional connectivity of fear and reward circuitry in comorbid PTSD and major depression

Xi Zhu Ph.D., Liat Helpman Ph.D., Santiago Papini M.A., Franklin Schneier M.D., John C. Markowitz M.D., Page E. Van Meter Ph.D., Martin A. Lindquist Ph.D., Tor D. Wager Ph.D., Yuval Neria Ph.D.

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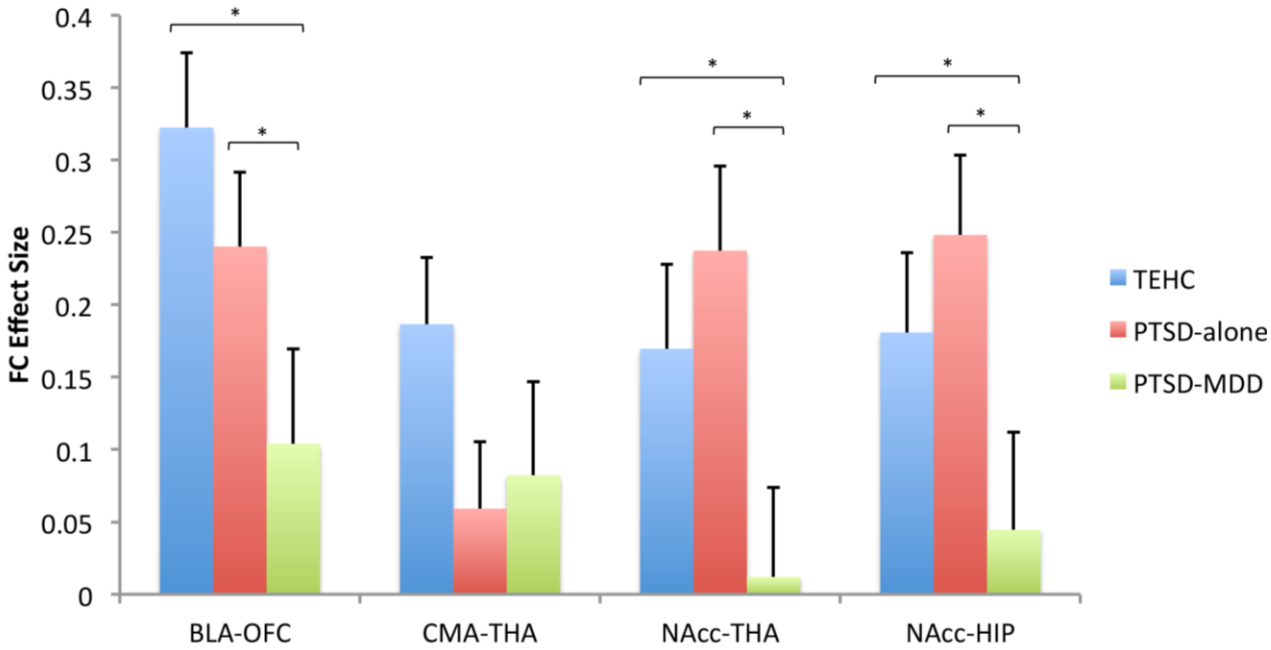
Pages 641–650



