Stress X Gender: What We Know and Don’t Know about the Neurobiology of PTSD in Women

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Current Prevailing Ideas Regarding Gender-Based Risk and Prevalence of PTSD

• The lifetime prevalence of PTSD is ~8% in the general population (Kessler et al. 1995).


• Lore: Despite common rates of trauma, women have ~twice the incidence and prevalence of PTSD (Breslau et al. 1998) when similar trauma type is considered (i.e., assault).
340 female and 252 male OEF/OIF veterans within one year of deployment:

1. Men showed modest increases over women in exposure to combat, the aftermath of battle, and difficult living/working environments.

2. But no difference between sexes in risk for posttraumatic stress symptoms, mental health functioning, or depression when controlling for exposure.

Street et al. (under review)

2,348 female and male Veterans, selected randomly within gender from a national roster of all OEF/OIF Veterans. Response rate was 48.6%.

1. Women experienced greater MST (OR=8.34); men greater combat (OR=.61).

If men and women do have equal risk for PTSD, why study gender effects on the neurobiology of PTSD?

To better understand mechanisms involved in the development of PTSD and devise improved treatments.
Background:

Basic Circuitry Involved in Fear Conditioning
Fear-Conditioned Associations

Neutral Stimulus → Unconditioned Threat Stimulus

ASSOCIATIVE LTP

BL → CE

HPA Axis
Cardiovascular
Behavioral
Information
Processing

Neutral Stimulus
Unconditioned Threat Stimulus
Species Specific Defense Response (SSDR) Elicited by Fear-Conditioned Stimuli

Conditioned Threat Stimulus

HPA Axis Activation
Cardiovascular Responses
Behavioral Responses
Changes in Information Processing
Frontal Lobe: working memory, tonic inhibition

FRONTAL LOBE INHIBITION OF AMYGDALA-MEDIATED DEFENSE RESPONSES

Amygdala

BL \rightarrow CE
(-) (-) (-)
INHIBITION OF FEAR-CONDITIONING BY THE HIPPOCAMPUS: LATENT INHIBITION & INHIBITORY CONDITIONING

Hippocampus: context & probability

Amygdala

BL CE

(-) (-) (-)
Increased $\alpha_1/\alpha_2$
Increased DA
Increased 5HT$_2A$
A Arnsten et al, 2009

Goldstein et al, 1996
Increased $\alpha_1/\alpha_2$

Increased DA

Increased 5HT$_2A$

Arnsten A et al, 2009
Morrow BA et al, 1999
Rasmusson AM, 1994

Goldstein LG et al, 1996
Optimization/Deterioration of Executive Capacities as a Function of Arousal: Inverted “U”-Shaped Curve
Neurotransmitters & Neuromodulators

Mediators/Modifiers of the Stress Response and of PTSD Risk, Recovery, and Comorbidity
Hypothalamic Pituitary Adrenal (HPA) Axis

Stress

Hypothalamus

CRF

(+/-)

Pituitary

ACTH

(+)

DHEA/Cortisol

ALLO/NPY

Adrenals
Adrenal Steroid Synthetic Pathways

Cholesterol

P450scC

Pregnenolone → P450c17 → 17-OH-Pregnenolone

P450c17

17-OH-Pregnenolone → 3βHSD

P450c17

Dehydroepiandrosterone (DHEA)

P450c17

17-KSR

Androstenedione

P450c17

17-KSR

Testosterone

P450aro

Estradiol

5α/β-Reductase

3α-HSD

5α-Dihydrotestosterone → 3α-diol

11-Deoxycorticosterone → Corticosterone → 18-OH-Corticostrone → Aldosterone

3α-Hydroxy-Steroid Oxidoreductase

5α-Reductase

P450c11B/P450c11AS

P450c11AS

P450c11AS

5α/β-Reductase or 3α-Hydroxysteroid Dehydrogenase

3α, 5α/β-Tetrahydroprogesterone

5α-Dihydroprogesterone → Allopregnanolone/Pregnanolone

5α/β-Reductase

3α-HSD

5α-dihydrotestosterone → 3α-diol
Allopregnanolone (ALLO)

* Positively modulates GABA\(_A\) receptor function, increasing Cl\(^-\) ion flux 7-10 times

