Presentation 3- Julia Golier

Neuroendocrine Functioning in Gulf War veterans: relationship to chronic health symptoms

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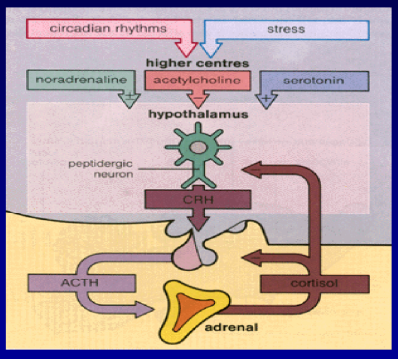
HPA Axis



Physiological consequences of the stress response

Increased cardiovascular tone
Immune activation
Energy Mobilization

Increased cerebral blood flow and glucose utilization
Loss of appetite
Enhanced memory consolidation

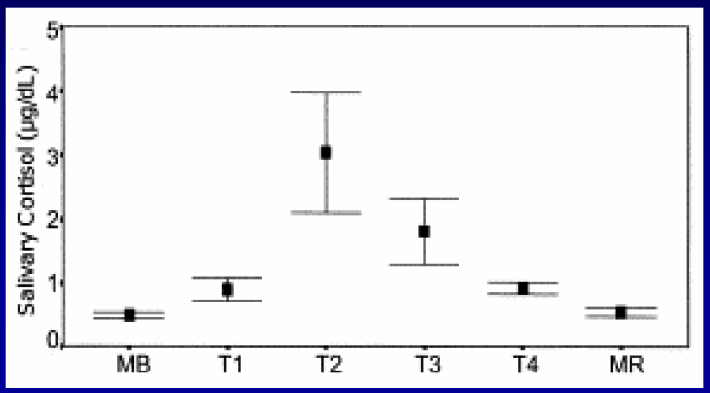
Loss of sexual behaviors

< 1 minute | < 10 minutes | < 1 hour

Adapted from Sapolsky et al., 2000

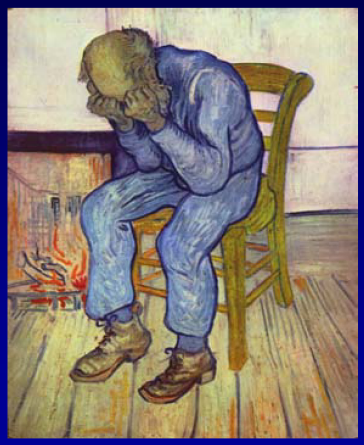
Acute Stress Response in American Soldiers

Salivary cortisol levels before, during and after capture and interrogation in military survival training