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Zhu et al., 2017

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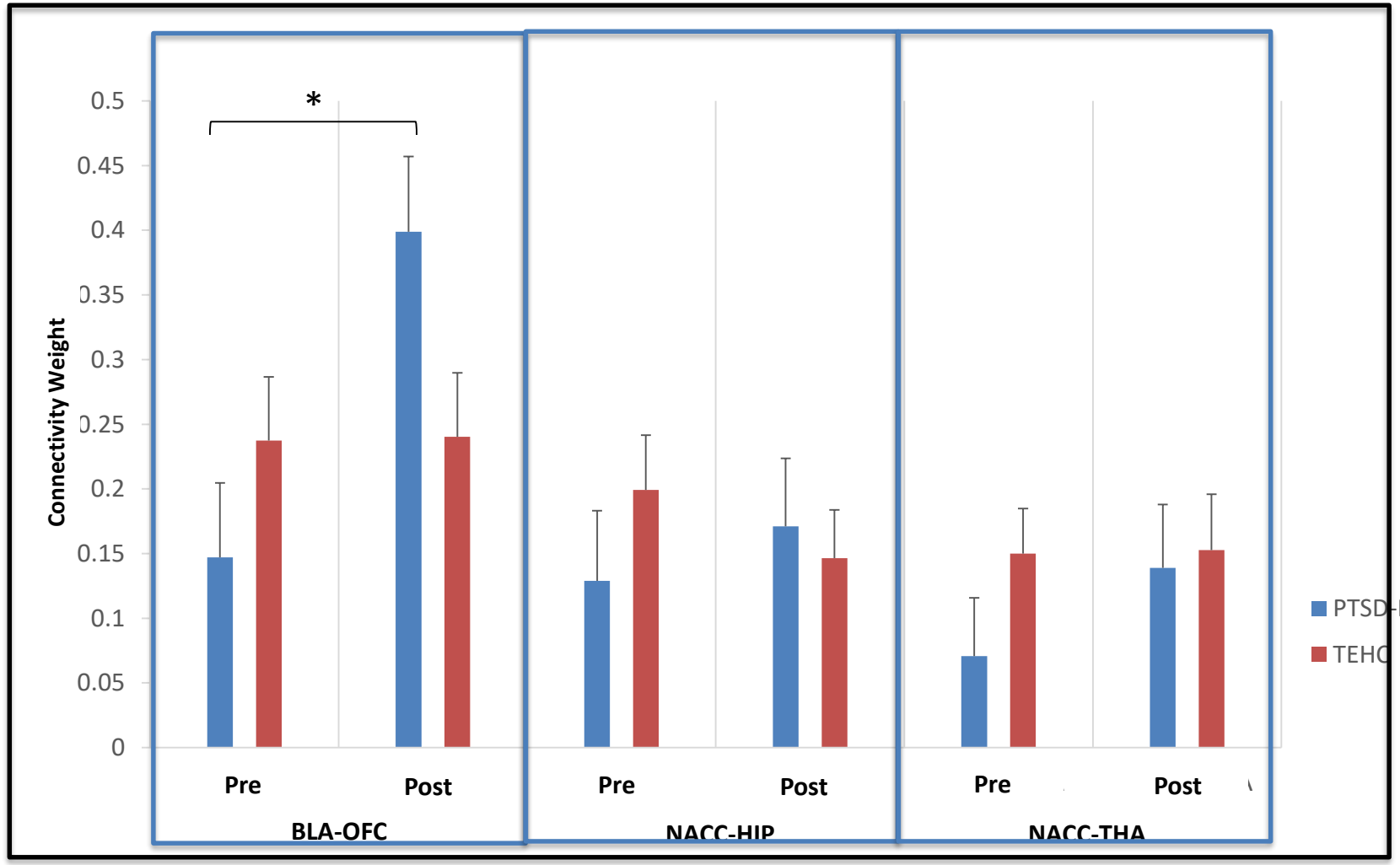
Can PE Address Reward Processing Deficits in PTSD-MDD?

- Prolonged Exposure treatment was designed to address fear processing dysfunction
- How effective is it in addressing both fear and reward processing dysfunction in patients with PTSD-MDD?

PE for Patients with PTSD-MDD



Part 3: Conclusions

- The definition of DSM diagnosis of PTSD is (too) heterogeneous, harming efforts to address treatment needs, and improve efficacy of treatments
- PTSD-MDD only partially overlap with PTSD alone: is it a unique diagnostic phenotype?
- Fear circuitry, but not reward circuitry, can be engaged with Prolonged Exposure (PE)
- Better targeted treatments are needed to address both fear and reward dysfunctions in PTSD
- Encouraging results from our IPT-PTSD (with John Markowitz); Equine Assisted Treatment (EAT-PTSD; with Prudence Fisher)
- Psychedelics (psilocybin; MDMA) and Ketamine studies have a promising start

Thanks

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