* Anxiolytic, anesthetic, anticonflict, neuroprotective

* Sedative, anticonvulsant

* Enhances mylenination and protects against ischemic brain injury

* Reduces pain at spinal and supra-spinal levels

* Provides negative feedback at the HPA axis (Barbaccio et al 2001)

* Reduces CRF and AVP in hypothalamus (Patchev et al 1994, 1996)

* Low in plasma and CSF in MDD (PTSD not examined) (Uzunova et al 1996)
Allopregnanolone in Male Rodents

• Decreased corticolimbic expression of the allopregnanolone in rodents increases:
  1) anxiety-like behaviors
  2) aggression
  3) contextual fear conditioning (Piribiri 2007)

• Administration of SSRIs, in turn, normalizes allopregnanolone levels and these aberrant behaviors (Pinna et al, 2005)
Allopregnanolone acts at: **Extrasynaptic GABA_A Receptors**

- Resistant to benzodiazepines
- Extra-sensitive to neurosteroids such as ALLO; also ETOH
- Composed of delta, alpha-4, alpha-6 subunits
- Reduce gain in the firing rate of stimulated neurons (Semyanov et al 2003, 2004; Mody et al 2004)
Extrasynaptic GABA$_A$ Receptors Reduce Gain in the Neuronal Firing Rate as Neuronal Excitation Increases

Semyanov et al. 2004
Allopregnanolone?
LUMBAR PUNCTURE

- Fasting except for water after midnight
- No medication or ETOH > 1 month except BCP’s
- Blood draw at -30 and -15 minutes before the LP
- Performed in the lateral decubitus position between 8:30 and 9:30 a.m. (Sprot needle to prevent post-LP headaches)
- Menstrual cycle phase monitored with LH surge kits and plasma progesterone measurements.
- Steroids measured with negative ionizing mass spectrometry after HPLC extraction of steroids and their respective deuterated internal standards (laboratory of Alessandro Guidotti, MD, University of Illinois).
LP During **Follicular Phase** when
Progesterone Levels are Low and Stable
(similar to male levels)
CSF Progesterone, 5α-DHP & Allopregnanolone

(fmol/ml)

<table>
<thead>
<tr>
<th></th>
<th>HEALTHY</th>
<th>PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROG</td>
<td>400</td>
<td>500</td>
</tr>
<tr>
<td>5-α-DHP</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>ALLO</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

n=10  n=9
PTSD allopregnanolone 39% of controls
\[ t = -2.77, \ p < 0.01 \]
The $5\alpha$-DHP/ALLO Ratio
PTSD vs. Healthy: $p = 0.006$ (MW test)
Allopregnanolone Synthesis Deficit in PTSD?

5α-Reductase → 5-α–DHP → Allopregnanolone

PTSD

Progesterone → 5-α–DHP → Allopregnanolone

Healthy

Progesterone → 5-α–DHP → Allopregnanolone

3α-HSD enzyme
Menstrual Cycle
Further Evidence of a Deficit in ALLO Production in PTSD

<table>
<thead>
<tr>
<th>Subjects</th>
<th>CSF Progesterone</th>
<th>CSF ALLO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early Follicular</td>
<td>Mid-Luteal</td>
</tr>
<tr>
<td></td>
<td>Day 2-6</td>
<td>Day 19-23</td>
</tr>
<tr>
<td>Healthy #1</td>
<td>175</td>
<td>420</td>
</tr>
<tr>
<td>Healthy #2</td>
<td>464</td>
<td>1077</td>
</tr>
<tr>
<td>PTSD #1</td>
<td>542</td>
<td>3058</td>
</tr>
</tbody>
</table>

*While progesterone increased as expected (or even more extremely) in the PTSD subject during the luteal phase, ALLO did not.*
Menstrual Cycle Phase Effects on Fear Conditioning

Pineles et al., 2008
Fear Conditioning Across the Menstrual Cycle

Table 1. Mean baseline startle as measured by heart rate response

<table>
<thead>
<tr>
<th></th>
<th>Follicular</th>
<th>Luteal</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma Control n=8</td>
<td>2.29 BPM (3.03)</td>
<td>5.08 BPM (3.71)</td>
<td>.82</td>
</tr>
<tr>
<td>PTSD n=8</td>
<td>2.27 BPM (1.44)</td>
<td>9.31 BPM (13.01)</td>
<td>.76</td>
</tr>
<tr>
<td>Cohen’s d</td>
<td>.01</td>
<td>.44</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Mean acquisition of fear conditioning as measured with C-EMGR

