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

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SUPPORT

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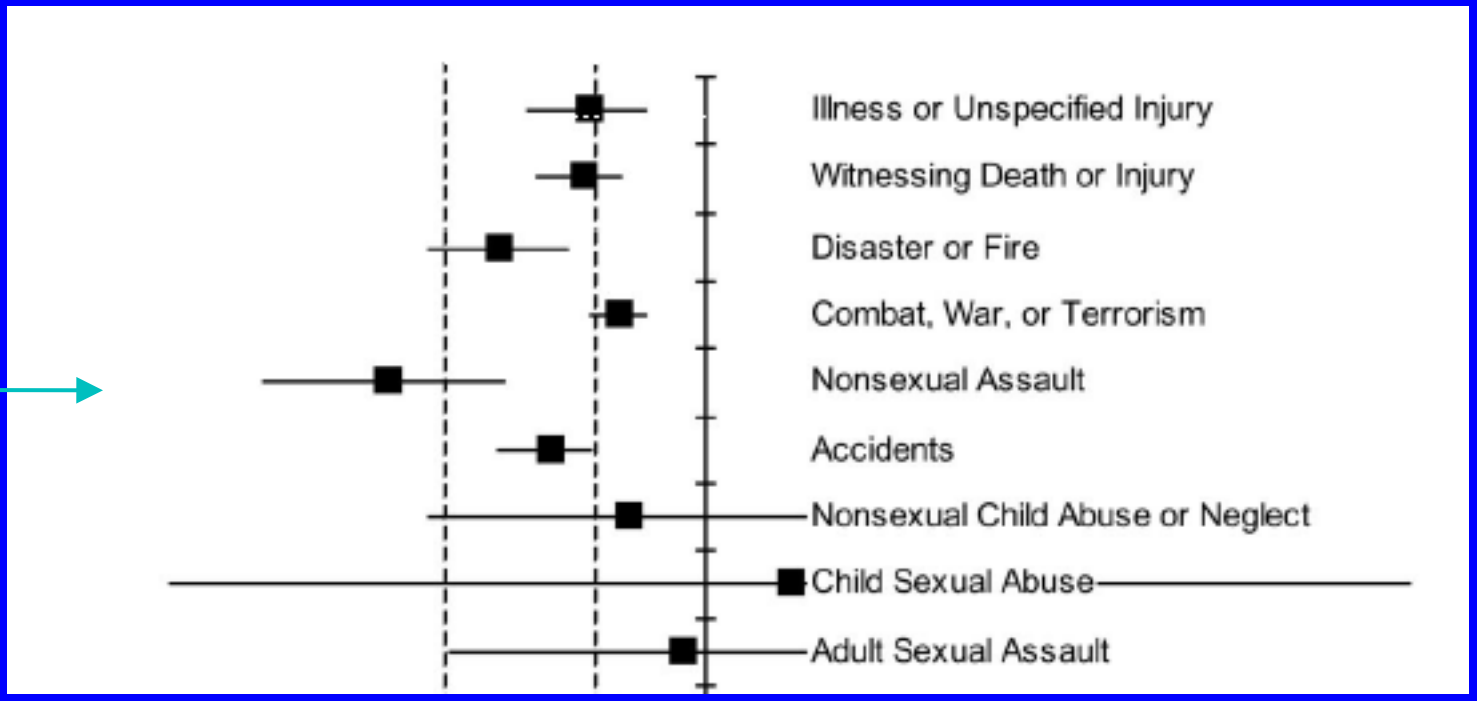
Current Prevailing Ideas Regarding Gender-Based Risk and Prevalence of PTSD

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

- It affects >15% of rape, combat, and compound community trauma victims (Kulka 1990, Kessler et al 1995, Breslau et al 1998, Lipschitz et al 2000, Thomas et al 2010; OEF/OIF cohort).

- 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).

Meta-Analysis: Gender Differences in Risk for PTSD following Potentially Traumatic Events



Tolin, D. F., & Foa, E. B. (2006). Sex differences in trauma and posttraumatic stress disorder: A quantitative review of 25 years of research. Psychological Bulletin, 132, 959-992

Changing Course?

Vogt et al. http://dx.doi.org/10.1027/a0023452.supp

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)

2.Association between combat stress and PTSD: 1.04 for men *and* women. Between harassment stress and PTSD: 1.07 for men; 1.04 for women.

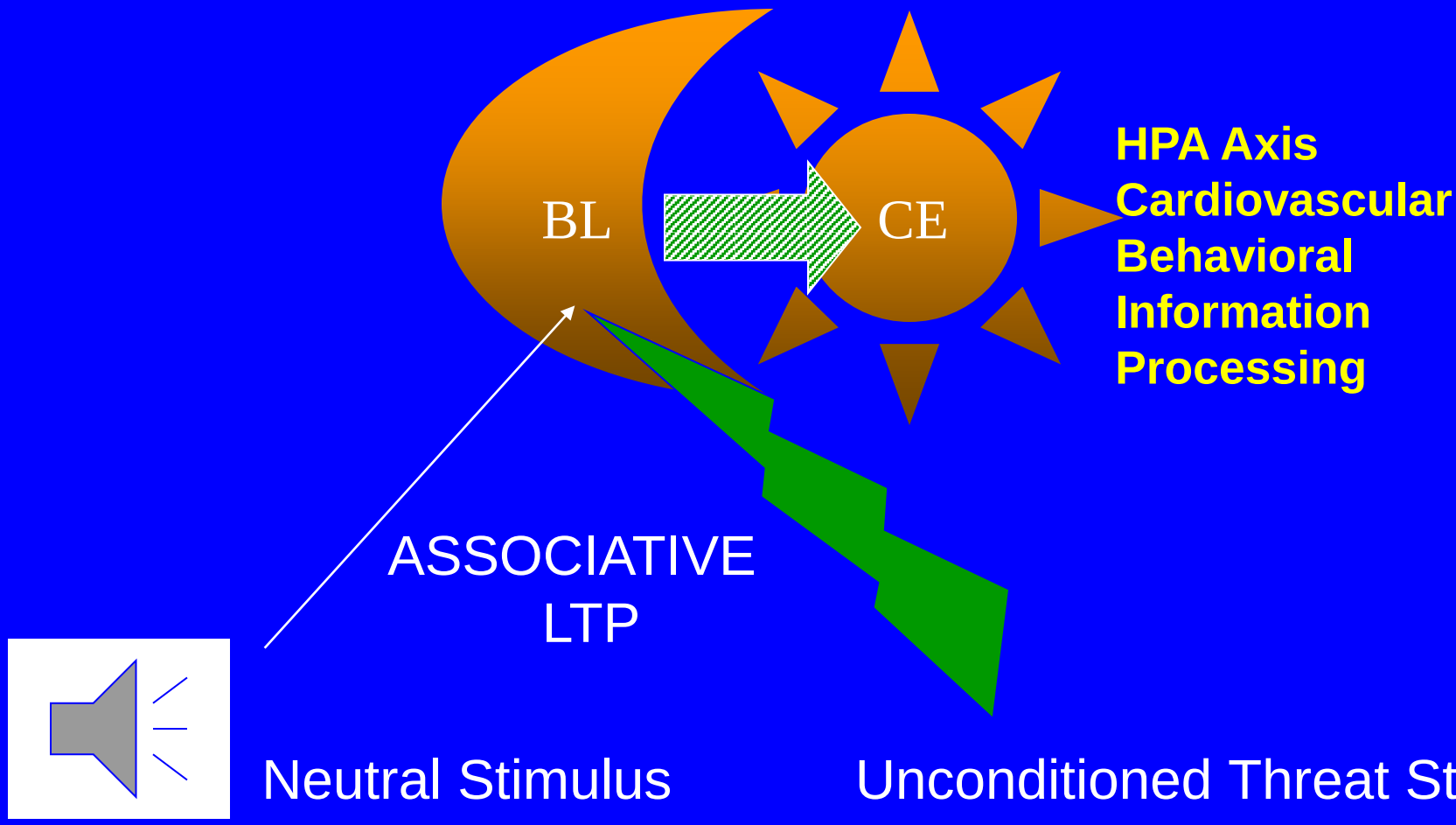
If men and women do have equal risk for PTSD, why study gender effects on the neurobiology of PTSD?

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

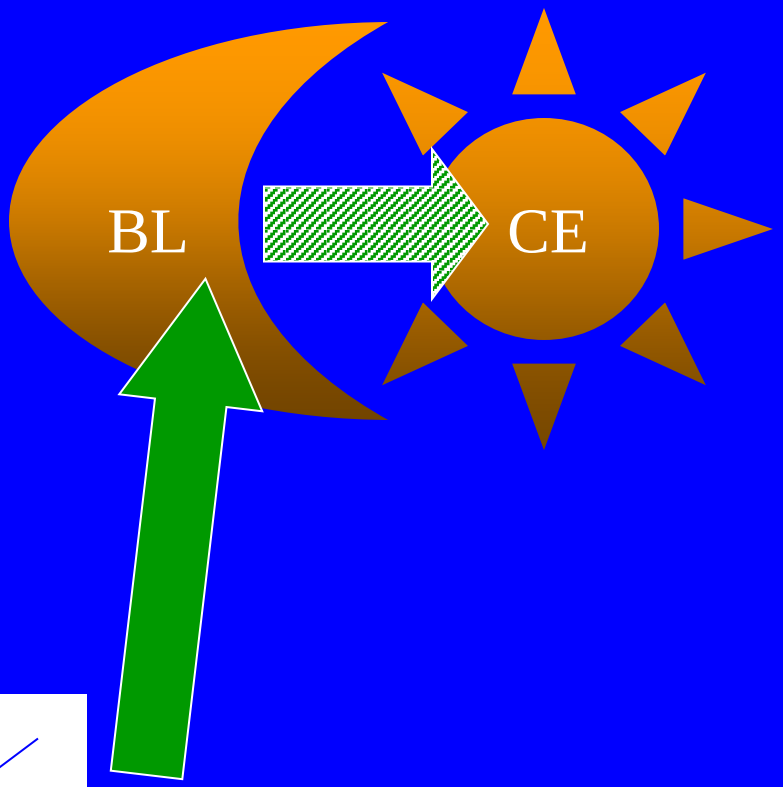
Background:

Basic Circuitry Involved in Fear Conditioning

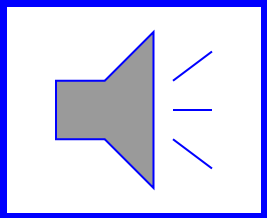
Fear-Conditioned Associations



Species Specific Defense Response (SSDR) Elicited by Fear-Conditioned Stimuli

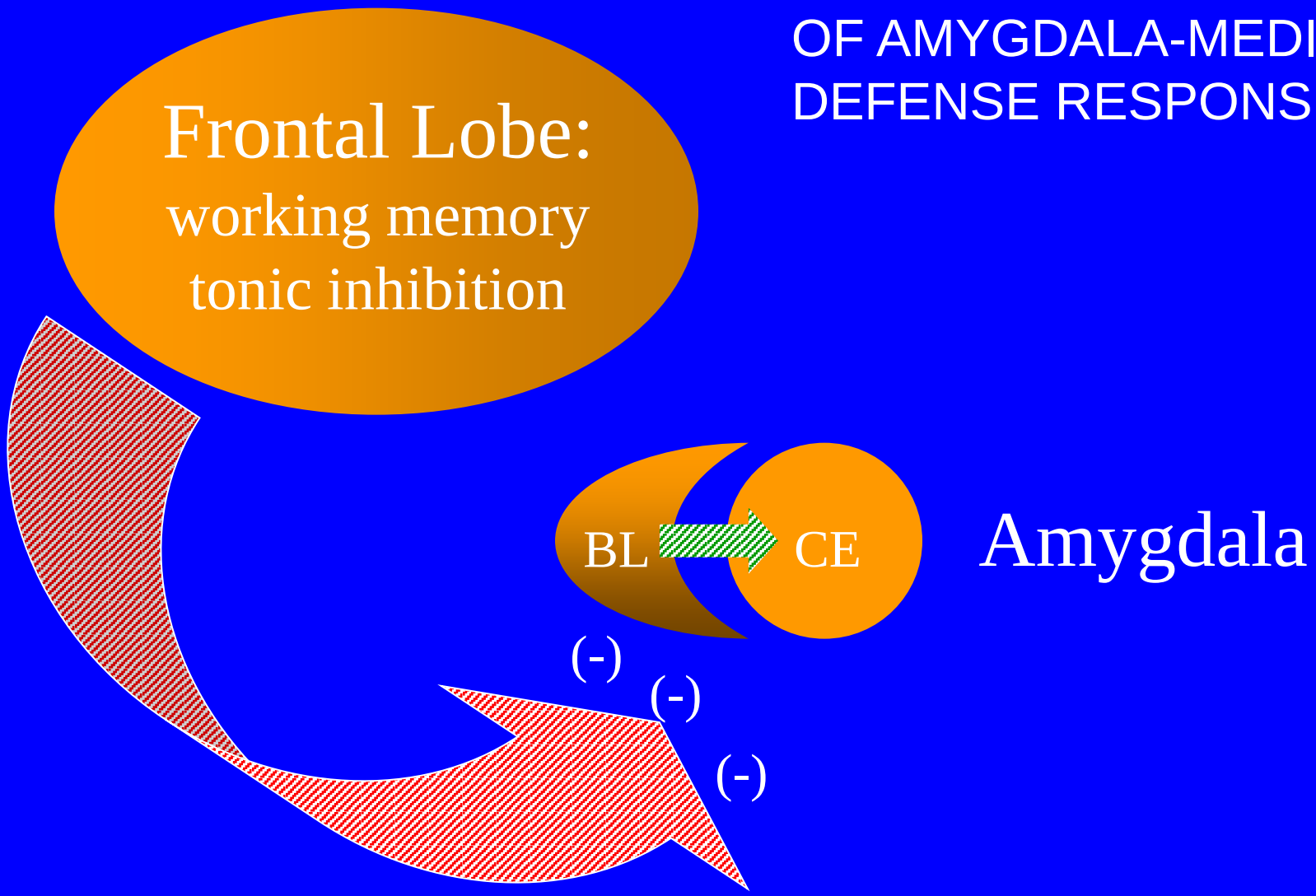


HPA Axis Activation
Cardiovascular Responses
Behavioral Responses
Changes in Information Processing