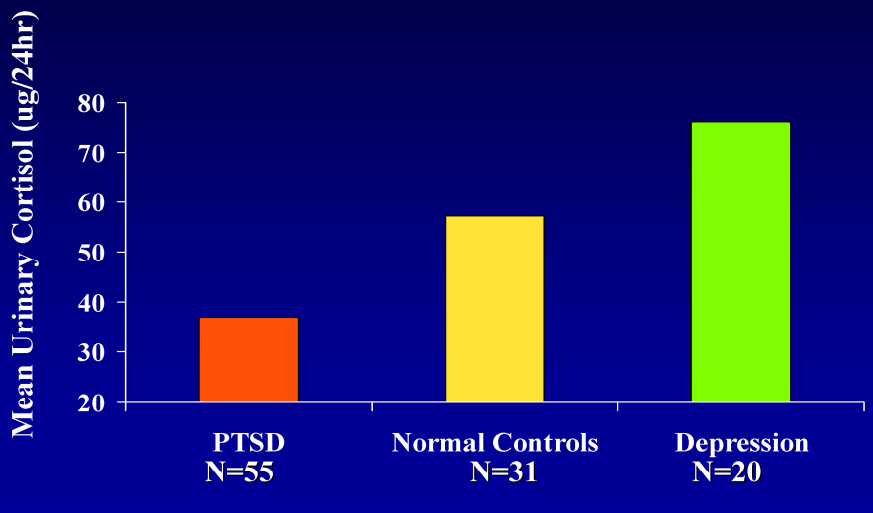
Morgan et al., 2000

Major Depression as a model of chronic stress



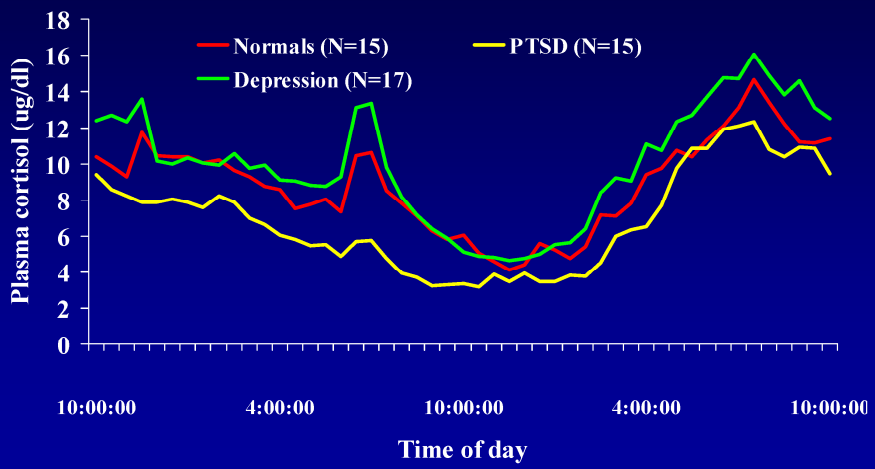
- Increased HPA axis activation and glucocorticoid receptor resistance
  - Hypercortisolism
  - Non-suppression of the HPA axis by Dexamethasone
  - Increased CRF
- Also
  - Reduced hippocampal volume
  - Memory impairment
  - Insulin resistance
  - Increased pro-inflammatory cytokines