<table>
<thead>
<tr>
<th></th>
<th>Follicular</th>
<th>Luteal</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma Control n=8</td>
<td>-.05 μV (.22)</td>
<td>.01 μV (.40)</td>
<td>.19</td>
</tr>
<tr>
<td>PTSD n=8</td>
<td>-.05 μV (.17)</td>
<td>.67 μV (1.19)</td>
<td>.85</td>
</tr>
<tr>
<td>Cohen’s d</td>
<td>.00</td>
<td>.74</td>
<td></td>
</tr>
</tbody>
</table>

Pineles et al., 2008
Brain Inhibitory Tone

- Allopregnanolone
- DHEA
<table>
<thead>
<tr>
<th></th>
<th>ALLO</th>
<th>ALLO/DHEA</th>
<th>5α-DHP/ALLO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anger/Irritation</td>
<td>-0.43 (0.06)</td>
<td>-0.57 (0.01)&lt;sup&gt;t&lt;/sup&gt;</td>
<td>0.58 (0.01)&lt;sup&gt;t&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anxiety/Tension</td>
<td>-0.46 (0.04)</td>
<td>-0.50 (0.03)</td>
<td>0.64 (0.003)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Confusion</td>
<td>-0.31 (0.20)</td>
<td>-0.43 (0.07)</td>
<td>0.56 (0.01)&lt;sup&gt;t&lt;/sup&gt;</td>
</tr>
<tr>
<td>Depression/Dejection</td>
<td>-0.52 (0.02)</td>
<td>-0.70 (0.0008)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.67 (0.002)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-0.50 (0.03)</td>
<td>-0.63 (0.004)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.60 (0.007)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vigor</td>
<td>0.23 (0.34)</td>
<td>0.03 (0.90)</td>
<td>-0.42 (0.08)</td>
</tr>
<tr>
<td>Total POMS</td>
<td>-0.45 (0.05)</td>
<td>-0.52 (0.02)</td>
<td>0.66 (0.002)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
SPEARMAN CORRELATIONS WITH CFA-DEFINED PTSD SYMPTOM CLUSTERS (Simms et al, 2002)

<table>
<thead>
<tr>
<th></th>
<th>ALLO</th>
<th>ALLO/DHEA</th>
<th>5α-DHP/ALLO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-experiencing</td>
<td>-.72 (.03)</td>
<td>-.82 (.007)*</td>
<td>.39 (.30)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
COMORBID PTSD/MDD:

NEUROBIOLOGICALLY DISTINCT
PTSD and Depression Comorbidity
(Treatment Seeking Sample)

Courtesy of P. Resick
While rates of depression increase after trauma, new depression is almost always in the context of PTSD.

Rates of depression alone do not significantly increase after trauma.

PTSD/MDD may simply be more severe PTSD.
### After Trauma: Vanishing Cell for MDD Alone

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Current</th>
<th>MDD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resick, P.A. (1991-97)</strong>&lt;br&gt;R01 MH 46992, NIMH Female Assault Victims&lt;br&gt;3 Month Comorbidity&lt;br&gt;N = 69</td>
<td>NO 48%</td>
<td>YES 3%</td>
<td>51%</td>
</tr>
<tr>
<td>No PTSD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTSD</td>
<td>36%</td>
<td>13%</td>
<td>49%</td>
</tr>
<tr>
<td>Total</td>
<td>84%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td><strong>Resick, P.A. (1997-‘02)</strong>&lt;br&gt;R01 MH55542, NIMH Domestic Violence&lt;br&gt;1-6 mo post recent event&lt;br&gt;N = 140</td>
<td>Current</td>
<td>MDD</td>
<td>Total</td>
</tr>
<tr>
<td>No PTSD</td>
<td>NO 19%</td>
<td>YES 5%</td>
<td>24%</td>
</tr>
<tr>
<td>PTSD</td>
<td>26%</td>
<td>49%</td>
<td>75%</td>
</tr>
<tr>
<td>Total</td>
<td>45%</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td><strong>Keane et al., 1998</strong>&lt;br&gt;Comorbidity Male Vietnam Veterans&lt;br&gt;N = 1325</td>
<td>Current</td>
<td>MDD</td>
<td>Total</td>
</tr>
<tr>
<td>No PTSD</td>
<td>NO 38.4%</td>
<td>YES 3.1%</td>
<td>41.5%</td>
</tr>
<tr>
<td>PTSD</td>
<td>37.2%</td>
<td>21.3%</td>
<td>58.5%</td>
</tr>
<tr>
<td>Total</td>
<td>75.6%</td>
<td>4.3%</td>
<td></td>
</tr>
</tbody>
</table>
## ALLO IS LOWEST IN CO-MORBID PTSD/DEPRESSION?*