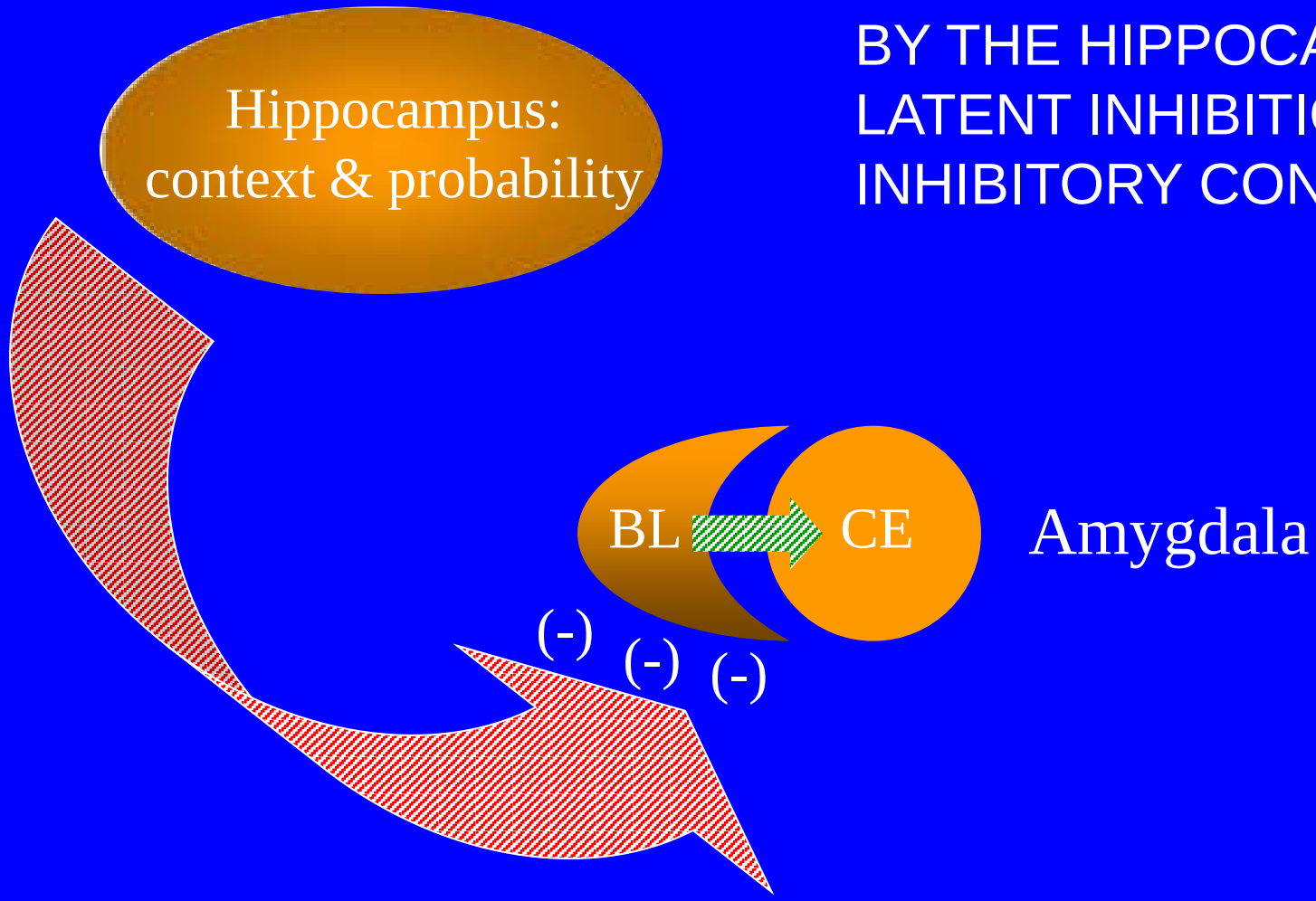


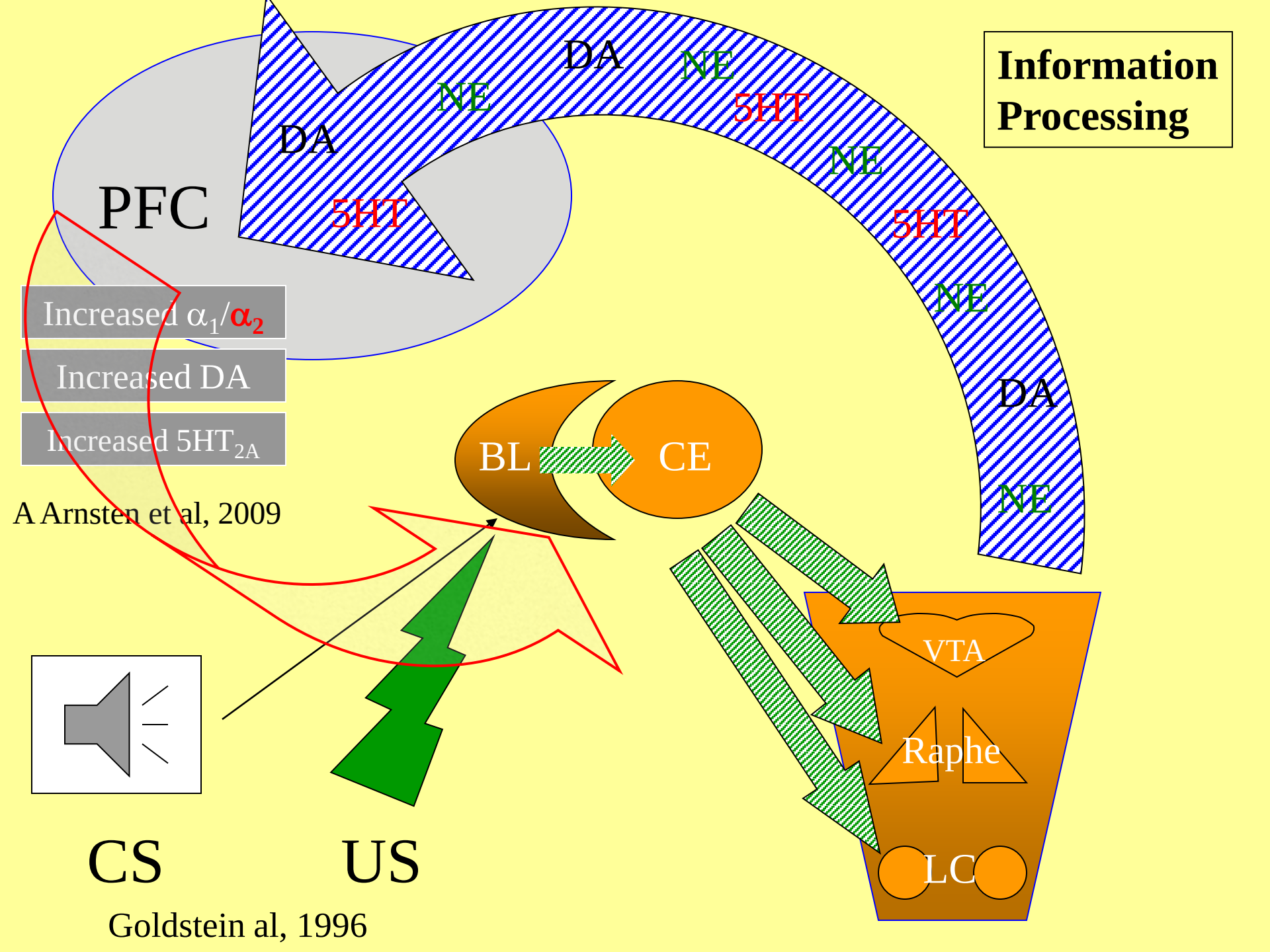
Conditioned Threat Stimulus

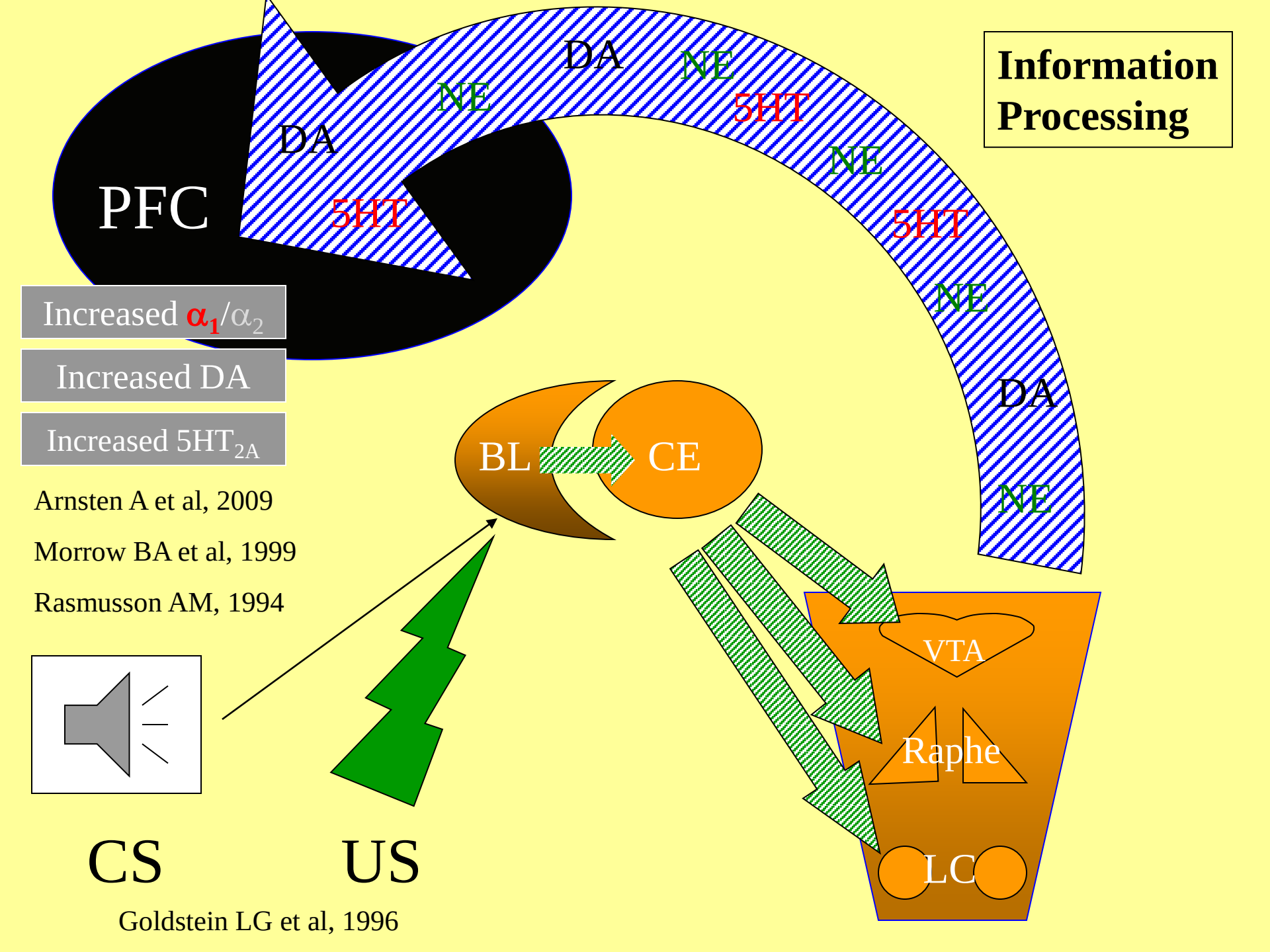
FRONTAL LOBE INHIBITION OF AMYGDALA-MEDIATED DEFENSE RESPONSES



INHIBITION OF FEAR-CONDITIONING BY THE HIPPOCAMPUS: LATENT INHIBITION & INHIBITORY CONDITIONING




Information Processing
PFC
DA
NE
5HT
DA
NE
5HT
NE
DA
NE
Increased α_1/α_2
Increased DA
Increased $5HT_{2A}$
A Arnsten et al, 2009
BL
CE
VTA
Raphe
LC
CS
US
Goldstein al, 1996



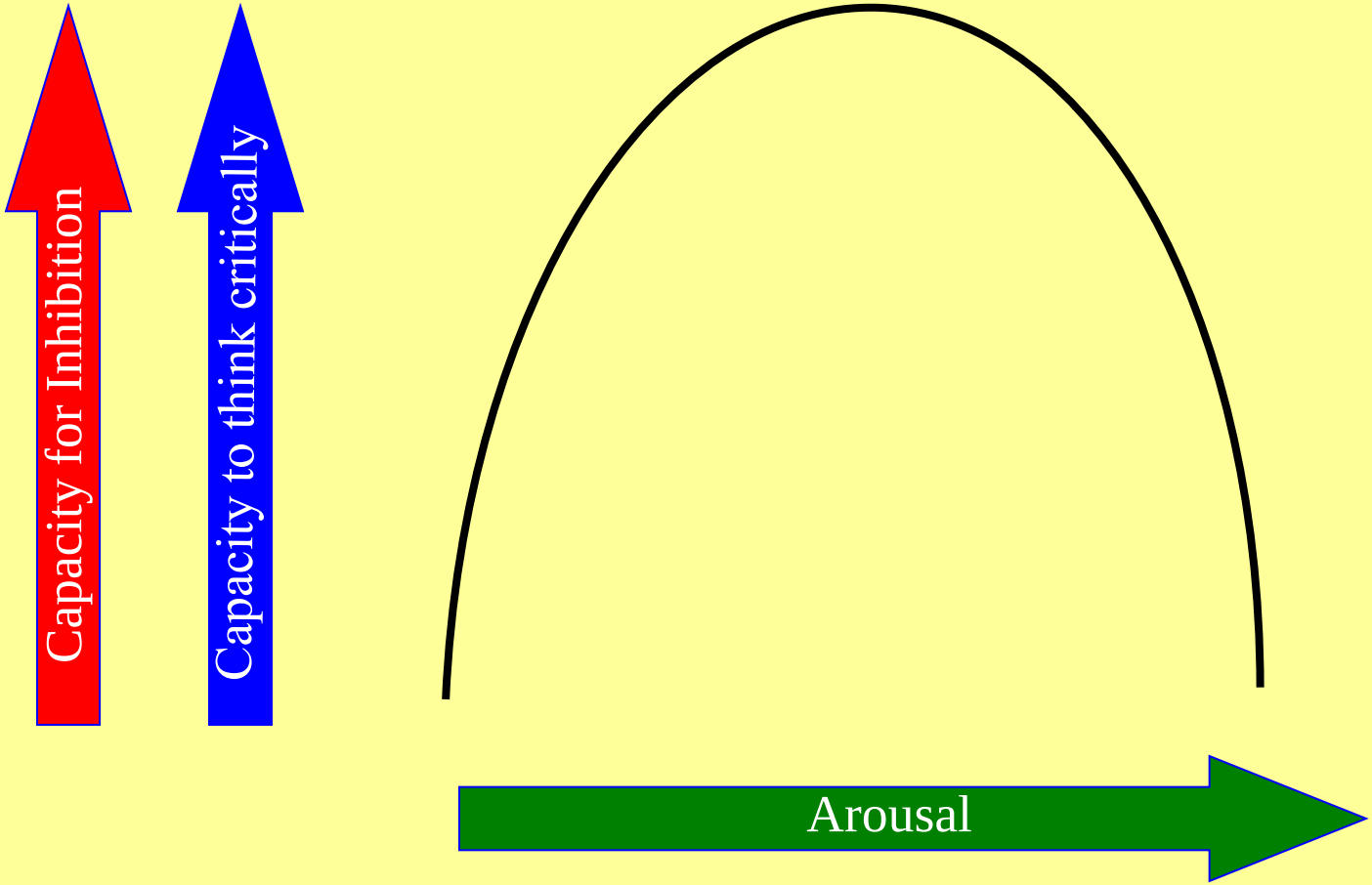
Arnsten A et al, 2009

Morrow BA et al, 1999

Rasmusson AM, 1994

Goldstein LG et al, 1996

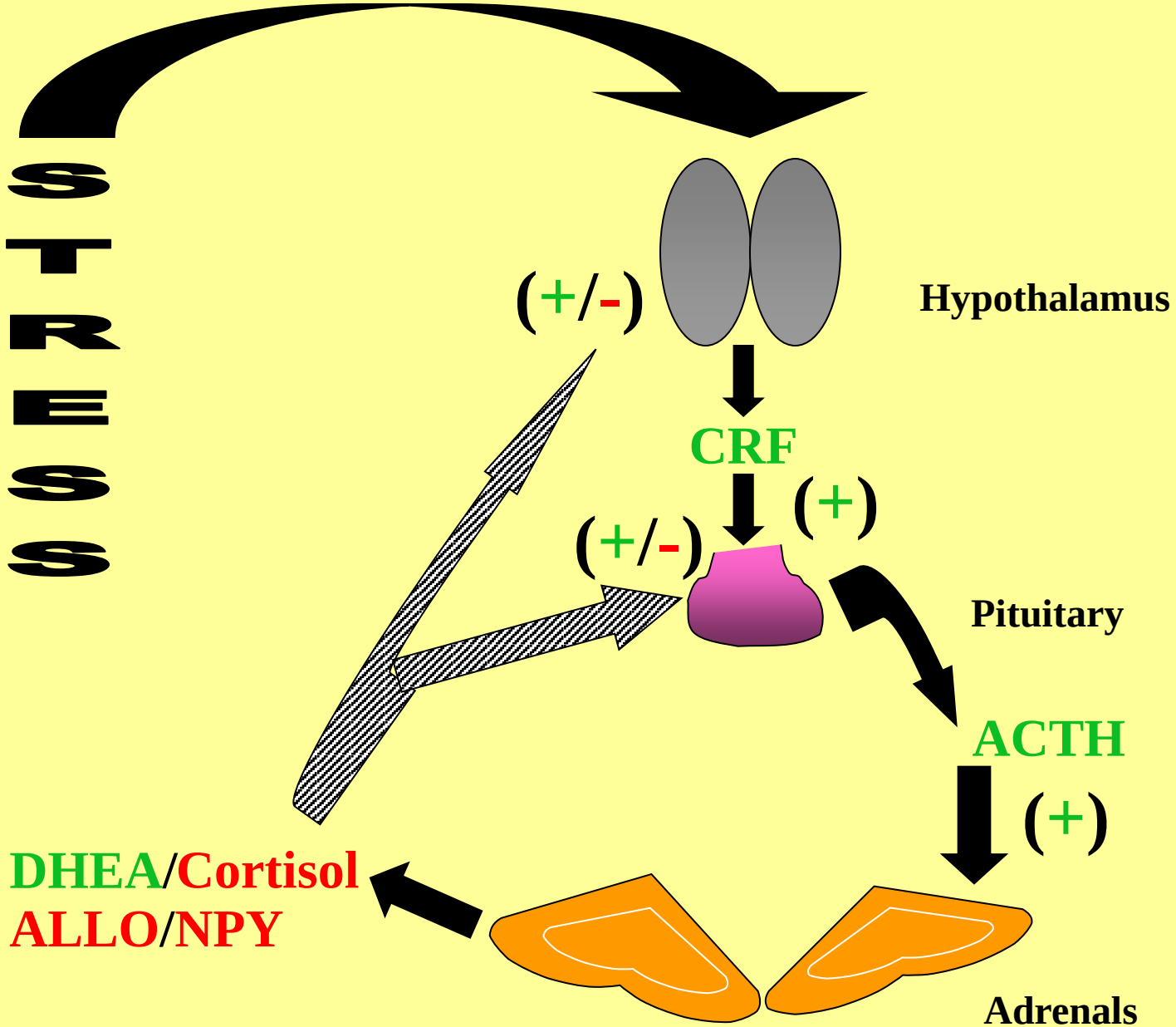
Optimization/Deterioration of *Executive Capacities* as a Function of Arousal: Inverted "U"-Shaped Curve