Cortisol levels are lower in chronic PTSD



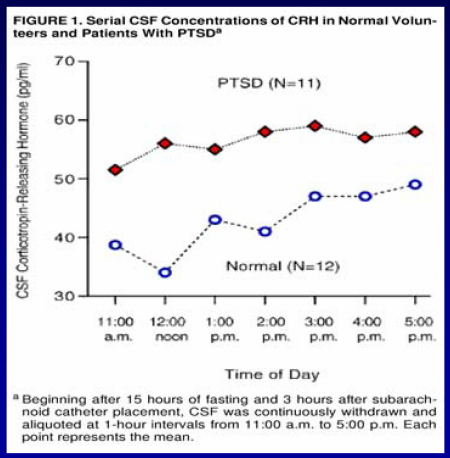
Yehuda et al., 2000

Circadian Rhythm of Cortisol

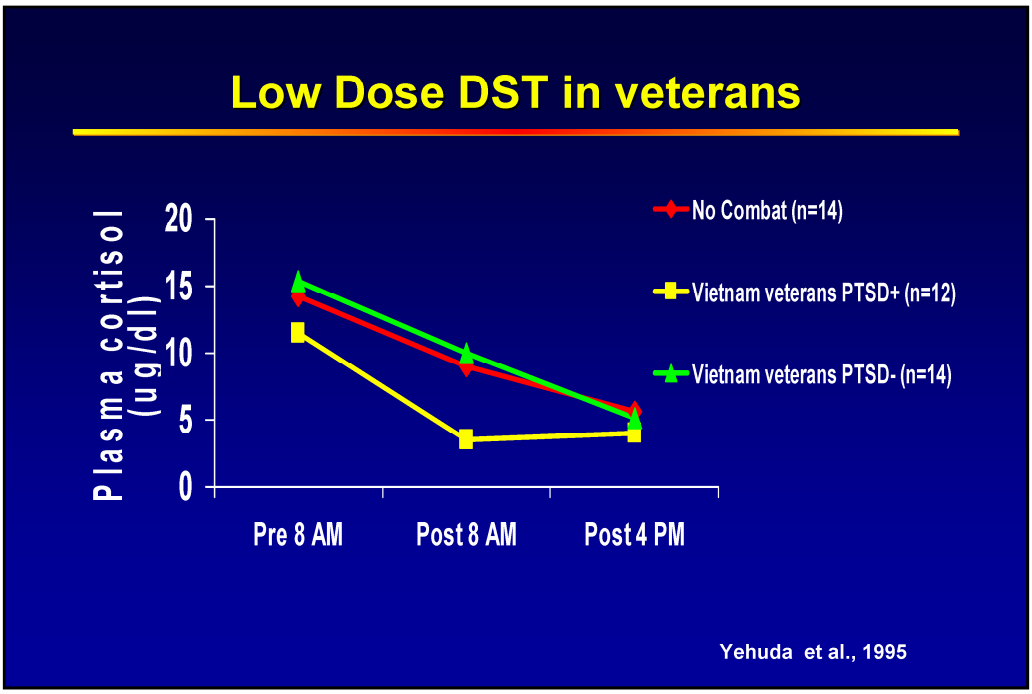


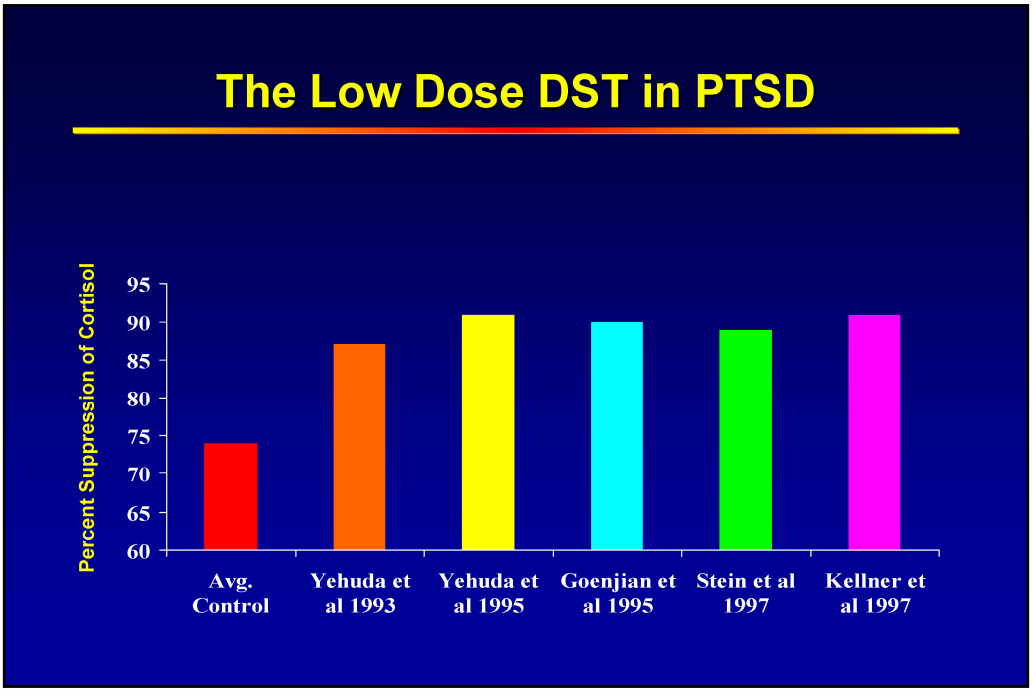
Yehuda et al., 1996

CRF in veterans with chronic PTSD

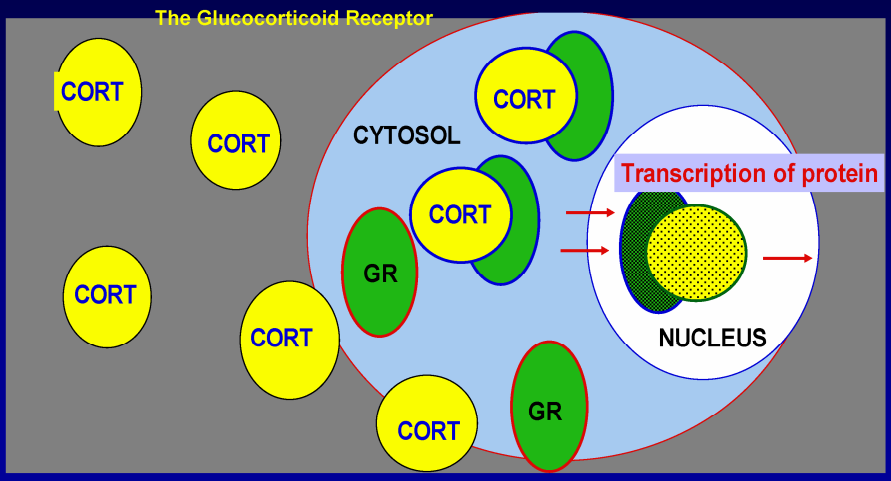


Baker et al., 1999

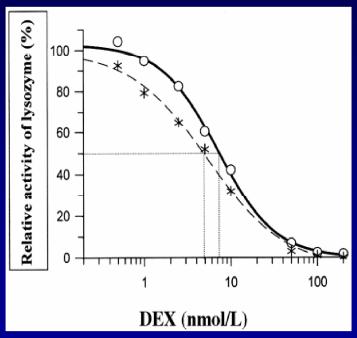

Low Dose DST in veterans
Plasma cortisol (ug/dl)
20
15
10
5
0
Pre 8 AM
Post 8 AM
Post 4 PM
No Combat (n=14)
Vietnam veterans PTSD+ (n=12)
Vietnam veterans PTSD- (n=14)
Yehuda et al., 1995