<table>
<thead>
<tr>
<th></th>
<th>PTSD (n=5)</th>
<th>PTSD/MDD (n=4)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLO (fmol/ml)</td>
<td>19.3±5.4</td>
<td>7.7±4.6</td>
<td>0.015</td>
</tr>
<tr>
<td>CAPS B re-experiencing</td>
<td>8.6±5.5</td>
<td>16.2±2.2</td>
<td>0.039</td>
</tr>
<tr>
<td>CAPS C avoidance</td>
<td>14.0±9.4</td>
<td>29.0±13.4</td>
<td>0.778</td>
</tr>
<tr>
<td>CAPS D hyperarousal</td>
<td>18.0±6.0</td>
<td>19.0±9.2</td>
<td>0.460</td>
</tr>
</tbody>
</table>

*Comorbid PTSD/MDD may be construed as more severe PTSD: Breslau et al. 2000
Higher PTSD & Depression Symptoms
Before & After CPT in Comorbid PTSD/MDD

<table>
<thead>
<tr>
<th></th>
<th>Pre-Treatment</th>
<th>Post-Treatment</th>
<th>9-Month FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD Symptom Scale (PSS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTSD</td>
<td>26.14 (7.66)</td>
<td>6.82 (4.71)</td>
<td>7.00 (7.51)</td>
</tr>
<tr>
<td>PTSD/MDD</td>
<td>33.93 (8.63)</td>
<td>12.19 (8.24)</td>
<td>13.83 (13.18)</td>
</tr>
<tr>
<td>Beck Depression Inventory (BDI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTSD</td>
<td>22.08 (10.09)</td>
<td>6.21 (5.70)</td>
<td>7.50 (7.60)</td>
</tr>
<tr>
<td>PTSD/MDD</td>
<td>28.29 (10.14)</td>
<td>9.57 (7.12)</td>
<td>12.64 (13.70)</td>
</tr>
</tbody>
</table>

PSS: $F(1, 92)=19.1, p = .000, \gamma^2=0.17$; BDI: $F(1, 92)=20.2, p = .000, \gamma^2=0.18$

Nishith et al 2005
Factors that Influence Expression of the Gene for the Enzyme that Synthesizes ALLO

Cortisol activates
Testosterone activates
OCT transcription factors binding to the NRE may reduce constitutive levels
Progesterone, estrogen, DHEA?

3-α-HSD Gene

NADPH

3α-HSD enzyme

NADP+

Progesterone

5-α–DHP

Allopregnanolone

Hou et al 1998, Mitev et al 2003
DECREASED CORTISOL OUTPUT IN MEN WITH PTSD/MDD

Young and Breslau 2004

Mason et al 1986
Maes et al 2000
Pitman and Orr 1990
Salivary Testosterone Response to SERE Stress (Morgan CA et al, 2000)

Salivary data of soldiers during Mean Baseline, time of capture (T1), time of interrogations (T2, T3) at release (T4) and Mean Recovery (MR)

--

Salivary Testosterone (ng/dl)

16
14
12
10
8
6
Male Rats: Heavy ETOH >50 Days & Detoxed x 2 Days

**ETOH Stimulates NADPH oxidase, thereby decreasing NADPH, decreasing ALLO & increasing superoxide radical formation**
Consequences of Low Allo in Women

*Provides negative feedback at the HPA axis (Barbaccio et al 2001)

*Reduces CRF and AVP in hypothalamus (Patchev et al 1994, 1996)
CORTISOL OUTPUT INCREASED IN WOMEN WITH PTSD/MDD

Urine Cortisol ug/8 hr.