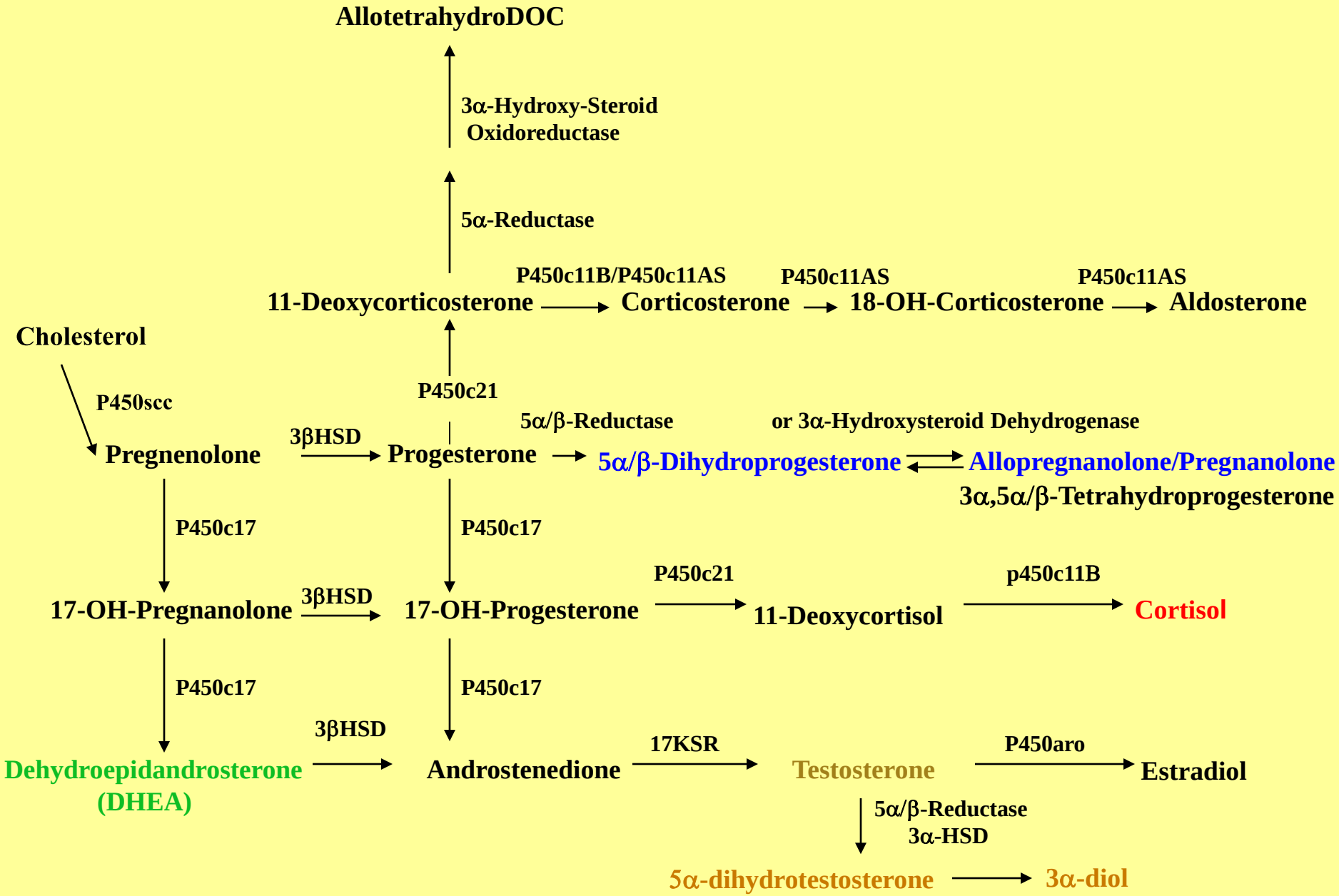
Neurotransmitters & Neuromodulators

Mediators/Modifiers of the Stress Response
and of
PTSD Risk, Recovery, and Comorbidity

Hypothalamic Pituitary Adrenal (HPA) Axis



Adrenal Steroid Synthetic Pathways



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

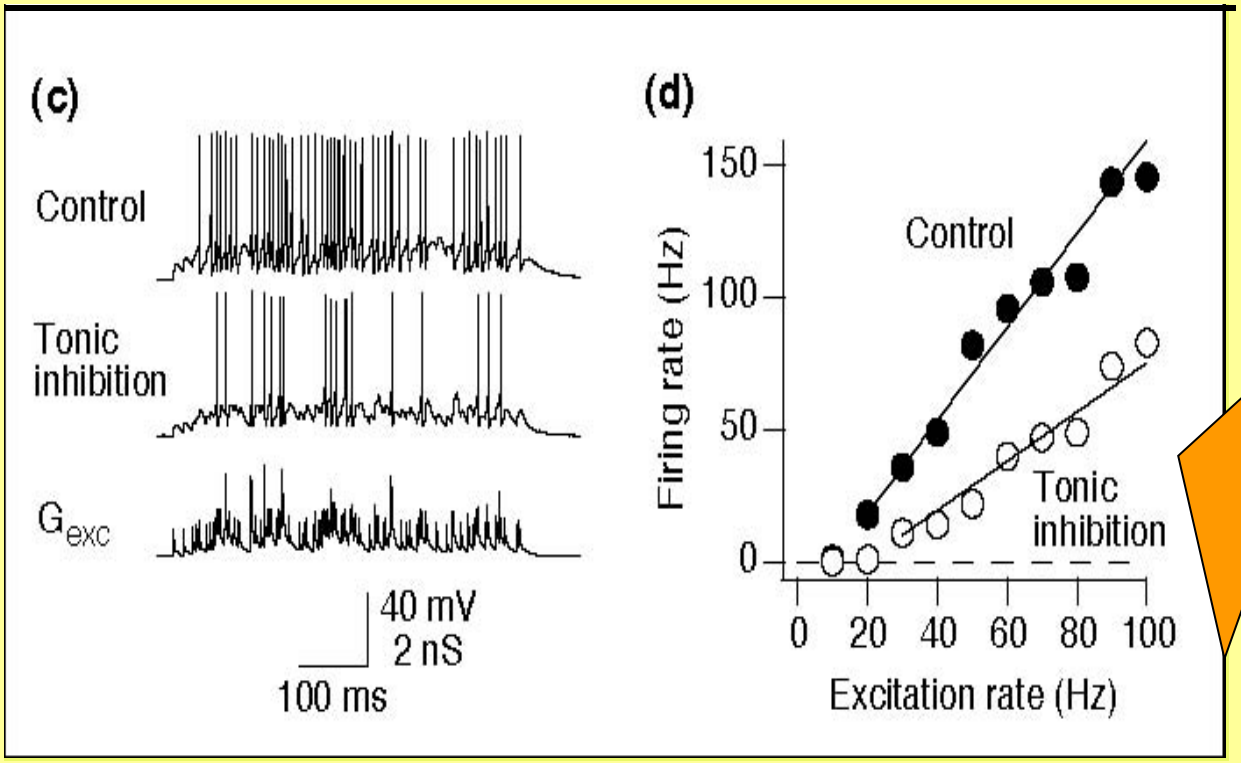
  3) contextual fear conditioning (Piribiri 2007)

- 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

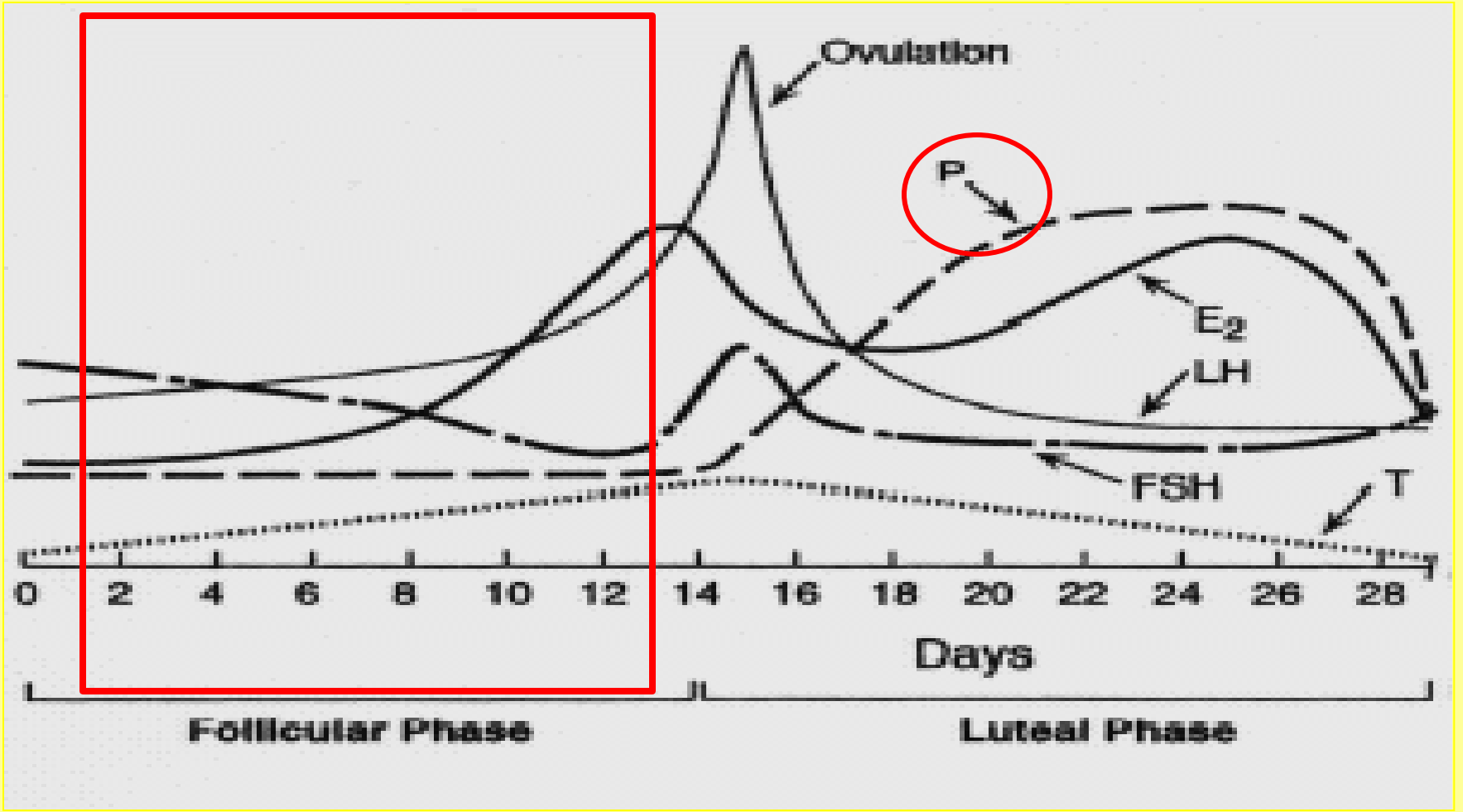
Allopregnanolone?

LUMBAR PUNCTURE

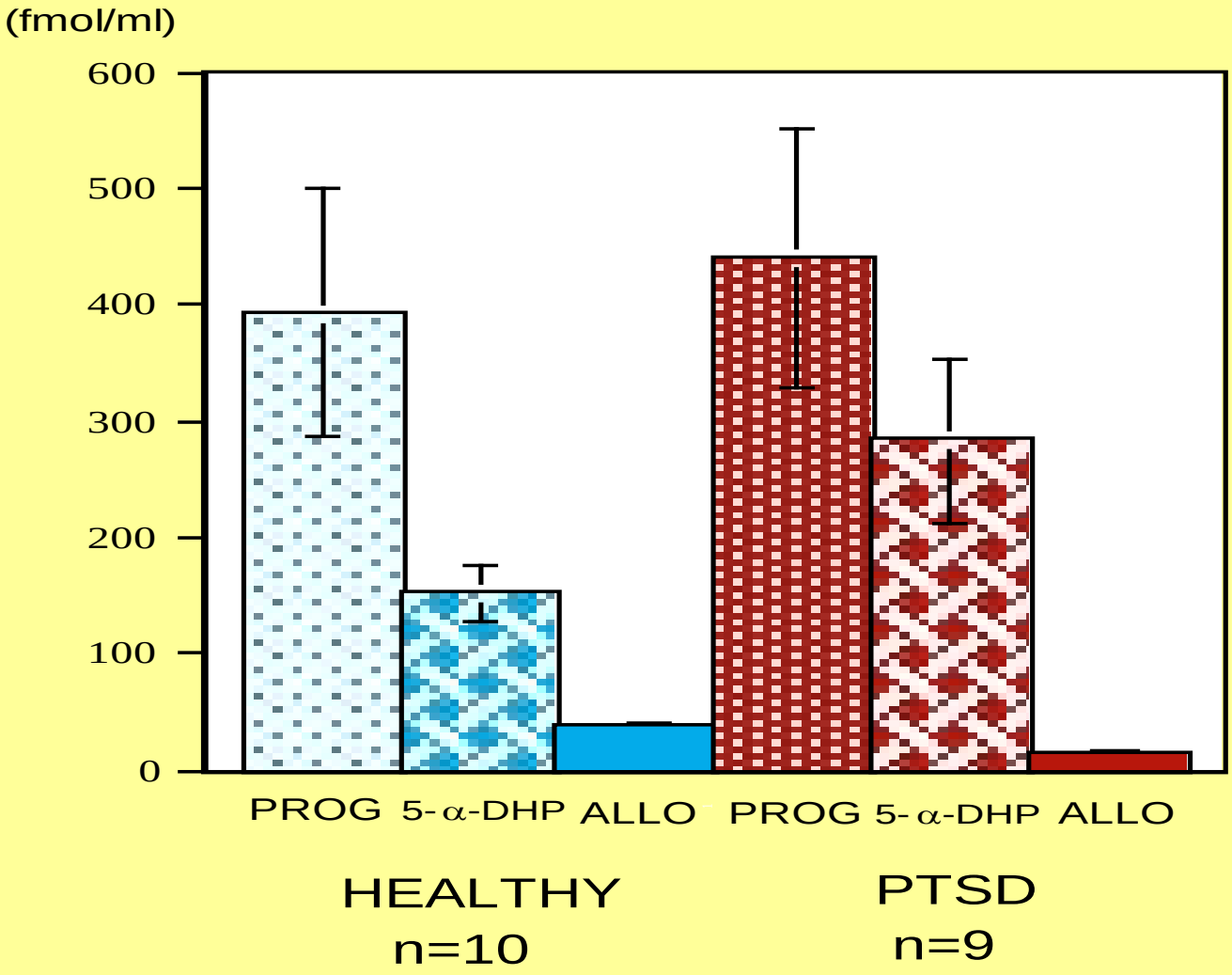
- Fasting except for water after midnight
- No medication or ETOH >1 month except BCP's
- Blood draw at -30 and -15 minutes before the LP
- Performed in the lateral decubitus position between 8:30 and 9:30 a.m. (Sprot needle to prevent post-LP headaches)
- Menstrual cycle phase monitored with LH surge 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)