The Low Dose DST in PTSD
Percent Suppression of Cortisol
95
90
85
80
75
70
65
60
Avg. Control
Yehuda et al 1993
Yehuda et al 1995
Goenjian et al 1995
Stein et al 1997
Kellner et al 1997

Why is Negative Feedback Inhibition Stronger in PTSD?



Increased glucocorticoid sensitivity in PTSD



Lysozyme Inhibition Test an *in vitro* measure of glucocorticoid receptor sensitivity ($IC_{50\text{-}DEX}$)

Subjects with PTSD had significantly lower mean concentration (nmol/L)) of dexamethasone at which 50% of lysozyme activity is inhibited

$IC_{50\text{-}DEX}$
PTSD (n=26) 4.9 ± 0.5
Controls (n=18) 7.2 ± 0.6
F(1,41)=7.3, p=0.009, controlling for BMI

Yehuda, Golier, Yang et al., 2004

Rationale for studying HPA axis in Gulf War veterans

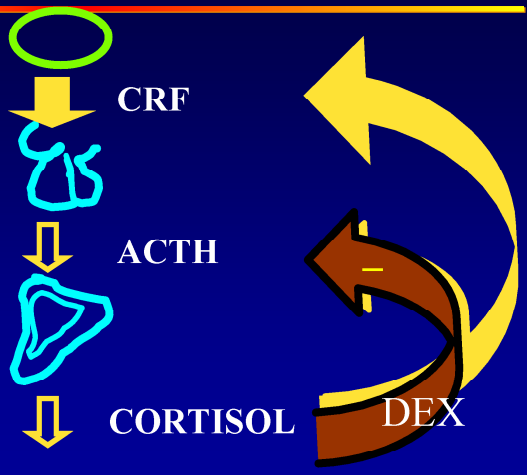
Study of HPA axis does not imply that etiology of GWI is psychological stress

	Gulf War Veterans			Non Deployed Veterans
	PTSD + MDD (n=16)	PTSD (n=12)	No Psych (n=14)	No Psych (n=12)
Age (yrs)	39	42	40	45
Educ (yrs)	13	13	13	14
Wt (lb)	195	192	180	186
CES***	23	17	14	2
CAPS***	68	65	13	6
Fatigue*	3	2	1	1
Mood-Cog***	16	12	2	5
Musculo.***	9	9	2	2
Total***	109	84	16	18

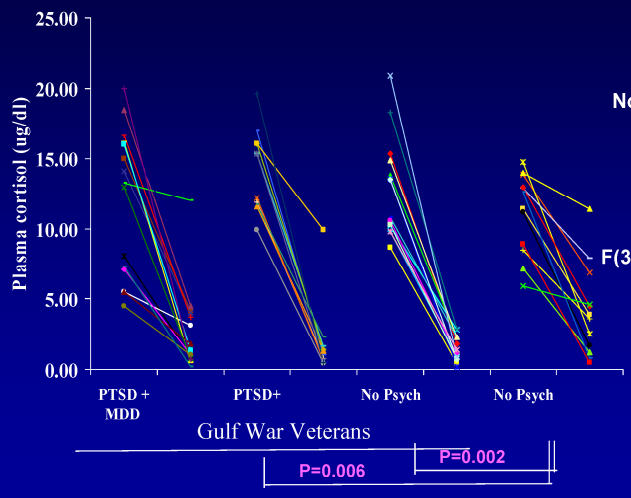
Dexamethasone Suppression Test (DST)