Night AM PM

PTSD/MDD

PTSD alone

Young and Breslau 2004

Lipschitz et al 2003
Rasmusson et al 2001
Heim et al 2000
ACTH Response to CRF

N=6  TC
N=12  PTSD
N=11  NTC
Cortisol Response to ACTH_{1-24}
Cortisol Response to CRF

- N=11 NTC
- N=12 PTSD
- N=6 TC

Baseline, +15, +30, +45, +60, +90, +120
Cortisol

* Helps mobilize energy reserves
* Induces gluconeogenesis in the liver (to raise blood sugar)
* Helps contain inflammatory response
* Can be toxic to hippocampal neurons: Sapolsky, Krey, McEwen 1985
* Interferes with catecholamine re-uptake in the frontal lobe, so prolongs effects (Grundemann et al 1998).
* Induces expression of the corticotropin releasing factor (CRF) gene (Schulkin et al 1998)
* Impairs memory (Lupien 1998, Newcomer et al 1999)
  • Impairs frontal lobe-mediated “working memory” (capacity for mental manipulation) (Lupien 1999)
  • Promotes NPY synthesis/NPY-Y2 receptor transcription in fat
Adrenal Steroid Synthetic Pathways

Cholesterol

- P450scc

Pregnenolone

- P450c17

17-OH-Pregnenolone

- P450c17

Dehydroepiandrosterone (DHEA)

AllotetrahydroDOC

- 3α-Hydroxy-Steroid Oxidoreductase

- 5α-Reductase

11-Deoxycorticosterone

- P450c11B/P450c11AS

Corticosterone

- P450c17

18-OH-Corticosterone

- P450c11AS

Aldosterone

5α-Reductase

5α-Reductase or 3α-Hydroxysteroid Dehydrogenase

3α,5α/β-Tetrahydroprogesterone

5α/β-Dihydroprogesterone

- Allopregnanolone/Pregnanolone

- P450aro

5α/β-Reductase

11-Deoxycorticosterone

- 3β-Hydroxysteroid Dehydrogenase

- 5α/β-Reductase

Cortisone

- P450c11B

Cortisol

- P450c11B

Androstenedione

- 17KSR

Testosterone

- P450aro

Estradiol

- 5α-Reductase

- 3α-Hydroxysteroid Dehydrogenase

5α-Dihydrotestosterone

3α-Diol
Increased 5α-dihydrotestosterone

Aggression?

NPY (Zofia Zukowska)
Neuropeptide Y

- Anxiolytic, anticonflict
- Antikindling and anticonvulsant
- Conserves bioenergy
- Involved in regulation of oxidative metabolism
- Protects the hippocampus
- Supports Neurogenesis

Functions like a high pressure valve:
- Inhibits release of NE at baseline
- Once released under conditions of high neuronal firing (lactate threshold/metabolic crisis), potentiates post-synaptic effects of NE
Yohimbine Induced Greater Increases in Plasma MHPG in PTSD

NPY Appears to Confer Stress Resilience

Lower NPY release in PTSD
(Rasmusson et al. 2000)

Higher NPY in hardy soldiers and non-PTSD
Peak NPY During Intense Training Stress Predicted Less Distress & Dissociation, and Better Performance

NPY and Dissociation

NPY & Objective Performance

Morgan et al 2000, 2002
In PTSD, NPY correlated with weight:

\[ r = +0.61, \ p<0.01 \]

(Rasmusson et al 2000)
What happens to mice and (wo)men during stress? (Kuo et al., 2006, Nature Medicine; Zukowska Laboratory)

Iced cold water  Aggressor intruder

No stress  Stress  High fat, no stress  High fat + Stress
NPY: a missing link between stress and weight gain
(Kuo et al., 2006, Nature Medicine; Zukowska laboratory)

STRESS

High fat/sugar diet

NPY

Adrenal gland

Glucocorticoids

Tissue expansion

Y2R antagonist or deletion or RU-486

Mesenteric white adipose tissue

Sympathetic nerve

NPY

Sympathetic nerve terminal

NPY

Preadipocyte proliferation

Adipogenesis

Macrophage infiltration

Angiogenesis

Insulin resistance
Deployment

Readjustment??