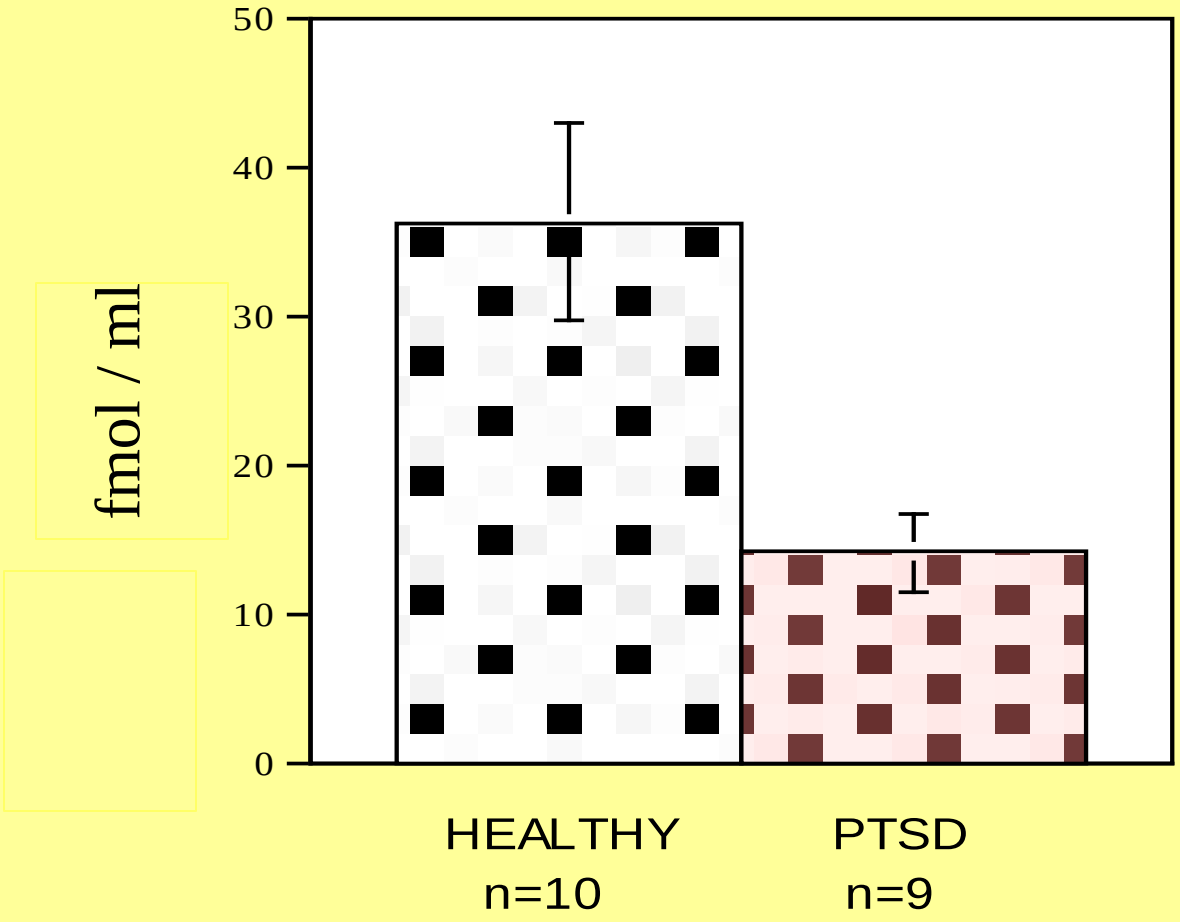


CSF Progesterone, 5α-DHP & Allopregnanolone



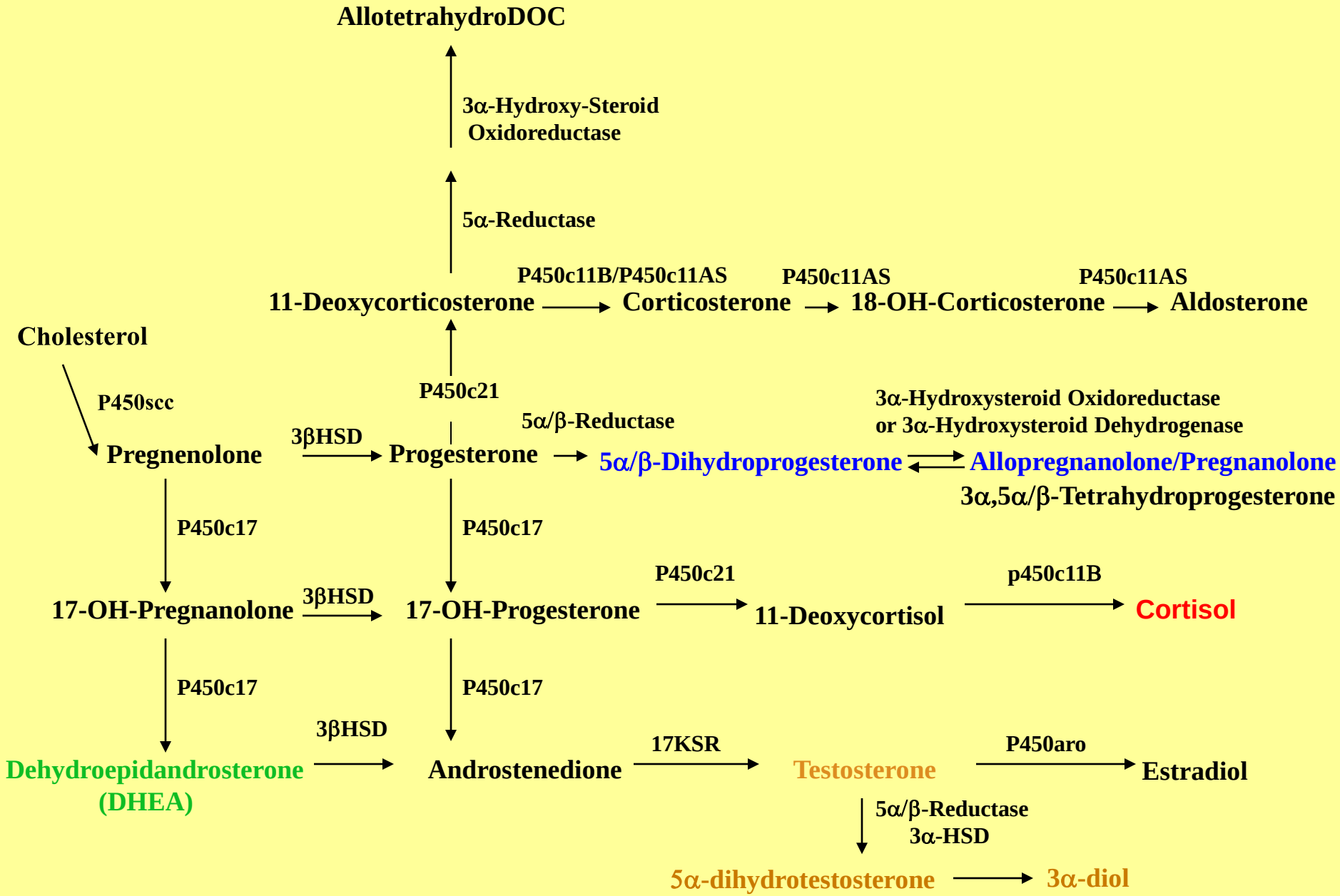
FOLLICULAR

PTSD allopregnanolone 39% of controls
t = -2.77, p < 0.01

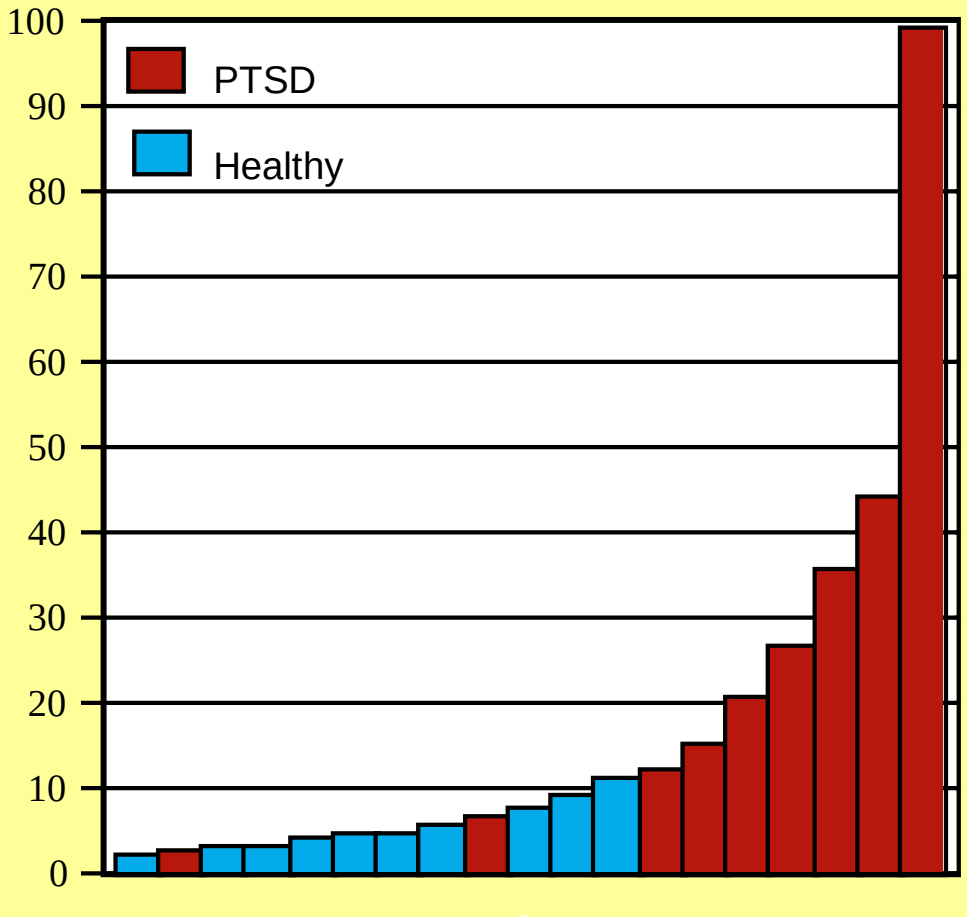


FOLLICULAR

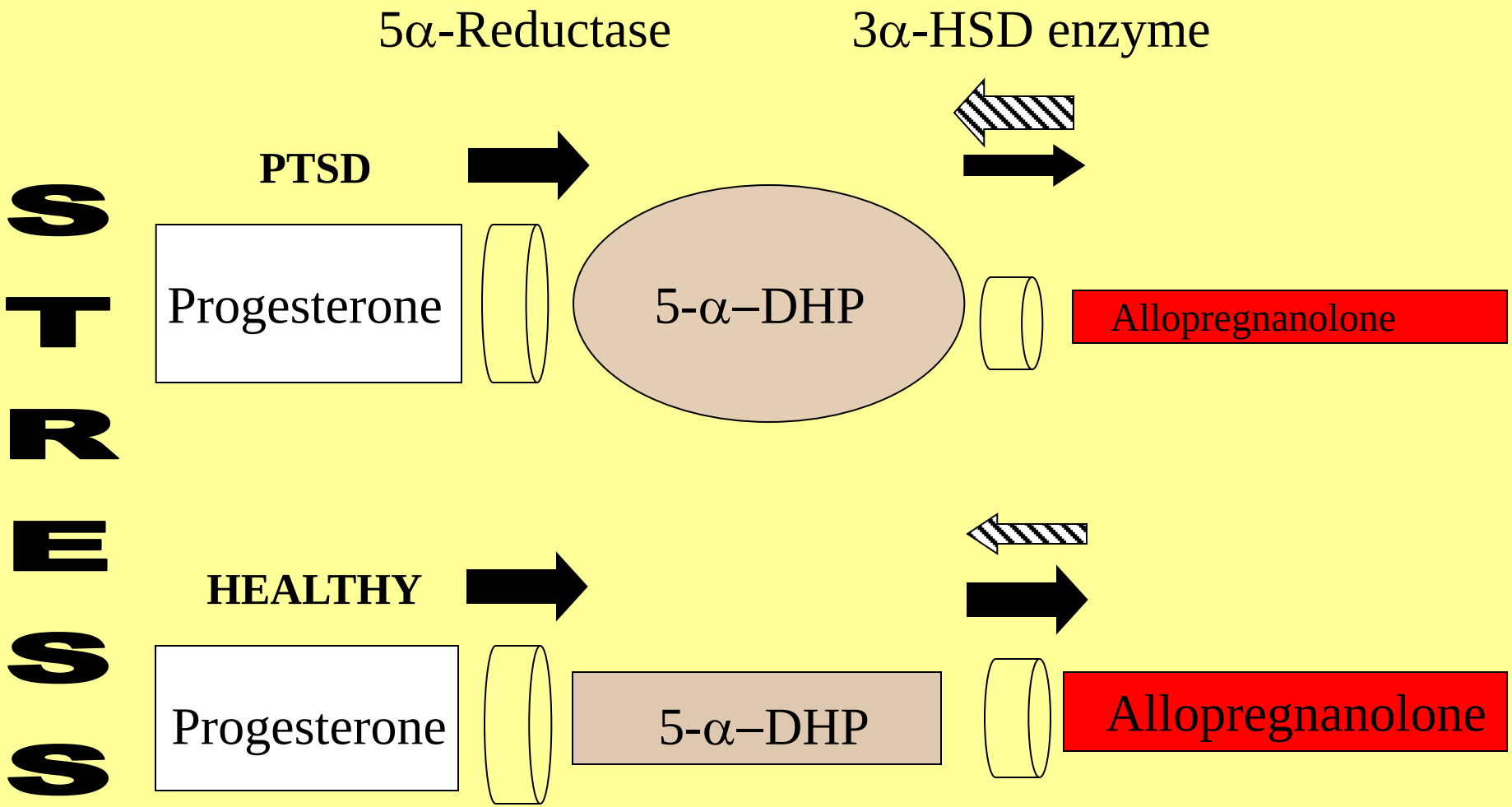
Adrenal Steroid Synthetic Pathways



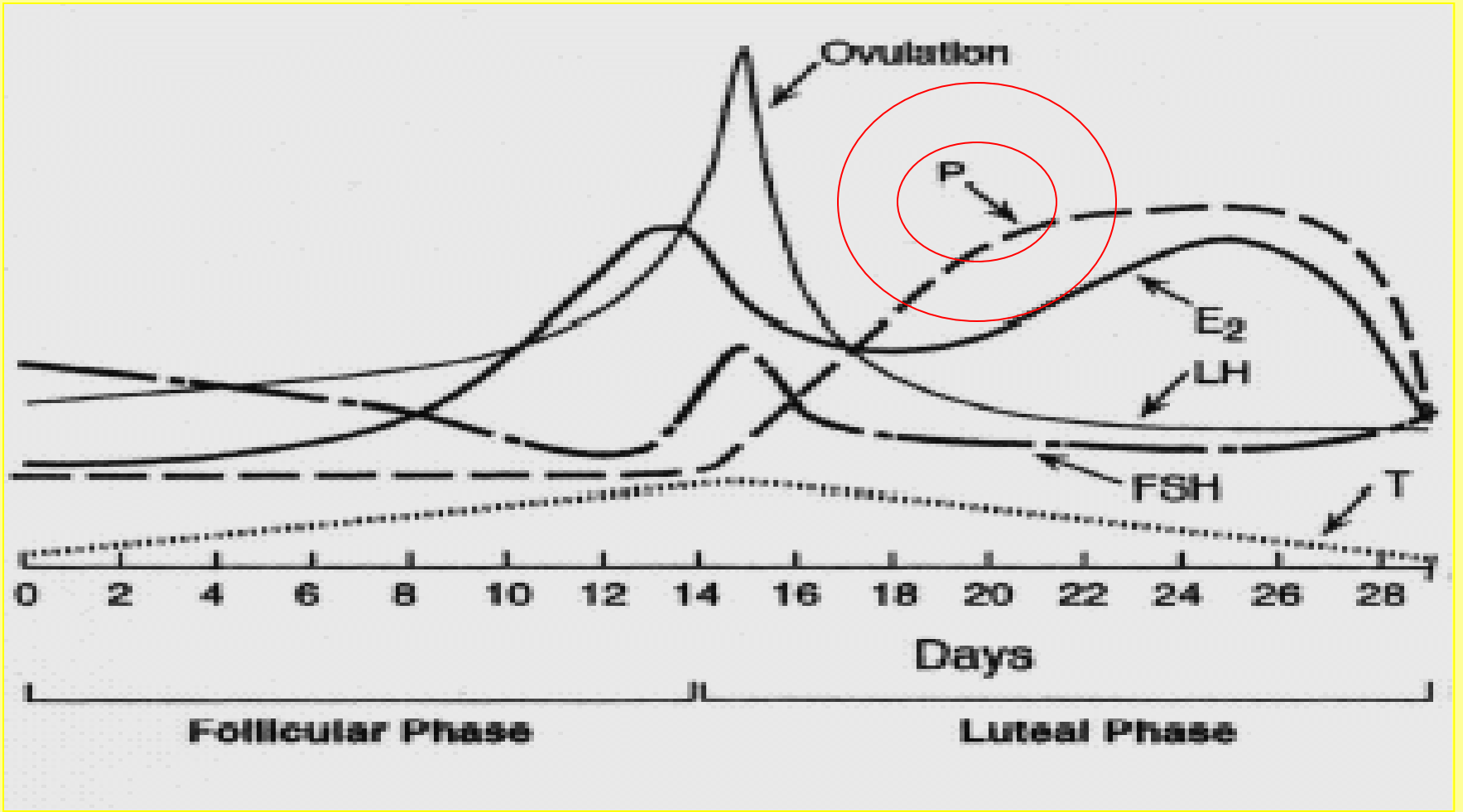
The 5α-DHP/ALLO Ratio
PTSD vs. Healthy: p = 0.006 (MW test)



Allopregnanolone Synthesis Deficit in PTSD?