Tests the strength of cortisol negative feedback inhibition of the HPA axis

At low doses DEX occupies GR in pituitary and not the CNS



Cortisol response to DEX



No group differences in basal 8 am cortisol levels

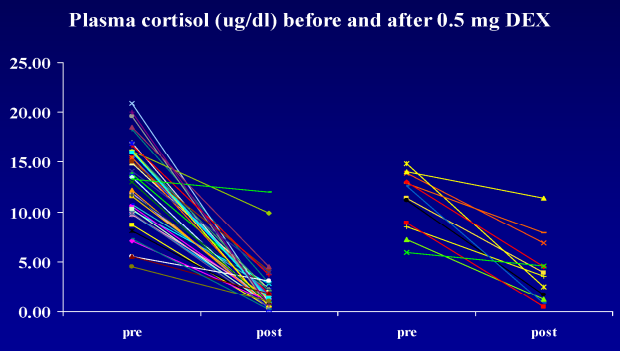
or dexamethasone level

Group by DEX interaction

F(3,48)=6.41, p=0.001 controlling for wt and smoking status

Golier et al., 2006

The cortisol response to DEX



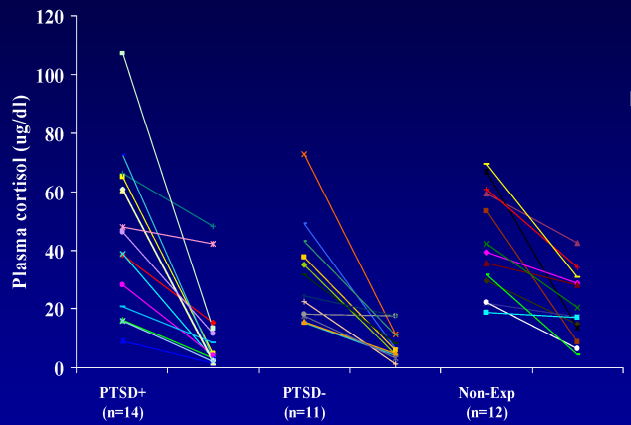
Gulf War Veterans (n=42) Non Deployed Veterans (n=12)

GWV had significantly greater percent cortisol suppression than non-deployed veterans controlling for weight, smoking, PTSD and MDD.

Adjusted percent suppression 91% vs. 47% ($F(1,48)=9.2$, $p=0.004$

Golier et al., 2006

The ACTH response to DEX



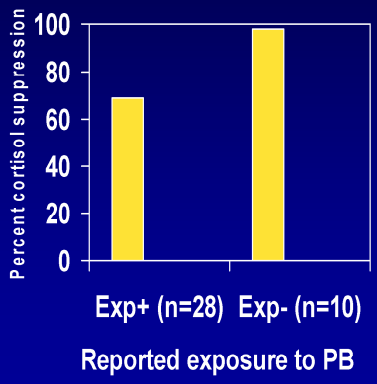
No group differences in basal 8 am ACTH levels

or dexamethasone level

Significantly lower post-DEX ACTH levels in GWV with ($p=0.03$) and without ($p=0.03$) PTSD as compared to non-exposed subjects.

Golier et al., 2006

DST findings associated with reported exposure to anti-nerve gas pills



Significant association ($p<0.05$) of reported anti-nerve gas pill exposure in GWV with cortisol response to DEX

In the absence of an association with other environmental exposures or with combat exposure severity

Golier et al., 2006

Partial correlations between percent cortisol suppression and symptoms in GWV

Health symptoms as measured with the ESCL

Mood-cognitive symptoms: r=0.15, df=32, p=0.40

Musculoskeletal symptoms: r= 0.44, df=32, p=0.009

Fatigue: r=0.13, df=32, p=0.45

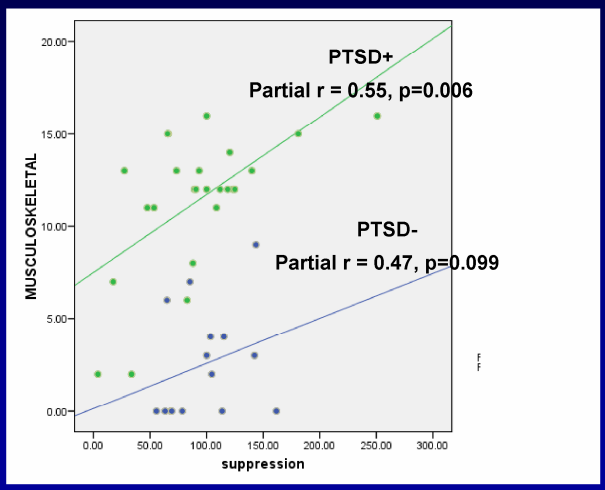
Controlling for weight, nicotine use and group

PTSD symptoms (CAPS)