Fernando Botero

Emily Sohn
Metabolic Syndrome and PTSD
(Heppner et al, 2009)

253 veterans admitted to Gulf War Screening or PTSD clinic

- 92% male; Age: 52 ± 9.0 yrs; 76% white, 19% black, 5% other
- Lifetime abuse/dependence: nicotine 39%; alcohol 69%
- Metabolic syndrome risk increased 1% for each 1 point increase in the CAPS
- Higher rate than National Health & Nutrition Examination Survey: 21-30%

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% with Metabolic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD (CAPS ≥ 65)</td>
<td>34%</td>
</tr>
<tr>
<td>MDD</td>
<td>29%</td>
</tr>
<tr>
<td>PTSD/MDD</td>
<td>46%</td>
</tr>
</tbody>
</table>
The greater FREQUENCY with which NPY is released, rather than the potential maximum amplitude of NPY reactions to stress, may critically distinguish trauma exposed persons with and without PTSD—an hypothesis yet to be tested.

Low allopregnanolone and high cortisol reactivity and high tissue levels of 5α-DHT would potentiate NPY facilitation of metabolic syndrome.
NPY in Women with PTSD?
DHEA

* Antiglucocorticoid (interferes with effects of cortisol)
* Positively modulates excitatory NMDA receptors
* Antagonizes inhibitory GABA_A receptors

* 7-hydroxylated metabolites of DHEA interfere with the nuclear uptake of activated glucocorticoid receptors in hippocampal neurons (Morfin et al 2000)—perhaps mediating protection
* Protects against excitatory amino acid- and oxidative stress-induced damage in hippocampus (Kimonides et al 1998)
  • Reverses decrements in LTP induced by cortisol
  • (Kaminska et al 2000)
• Regulates programmed cell death (Zhang et al 2002) and promotes neurogenesis (Karishma et al 2002)
DHEA Response to ACTH$^{1-24}$
Time x Diagnosis Effect: $F(4,59)=2.96, p<0.03$
DHEA/Cortisol Change after ACTH$_{1-24}$

Time x Diagnosis Effect: $F(2,60)=5.95$, $p<0.005$
The peak change in DHEA after maximum adrenal activation by ACTH* correlated negatively with total PTSD symptoms: \( r = -0.57, p < 0.04 \).

- Criterion C Avoidance: \( r = -0.70, p < 0.008 \)
- Criterion D Hyperarousal: \( r = -0.53, p < 0.07 \),
- Criterion B Reexperiencing: \( r = -0.19, p < 0.60 \)

*Laboratory study: ACTH given IV to women with and without PTSD.
DHEA & PTSD Symptoms

• The peak change in DHEA correlated negatively with all PTSD symptom except for “difficulty falling or staying asleep” which correlated positively:

  \[ r = 0.52, \ p < 0.08 \]

• Without inclusion of “sleep disturbance”, the peak change in DHEA correlated negatively, strongly, and significantly with PTSD hyperarousal symptoms:

  \[ r = -0.81, \ p < 0.0009. \]

*So even under conditions of sleep deprivation, maladaptive PTSD symptoms are lower in persons with higher DHEA release.*
DHEA/Cortisol Ratio After ACTH & Negative Mood Symptoms

• Negative correlation between the DHEA/cortisol ratio and negative mood symptoms measured by the Profile of Mood States (POMS) scale: $r = -0.63$, $p < 0.04$

*Laboratory study: ACTH given IV to women with and without PTSD.*
DHEA(S) and SERE School Interrogation Stress Exposure
DHEA(S)/Cortisol Ratio and Symptoms of Dissociation in Response to Interrogation Stress

Morgan et al., Arch Gen Psychiatry, 2004
DHEA(S)/Cortisol Ratio and Objective Military Performance
In women at SERE school, post-training health-related symptoms were significantly correlated with pre- 
(r=0.58, p<0.01) and post-training stress r=0.76,
p<0.0001 Clinician-Administered Dissociation 
Symptoms Scale scores, 
as well as the CADSS difference scores from baseline to 
stress (r=0.63, p<0.005)

The biology of these responses in women 
yet need to be studied at SERE.
PTSD & Depression in Women or ETOH Abuse in Men: Perfect Storm for the Development of **Metabolic Syndrome**