Menstrual Cycle

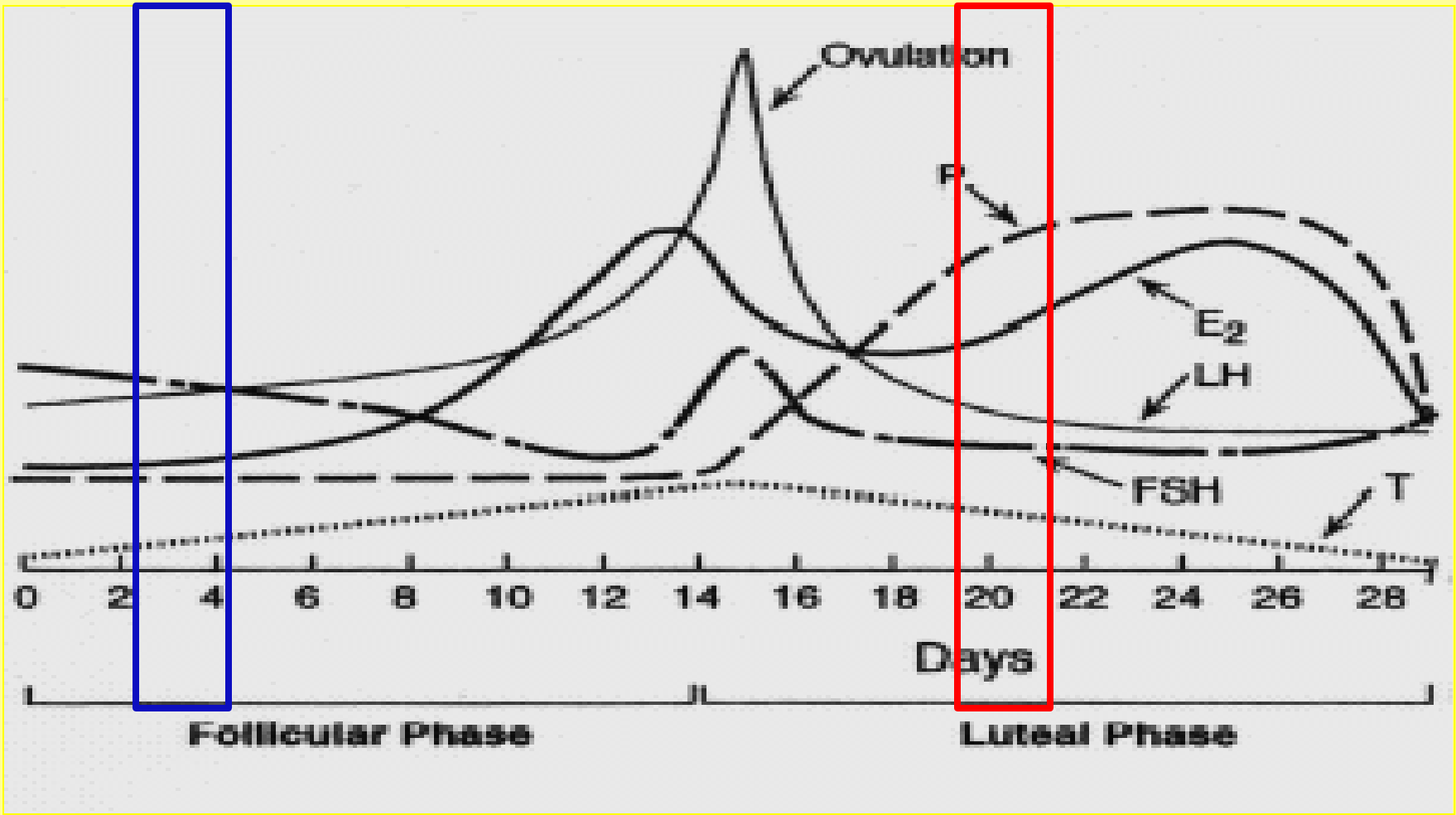


Further Evidence of a Deficit in ALLO Production in PTSD

Subjects	CSF Progesterone		CSF ALLO	
	Early Follicular Day 2-6	Mid-Luteal Day 19-23	Early Follicular Day 2-6	Mid-Luteal Day 19-23
Healthy #1	175	420	39	98
Healthy #2	464	1077	20	65
PTSD #1	542	3058	15	19

***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

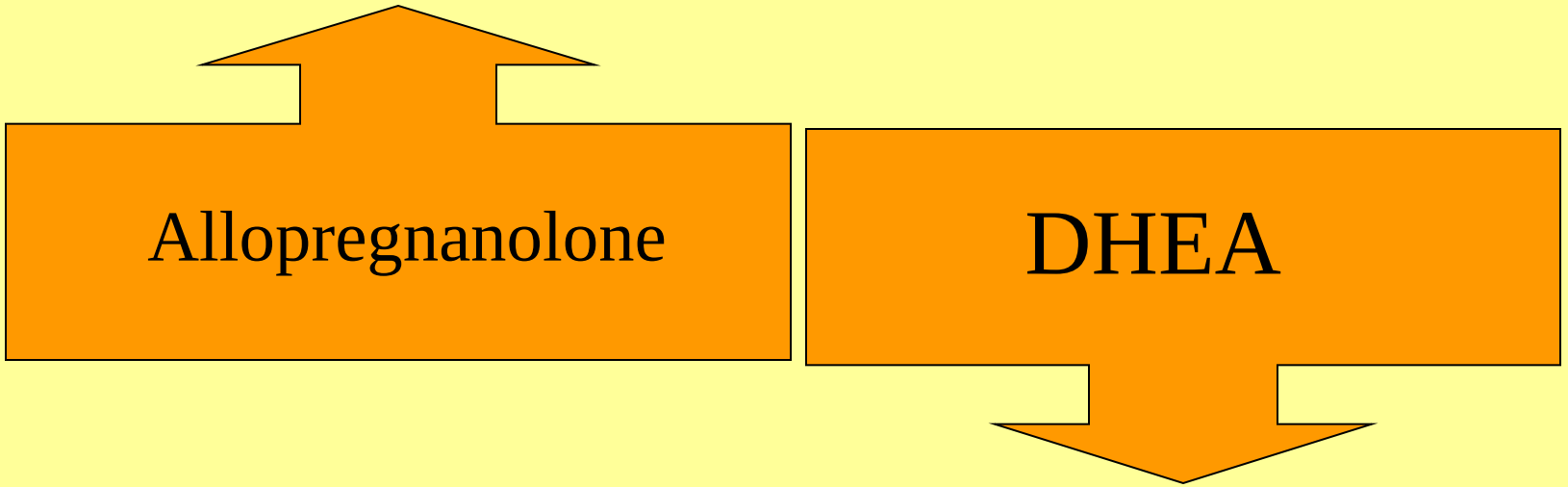
	Follicular	Luteal	Cohen's *d*
Trauma Control n=8	2.29 BPM (3.03)	5.08 BPM (3.71)	.82
PTSD n=8	2.27 BPM (1.44)	9.31 BPM (13.01)	.76
Cohen's *d*	.01	.44	

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

	Follicular	Luteal	Cohen's *d*
Trauma Control n=8	-.05 μV (.22)	.01 μV (.40)	.19
PTSD n=8	-.05 μV (.17)	.67 μV (1.19)	.85
Cohen's *d*	.00	.74	

Pineles et al., 2008

Brain Inhibitory Tone



SPEARMAN CORRELATIONS WITH PROFILE OF MOOD STATE SCORES IN ALL SUBJECTS (n=19)

	ALLO	ALLO/DHEA	5α-DHP/ALLO
Anger/Irritation	-.43 (.06)	-.57 (.01)^{t}	.58 (.01)^{t}
Anxiety/Tension	-.46 (.04)	-.50 (.03)	.64 (.003)*
Confusion	-.31 (.20)	-.43 (.07)	.56 (.01)^{t}
Depression/Dejection	-.52 (.02)	-.70 (.0008)*	.67 (.002)*
Fatigue	-.50 (.03)	-.63 (.004)*	.60 (.007)*
Vigor	.23 (.34)	.03 (.90)	-.42 (.08)
Total POMS	-.45 (.05)	-.52 (.02)	.66 (.002)*

SPEARMAN CORRELATIONS WITH CFA-DEFINED PTSD SYMPTOM CLUSTERS (Simms et al, 2002)

	ALLO	ALLO/DHEA	5α-DHP/ALLO
Re-experiencing Symptoms	-.72 (.03)	-.82 (.007)*	.39 (.30)

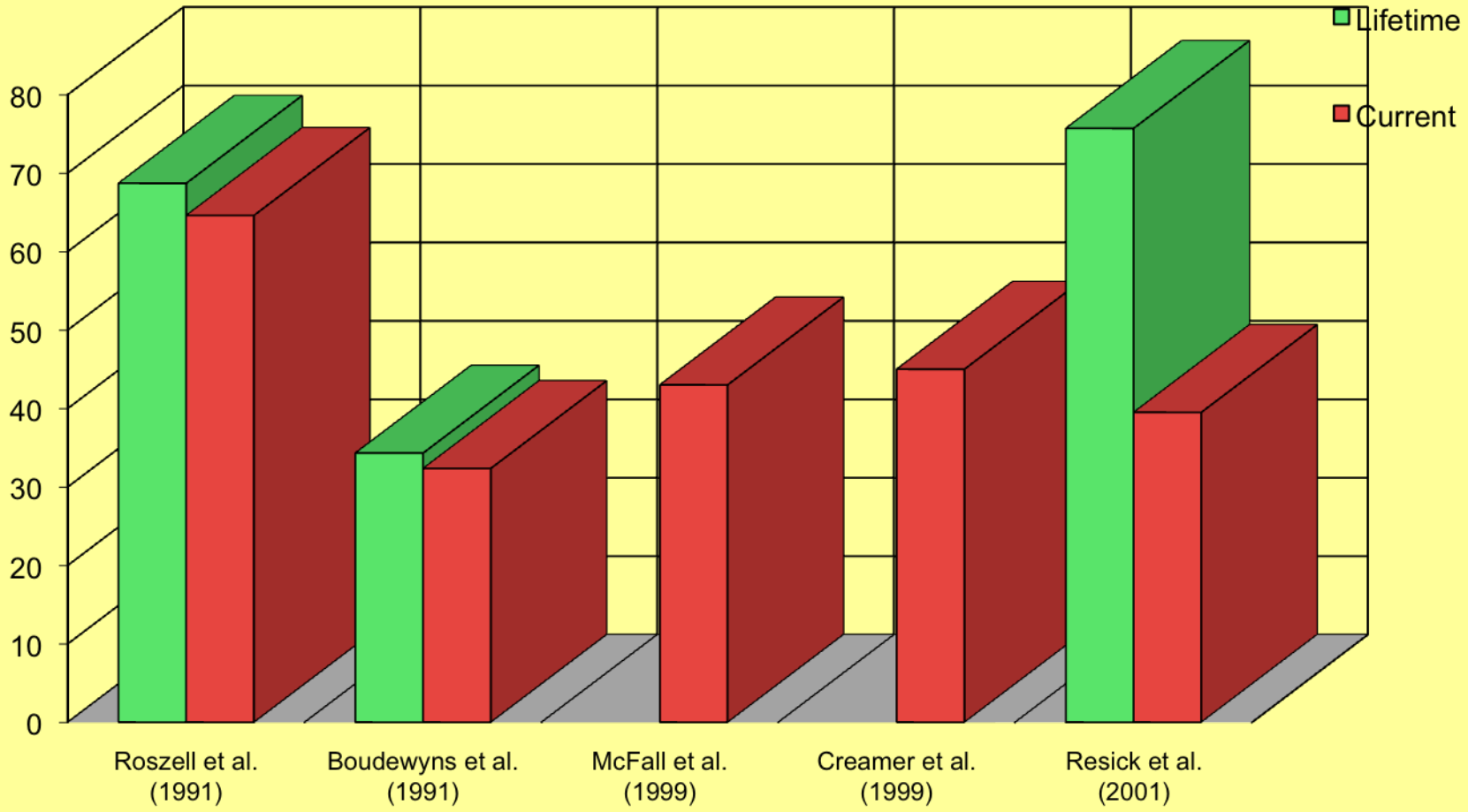
COMORBID PTSD/MDD:

NEUROBIOLOGICALLY

DISTINCT

PTSD and Depression Comorbidity

(Treatment Seeking Sample)



Courtesy of P. Resick

Breslau et al., Biol. Psychiary 2000

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

Resick, P.A. (1991-97) R01 MH 46992, NIMH Female Assault Victims 3 Month Comorbidity N = 69		Current	MDD	
		NO	YES	Total
	No PTSD	48%	**3%**	51%
	PTSD	36%	13%	49%
	Total	84%	16%	
Resick, P.A. (1997-'02) R01 MH55542, NIMH Domestic Violence 1-6 mo post recent event N = 140		Current	MDD	
		NO	YES	Total
	No PTSD	19%	**5%**	24%
	PTSD	26%	49%	75%
	Total	45%	54%	
Keane et al., 1998 Comorbidity Male Vietnam Veterans N = 1325		Current	MDD	
		NO	YES	Total
	NO PTSD	38.4%	**3.1%**	41.5%
	PTSD	37.2%	21.3%	58.5%
	Total	75.6%	2 4.3%	