PTSD total: r=-0.13, df=32, p=0.45

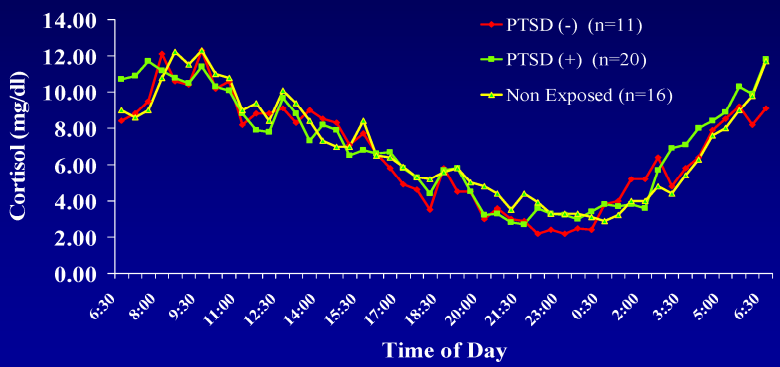
Golier et al., 2006

Relationship of musculoskeletal symptoms to percent cortisol suppression in GWV with and without PTSD



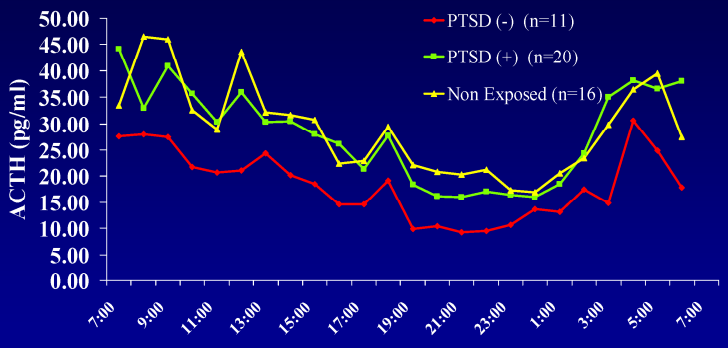
Golier et al., 2006

24-hour plasma cortisol levels



Golier et al., 2007, in press

24-hour plasma ACTH levels



	PTSD+	PTSD-	Non Exposed
Cortisol AUC ug/dl-hr	154.3 (53.3)1	54.2 (34.4)	158.3 (27.4)
ACTH AUC pg/ml-hr**	619.3 (237.6)	419.1 (197.6)	637.6 220.6)
Cortisol:ACTH ratio**	0.28 (0.12)	0.45 (0.26)0	0.30 (0.18)

Golier et al., 2007 in press

ACTH AUC: relationship to self-reported environmental exposures in GWV

	Not Exposed	Exposed Not Ill	Exposed Ill
Pesticides (p=0.004)	512 (192) (n=14)	671 (248) (n=7)	230 (20) (n=2)
Anti-nerve gas pills (p<0.05)	463 (133) (n=6)	638 (242) (n=12)	378 (196) (n=5)
Smoke from tent heater (p<0.05)	592 (218) (n=13)	501 (251) (n=8)	309 (93) (n=2)

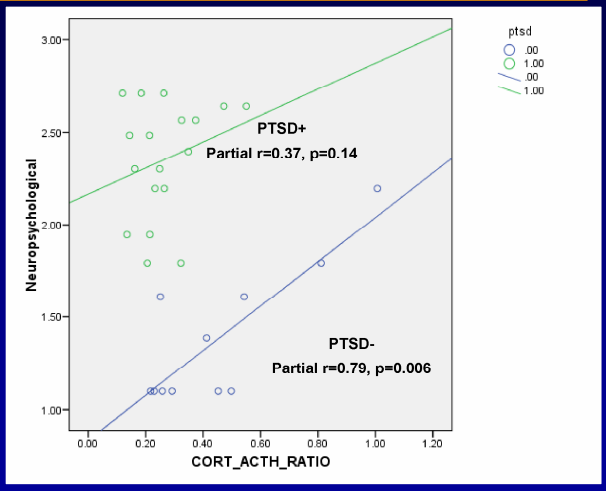
Adjusted means, controlling for BMI and PTSD

No difference by remaining exposures: smoking from oil wells or human waste, vehicle exhaust, debris from SCUD, ammunition, contaminated shower water or combat exposure