- Enhanced NADPH oxidase activity or other cause $\downarrow$ 3α-HSD
- Superoxide radicals; Low allopregnanolone
- Increased PTSD reexperiencing /Depression
- Increased tissue levels of 5α-dihydrotestosterone
- Increased, prolonged cortisol responses to stress
- Increased tissue NPY & NPY-Y2 receptor expression
- Increased fat, vascular smooth muscle & HTN, blood glucose
- Increased interleukin-6 $\downarrow$
- Increased C-reactive protein
  
  **Inflammation**

ETOH

**Oxidative damage to brain;**
Decreased myelination;
Decreased regional connectivity
Recommendations

1. Epidemiological studies of PTSD RISK X GENDER may require different methodology than neurobiological studies. For epidemiological studies, effects of sex should be studied within the larger sample model.
   
a) Assessment of PTSD RISK X GENDER may require over-sampling of women (e.g., when considering risk associated with combat) or over-sampling of men (e.g., when considering risk associated with MST).
   
b) The quality and gender-prevalence of the typical trauma categories must be considered. For example, domestic assault, which is more prevalent in women, usually occurs over time in repeated episodes within the “trappings” of a relationship and confers a high risk for PTSD. Non-intimate assault occurs more frequently in men, is more likely to occur as a discrete, out-of-usual context event, and confers a lower PTSD risk.

2. Neurobiological studies of mechanism may best be conducted using parallel designs in men and women separately because of the impact of sex-steroids on the factors studied.
The neurobiology of stress and PTSD is complex. Survival depends on redundant protective systems.

Thus, biological risk/resilience factors may vary among individuals and by sex, yet contribute to the same downstream negative/positive outcomes or phenotypes.

There are many biological checks and balances, which may interact synergistically or cancel one another out.

Therefore:
Recommendations

a) Biological studies should focus on *patterns* of risk and resistance factors, rather than single components.

b) Stress *responses* need to be studied in women (as in men), in addition to the usual baseline studies. Military settings are in many ways ideal places to conduct such studies. The pairing of access and experts has been a barrier.

c) Comorbid PTSD/depression (more severe PTSD?) appears to have a distinct *neurobiological signature* and is related to worse psychiatric *and* comorbid medical outcomes. This is an opportunity; beware of just covarying for depression.

d) There is much to be learned about PTSD risk and resistance from studies conducted in women across the menstrual cycle and in other reproductive states such as menopause. These studies are not difficult, but funding levels and timeframes may need to be adjusted. Recruitment networks for female veterans?
Recommendations cont.

a) Sex-specific reproductive system steroids are stress reactants and stress modulators in both sexes. Possibly, some play more prominent roles in modulating stress in one sex or another (e.g. testosterone/NPY; progesterone/ALLO)

b) Genetic studies should look at genes in context of mechanistic systems (e.g., high output NPY gene polymorphism could be effectively countered by a particular NPY-Y2 receptor gene with regard to risk for metabolic syndrome. Such could account for the contradictory genetic studies that abound.

b) Epigenetically-mediated changes in gene expression can mimic deleterious gene polymorphisms, so could be used in concert with genetic studies to better understand the pathophysiology of the PTSD phenotype. Genes in both the NPY and ALLO synthetic pathways are epigenetically mediated.

a) Biomarker studies should consider publishing specificity/sensitivity analyses—as prediction of phenotype or possible treatments is the goal.

b) Towards gender-based, individualized medicine . . .
Neuroactive Steroid Synthetic Pathways

Cholesterol

- P450sc
- Pregnenolone
- P450c17
- 17-OH-Pregnenolone
- P450c17
- DHEA

Progesterone

- P450c21
- Progesterone
- 17-OH-Progesterone
- P450c17
- Androstenedione

11-Deoxycorticosterone

- P450c11B/P450c11AS
- Corticosterone
- 18-OH-Corticosterone
- P450c11AS
- DHEA
- P450c17
- 17KSR
- Testosterone

5α-Reductase

3α-Hydroxy-Steroid Oxidoreductase

5α-Reductase

SSRIs

3α-Hydroxysteroid Dehydrogenase

Aldosterone

Cortisol

Estradiol
SSRI-Induced Increases in ALLO Correlate with Improvements in Depression Symptoms

Uzunova et al 2005
Of potential interest . . . ganaxolone

Synthetic allopregnanolone

Prevents enhancement of contextual fear due to ALLO deficits in male mice

*Phase II multi-site trial sponsored by DOD VA PTSD/TBI Consortium
Thank you.