ALLO IS LOWEST IN CO-MORBID PTSD/DEPRESSION?*

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

*Comorbid PTSD/MDD may be construed as more severe PTSD: Breslau et al. 2000

Higher PTSD & Depression Symptoms

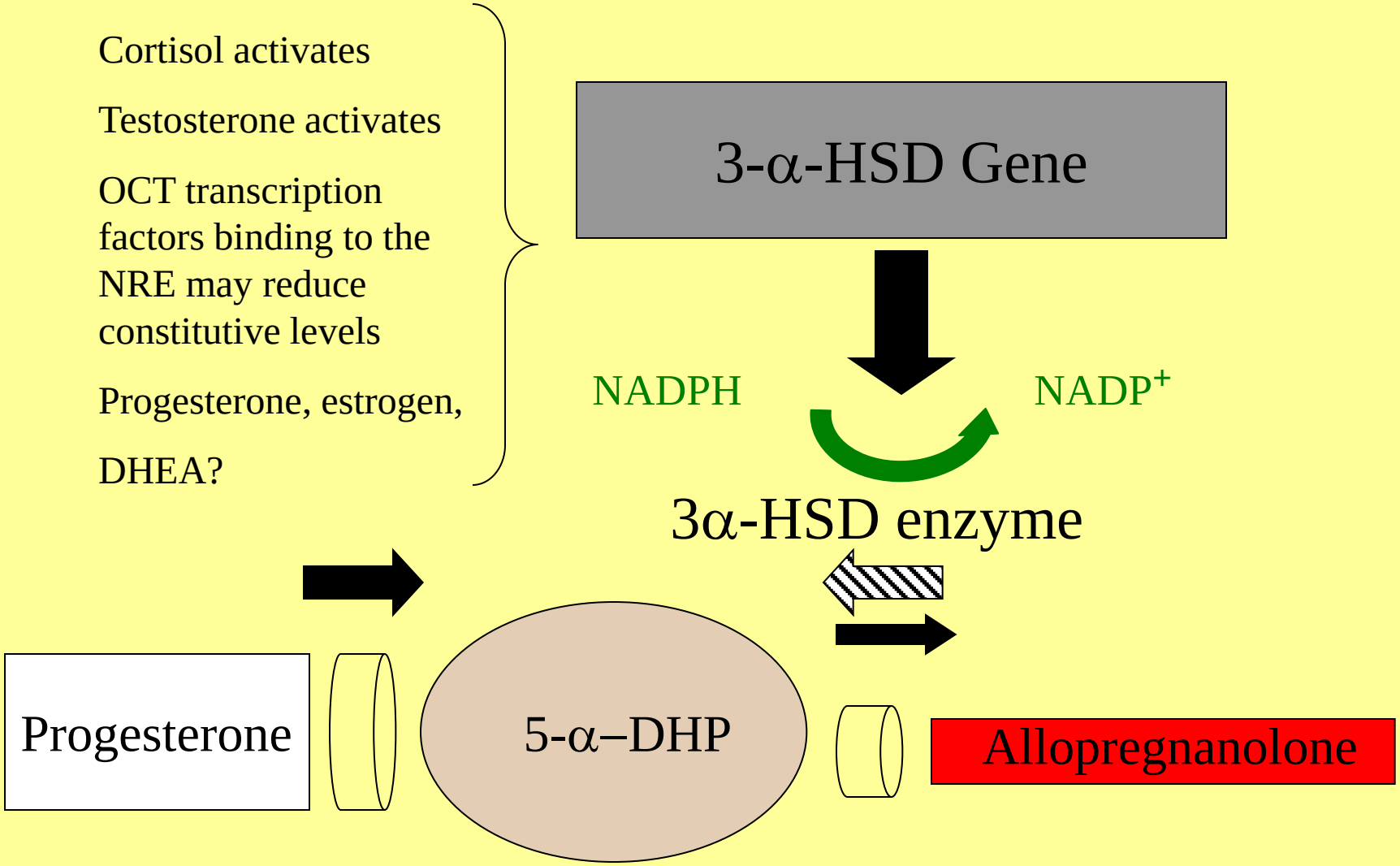
Before & After CPT in Comorbid PTSD/MDD

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

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

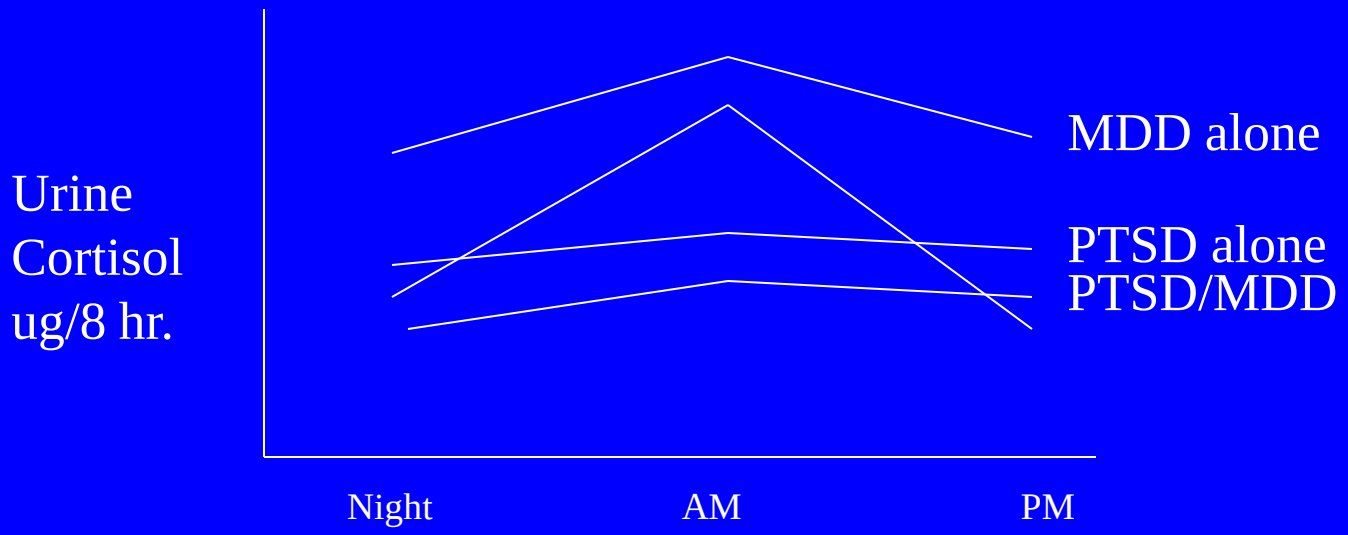
Nishith et al 2005

Factors that Influence Expression of the Gene for the Enzyme that Synthesizes ALLO



Hou et al 1998, Mitev et al 2003

DECREASED CORTISOL OUTPUT IN MEN WITH PTSD/MDD



Young and Breslau 2004

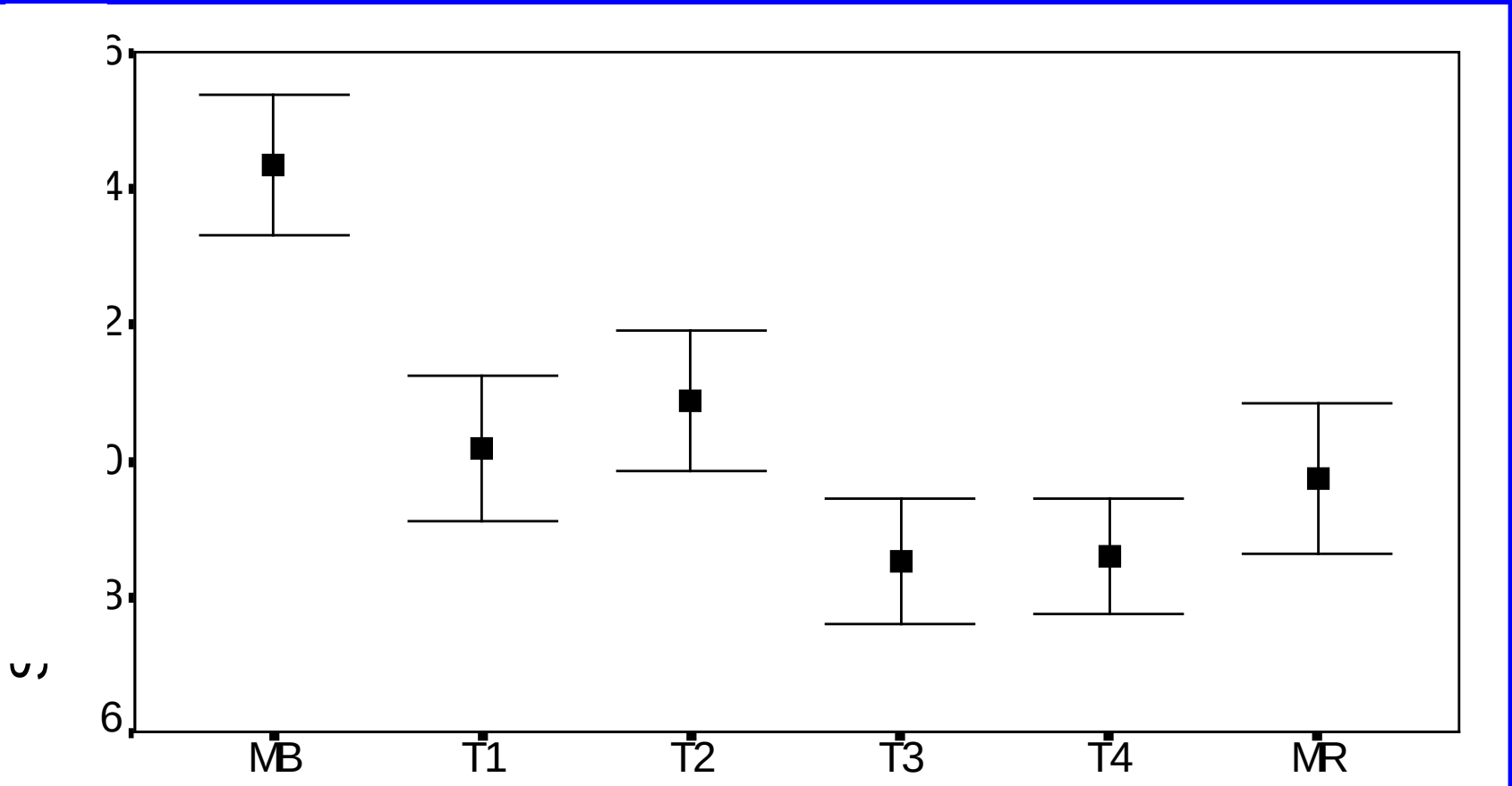
Mason et al 1986 ↓

Yehuda et al 1990, 1993, 1995 ↓

Maes et al 2000 ↑

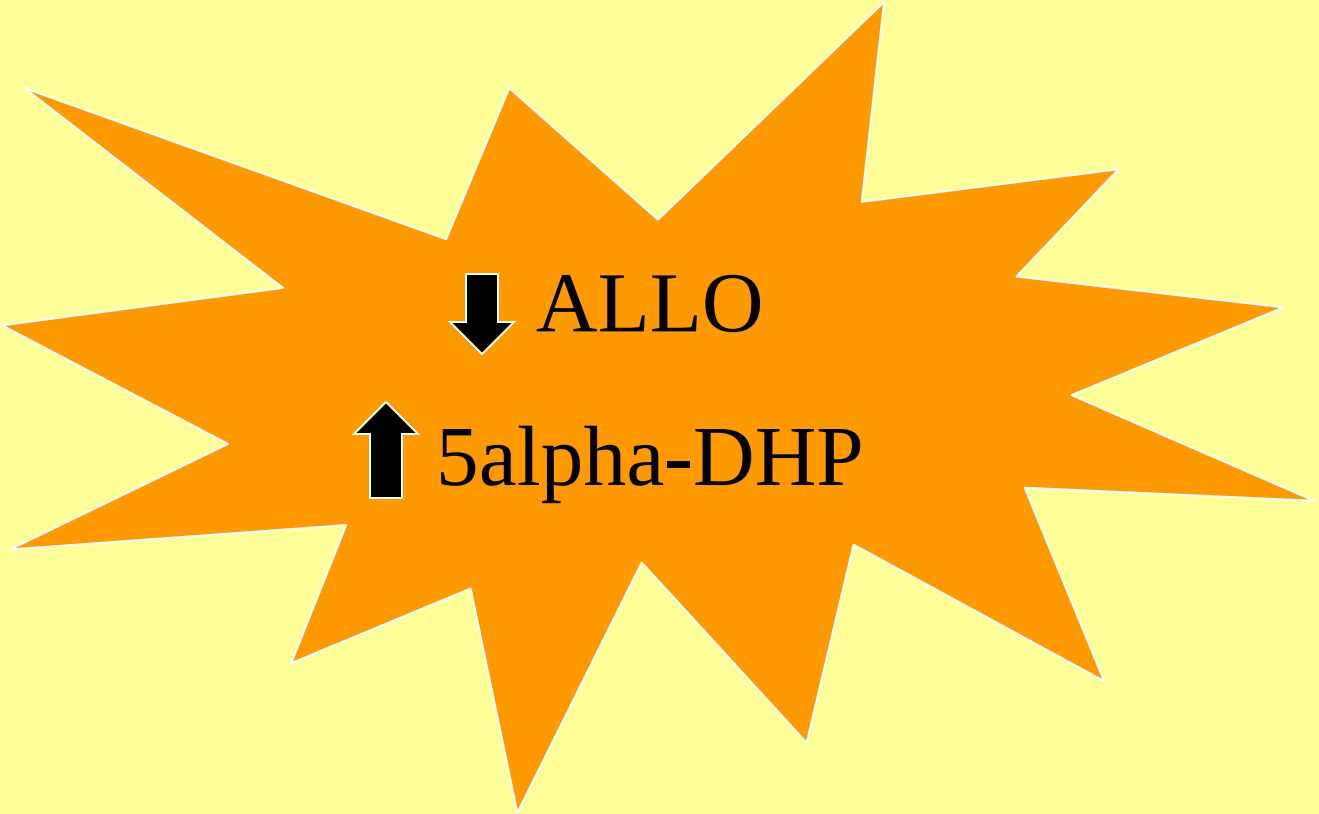
Pitman and Orr 1990 ↑

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)

Male Rats: Heavy ETOH >50 Days & Detoxed x 2 Days



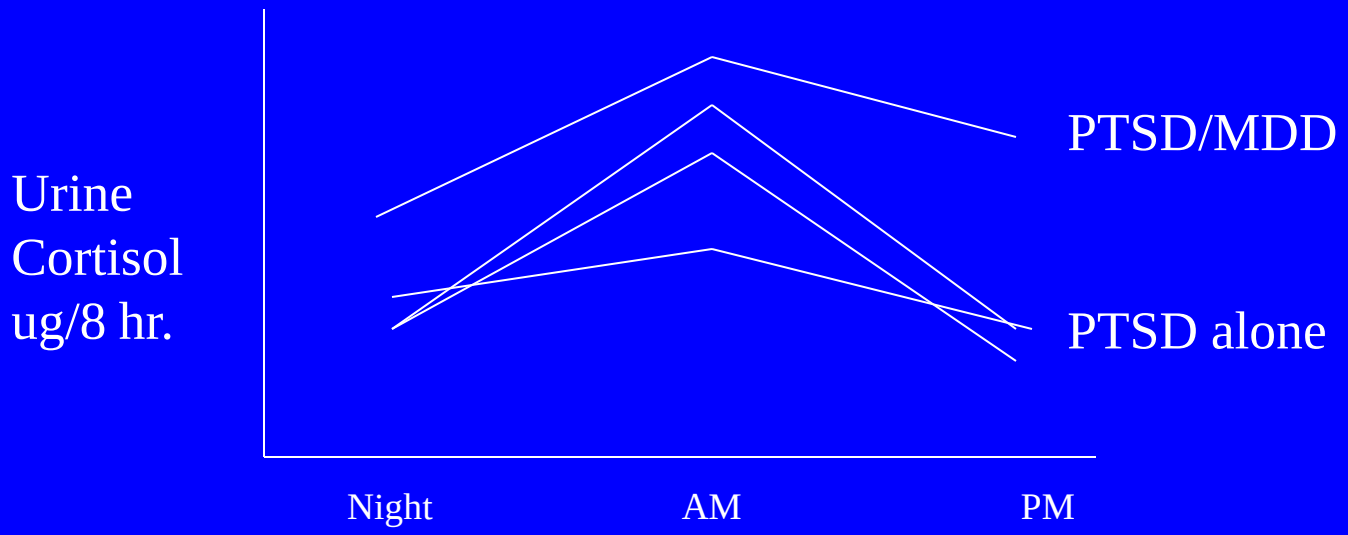
**ETOH Stimulates NADPH oxidase, thereby decreasing NADPH, decreasing ALLO & increasing superoxide radical formation