Golier et al., 2007, in press

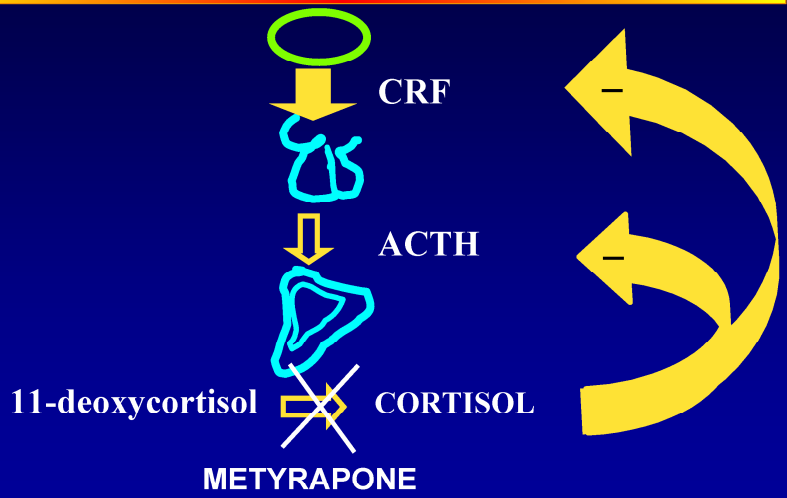
Cortisol:ACTH ratio associated with neuropsychological symptoms

- Neuropsychological sx (r=0.64, p<0.001) and psychological sx (r=0.61, p=0.001) were positively associated with cortisol:ACTH ratio controlling for BMI and PTSD
- Hyperarousal symptoms of PTSD were significantly inversely associated with the cortisol:ACTH ratio controlling for BMI (r= -0.45, p=0.017)

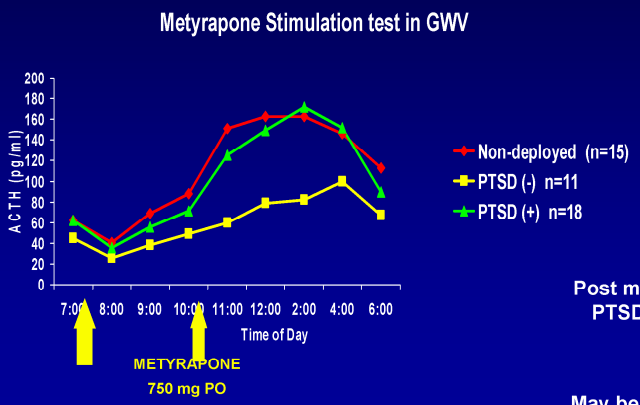


Golier et al., 2007, in press

Metyrapone Stimulation Test



Suprapituitary activation in GWV



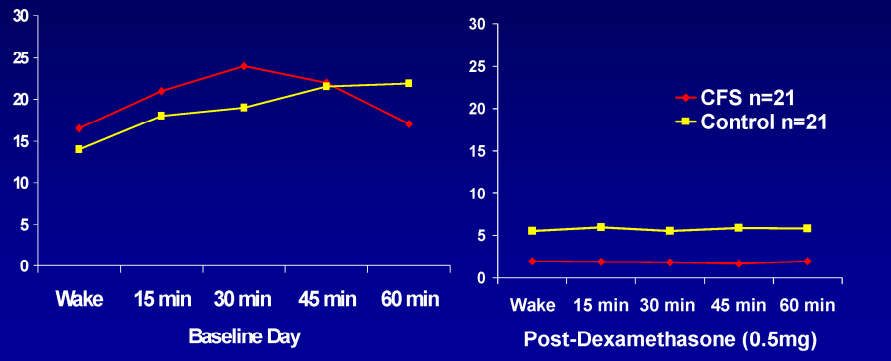
Post metyrapone ACTH lower in PTSD- than PTSD+ and non-exposed ($p<0.05$)

May be reduced CRF stimulation in GWV

Summary of Findings

- Neuroendocrine profile in Gulf War veterans without psychiatric illness:
  - Enhanced negative feedback inhibition
  - Low basal and metyrapone stimulated ACTH levels
  - Elevated cortisol to ACTH ratio
- Profile associated with some aspects of Gulf War deployment but not with combat exposure
- HPA axis alterations are associated with chronic health symptoms and are distinct from those associated with PTSD in GWV