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



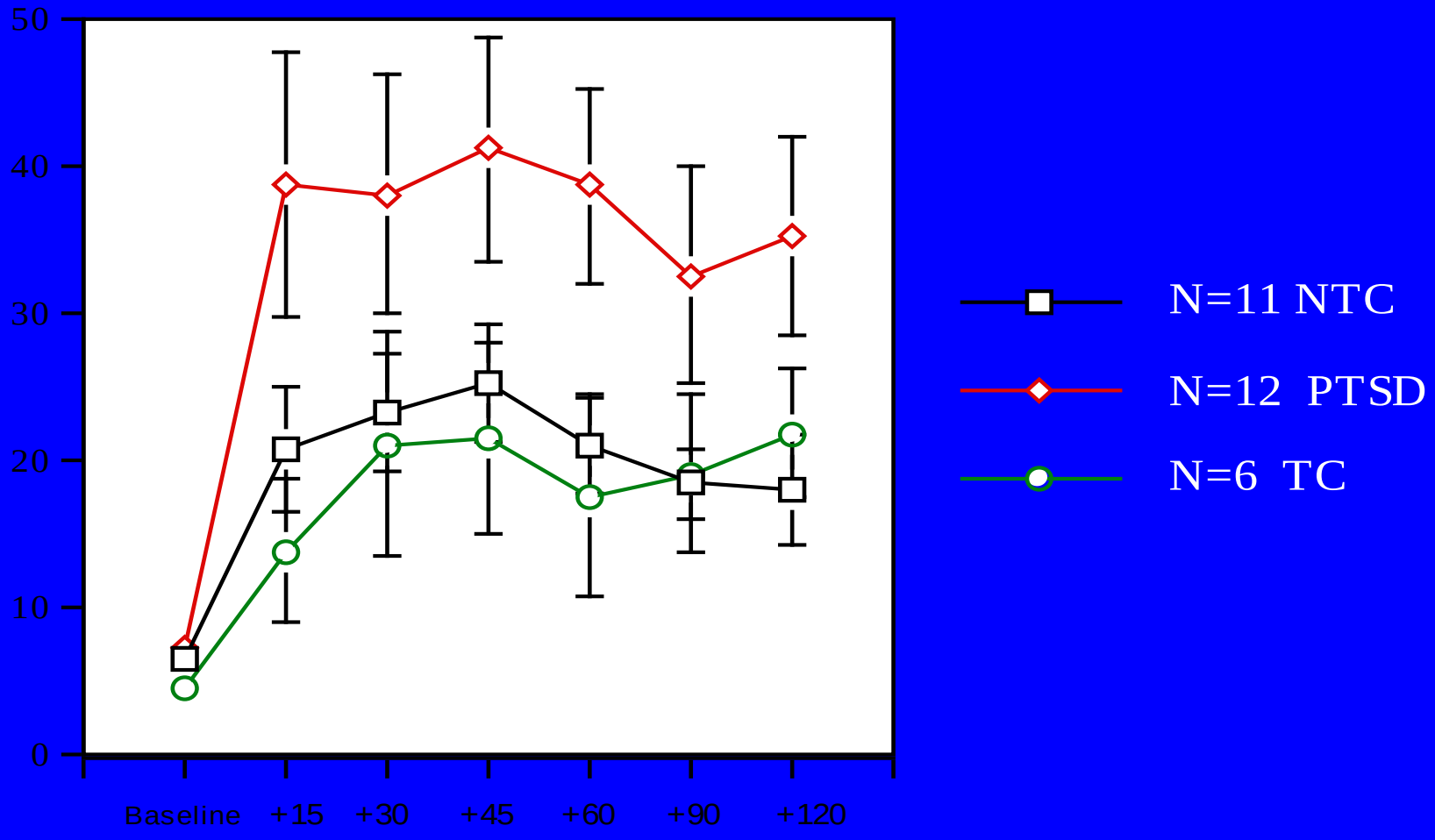
Young and Breslau 2004

Lipschitz et al 2003

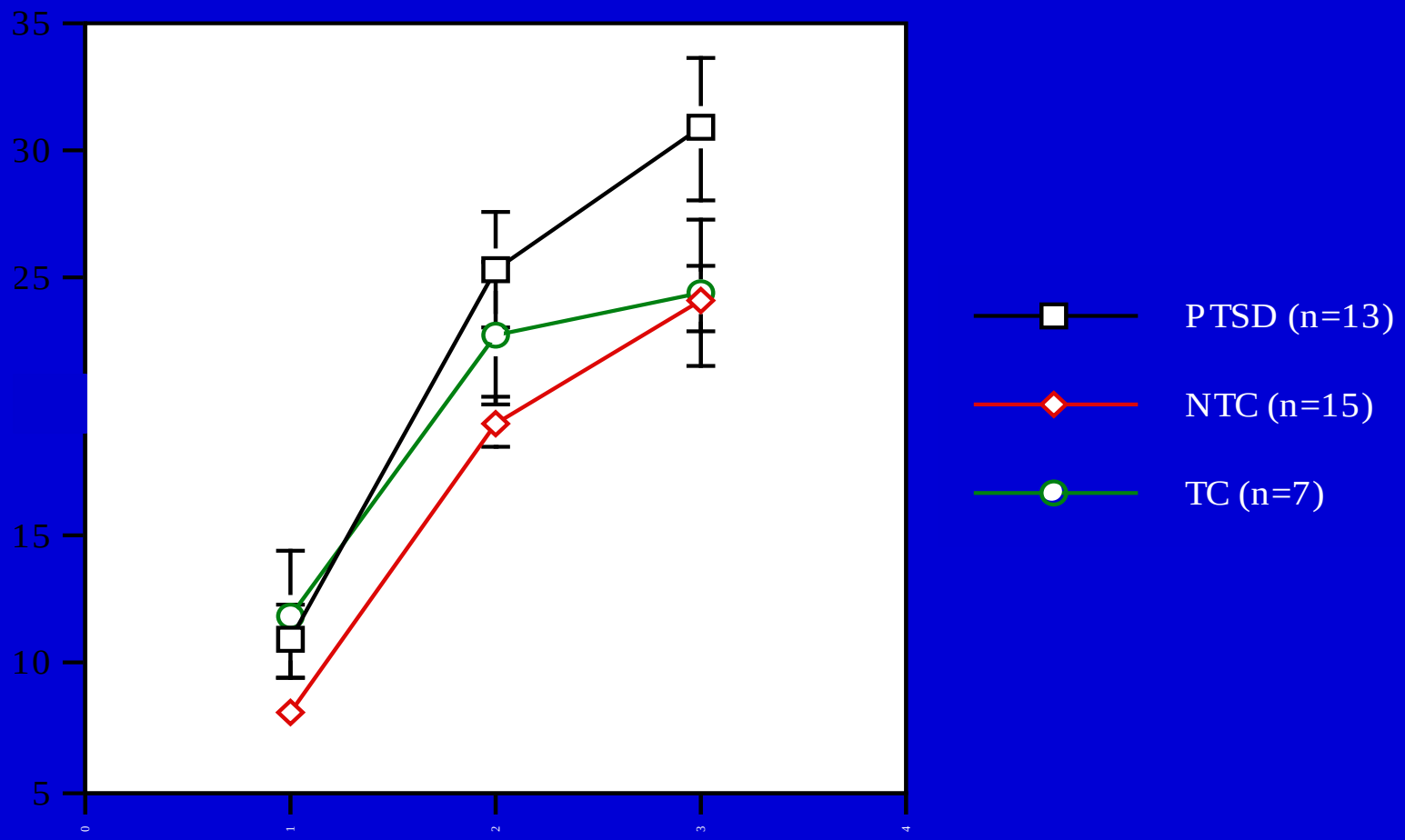
Rasmusson et al 2001

Heim et al 2000

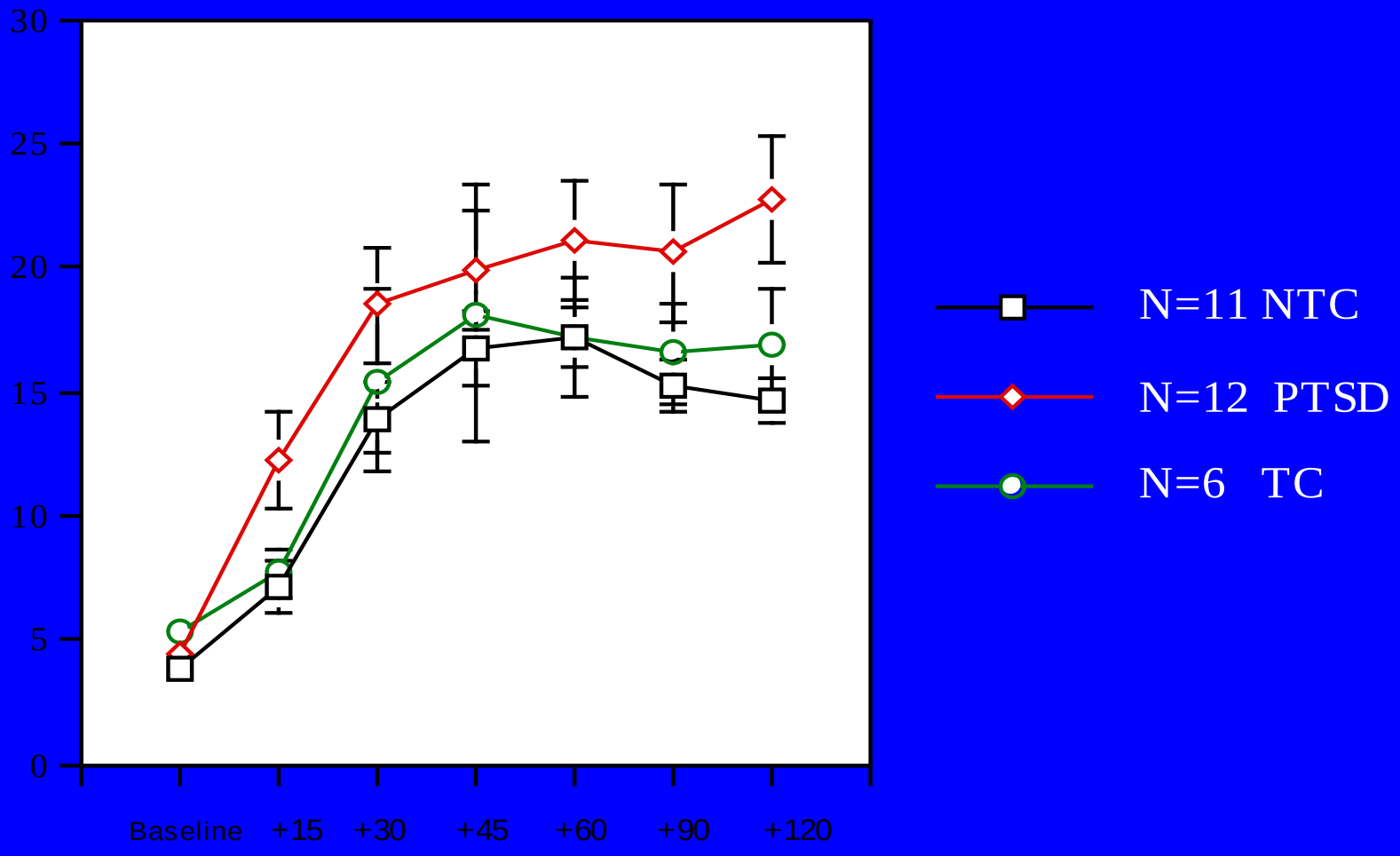
ACTH Response to CRF



Cortisol Response to ACTH $_{1\text{-}24}$



Cortisol Response to CRF



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).**

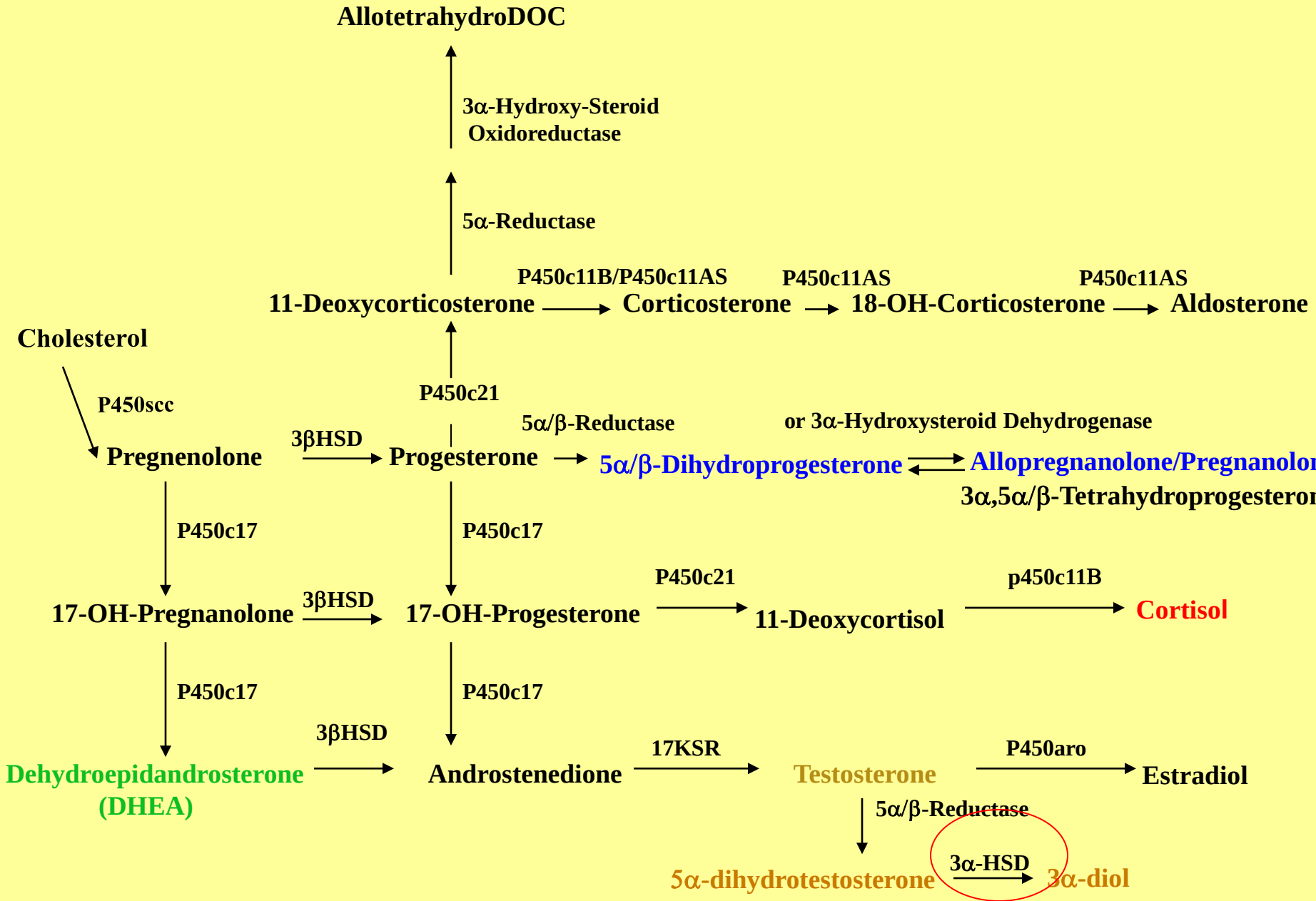
*** Induces expression of the corticotropin releasing factor (CRF) gene (Schulkin et al 1998)**