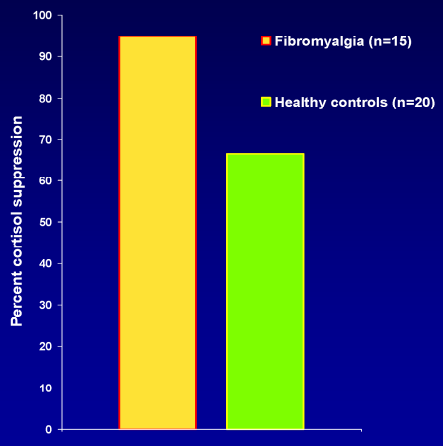
Salivary DST in Chronic Fatigue Patients



Adapted from Gaab et al., 2002

Low Dose DST in women with fibromyalgia

- No significant group differences in basal cortisol, ACTH
- FMS associated with enhanced cortisol but not ACTH suppression to DEX
- Suppression related to pain, fatigue, total physical symptoms
- Suggests enhanced suppression at the adrenal level.



Wingenfeld et al., 2007

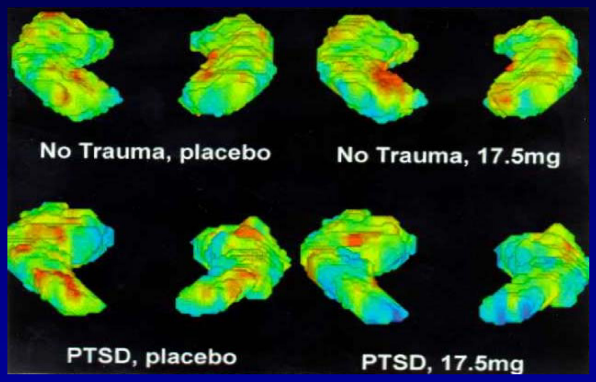
Gulf War veterans share a neuroendocrine characteristic with other chronic multisymptom illnesses and PTSD

-but the overall neuroendocrine profile is unique

Current Ongoing Studies

- Study of effect of chronic multisymptom illness, PTSD and their co-occurrence in GWV on
  - CRF challenge test
  - ACTH challenge test

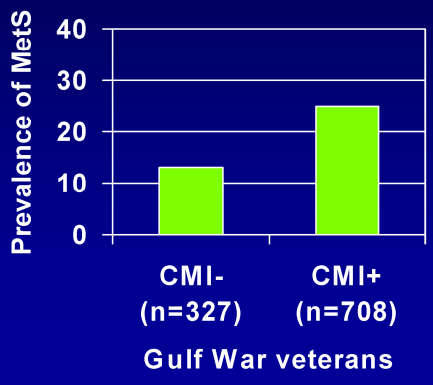
^{18}FDG PET Imaging: Response of the Hippocampus to Hydrocortisone



- ^{18}FDG is taken up by the glucose transporter systems allowing for PET imaging.
- Cortisol normally causes a reduction in glucose transporter systems.
- If receptors more sensitive, same amount of cortisol would result in a greater reduction of transporter systems as labelled by FDG.

What are the clinical and treatment implications of these neuroendocrine findings?

Metabolic Syndrome in GWV with CMI

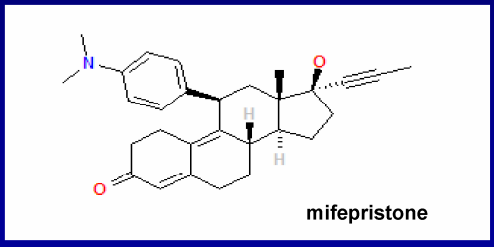


Blanchard et al., 2006

- Increased glucocorticoid activity has been associated with insulin resistance and the development of the metabolic syndrome
- Enhanced DST observed in
  - Hypertension
  - Genetic polymorphisms associated with adverse metabolic outcomes
  - Diabetic men

Treatment Implications

Double-blind placebo-controlled crossover trial of mifepristone in GWV with chronic multisymptom illness



mifepristone

Mifepristone

- Mifepristone (RU486)
  - Selective type II glucocorticoid receptor antagonist
  - Neuroendocrine actions
    - GR blockade diminishes negative feedback inhibition
    - Dose-dependent increase in ACTH and cortisol
    - Net effect balance between glucocorticoid receptor blockade and cortisol levels

Aims

- Determine efficacy of mifepristone in improving physical health and cognitive functioning in GWV with CMI
- Determine whether baseline HPA axis activity (glucocorticoid sensitivity (DST, lysozyme $IC_{50\text{-}DEX}$), 24-hr urinary cortisol, plasma cortisol or ACTH) or change in HPA axis activity predict clinical response