*** 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



Increased 5α-dihydrotestosterone

Neuropeptide Y

*Anxiolytic, anticonflict

*Antikindling and anticonvulsant

*Conserves bioenergy

*Involved in regulation of oxidative metabolism

*Protects the hippocampus

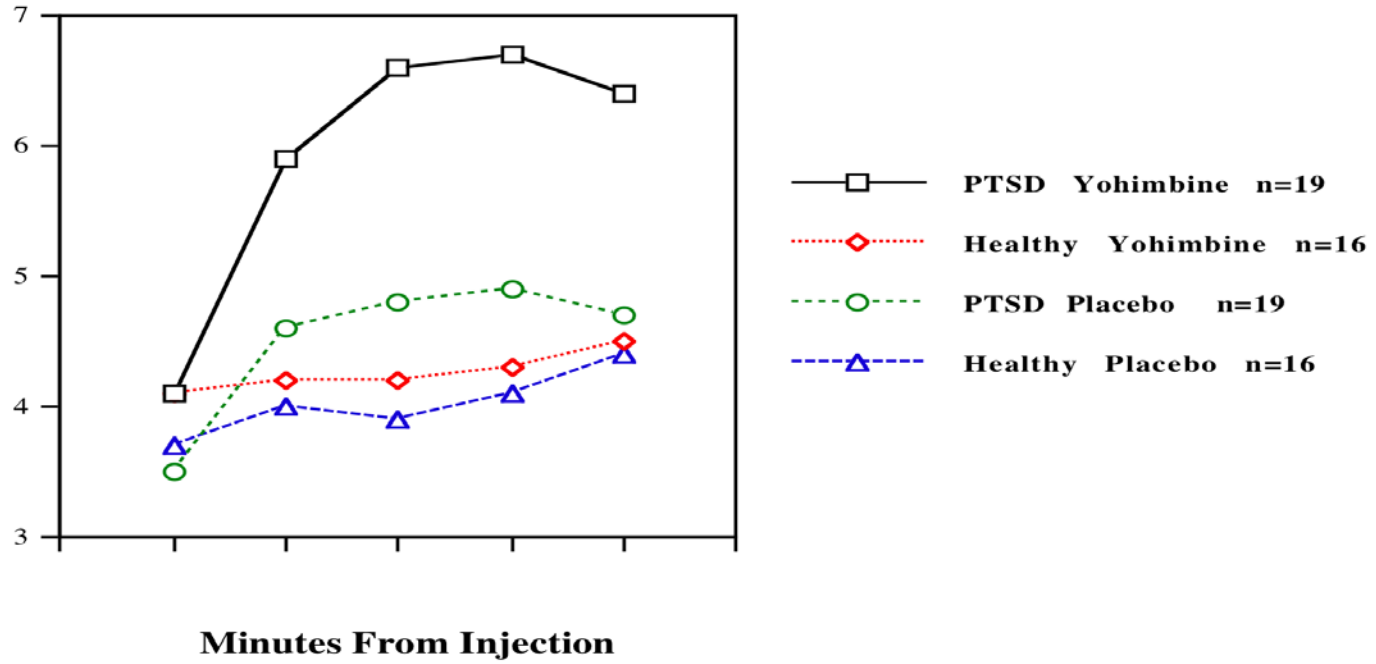
*Supports Neurogenesis

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

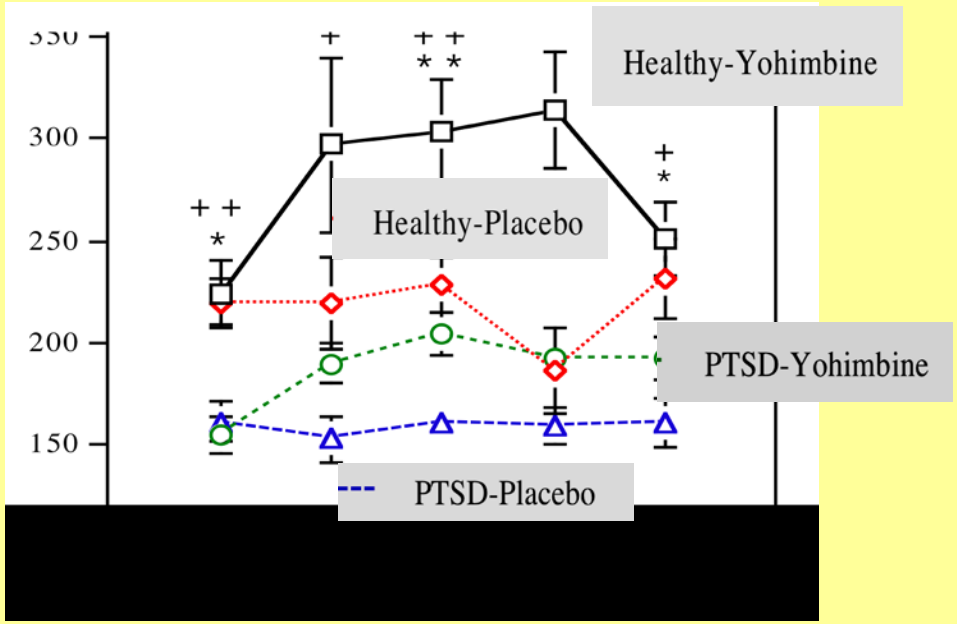


Southwick et al: Arch. Gen. Psychiatry 50:266-274,1993

NPY Appears to Confer Stress Resilience

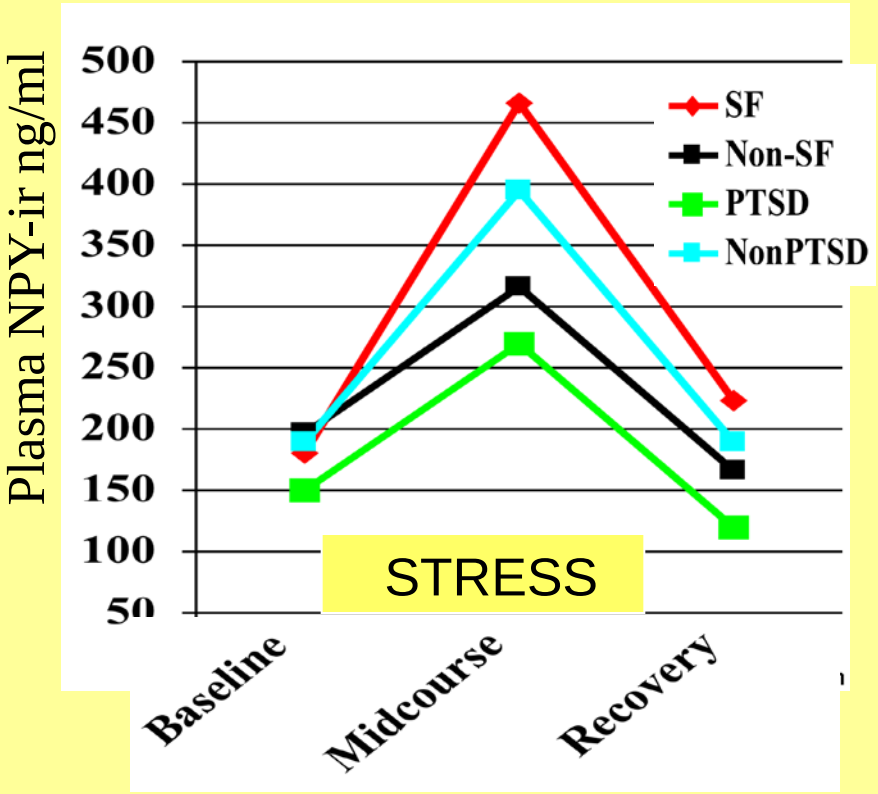
Lower NPY release in PTSD

(Rasmusson et al. 2000)



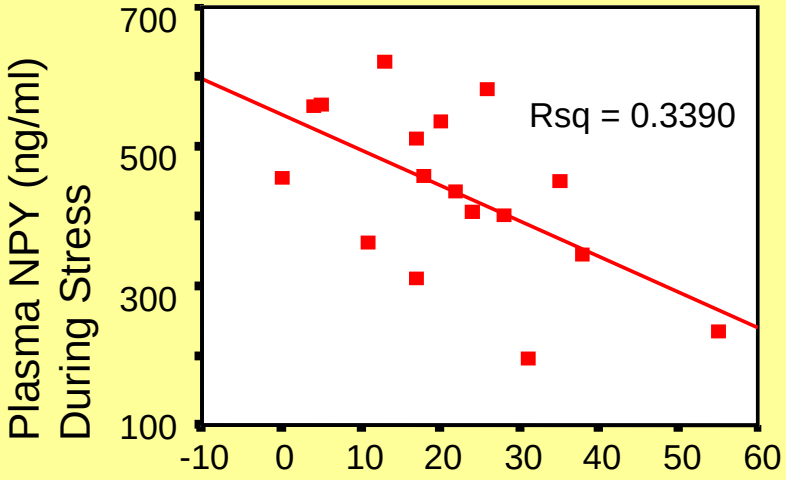
Higher NPY in hardy soldiers and non-PTSD

(Rasmusson et al. 2000, Morgan et al. 2000, 2004)



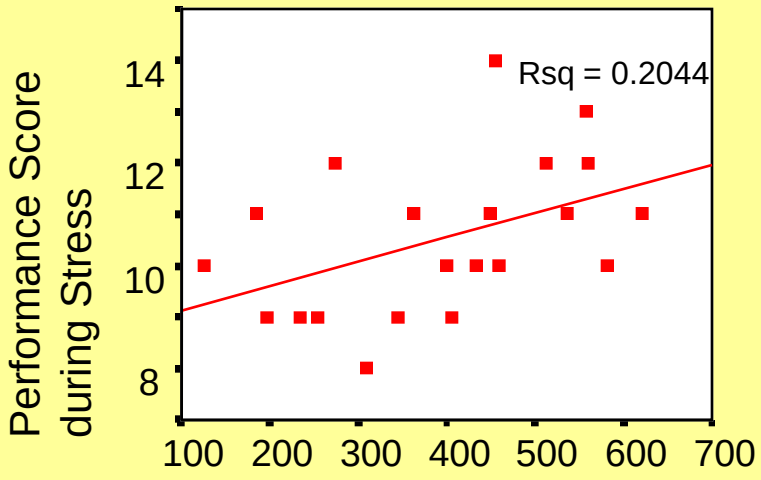
Peak NPY During Intense Training Stress Predicted Less Distress & Dissociation, and Better Performance

NPY and Dissociation



Dissociation Score (CADSS),
r = -.58; p<0.01

NPY & Objective Performance



Plasma NPY (ng/ml) during stress,
r = .49; p<0.02

Morgan et al 2000, 2002

In PTSD, NPY correlated with weight:

$r = +0.61$, $p<0.01$

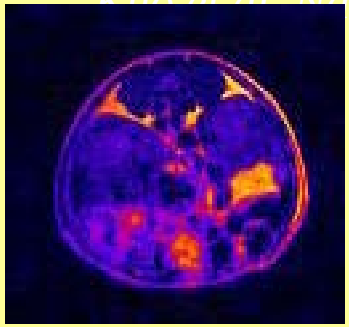
(Rasmusson et al 2000)

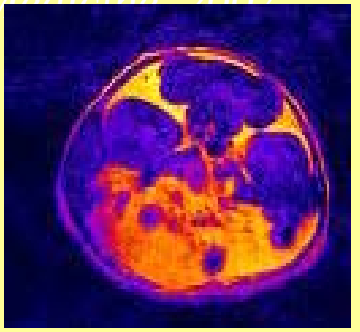
What happens to mice and (wo)men during stress?

(Kuo et al., 2006, Nature Medicine; Zukowska Laboratory)

Iced cold water

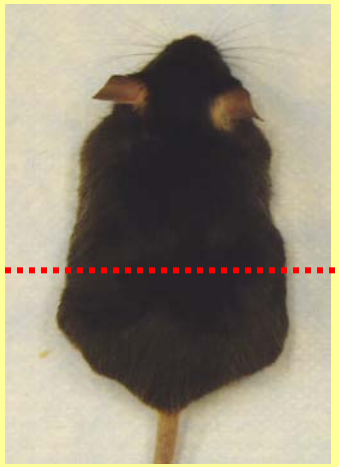
Aggressor intruder

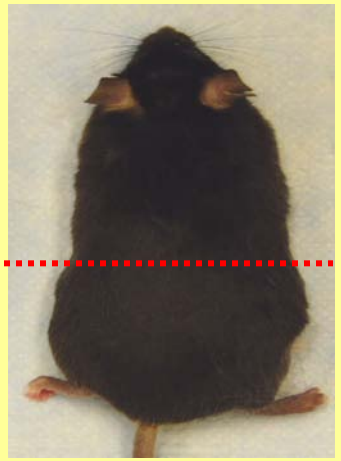




No stress

Stress



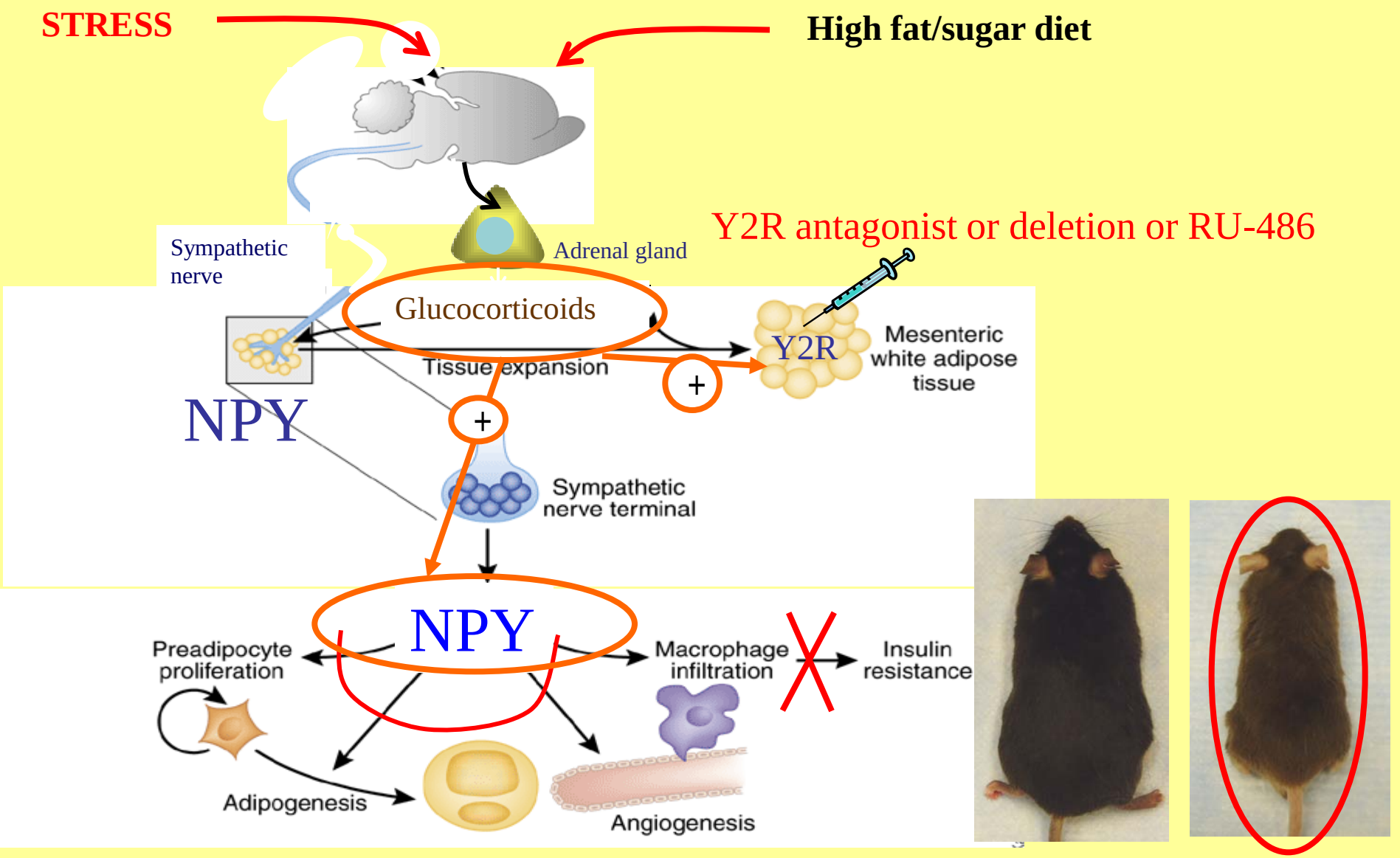


High fat, no stress

High fat + Stress

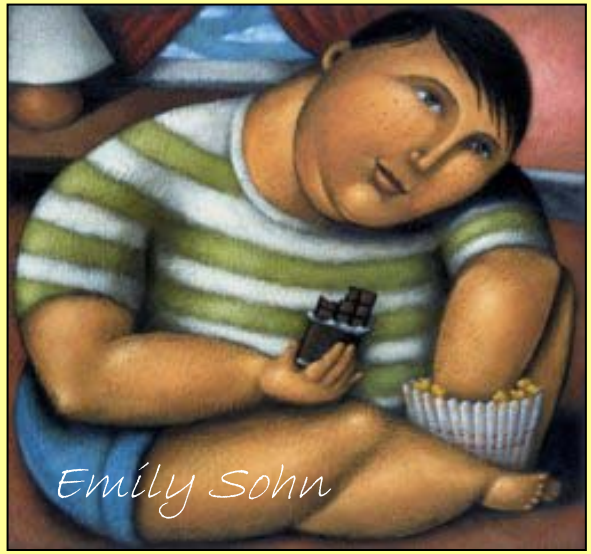
NPY: a missing link between stress and weight gain

(Kuo et al., 2006, Nature Medicine; Zukowska laboratory)



Deployment

Readjustment??



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%

Diagnosis	% with Metabolic Syndrome
PTSD (CAPS ≥ 65)	34%
MDD	29%
PTSD/MDD	46%

The Not-Paradoxical Link Between PTSD and Metabolic Syndrome

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 allopgregnanolone 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-hydoxylated 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)**

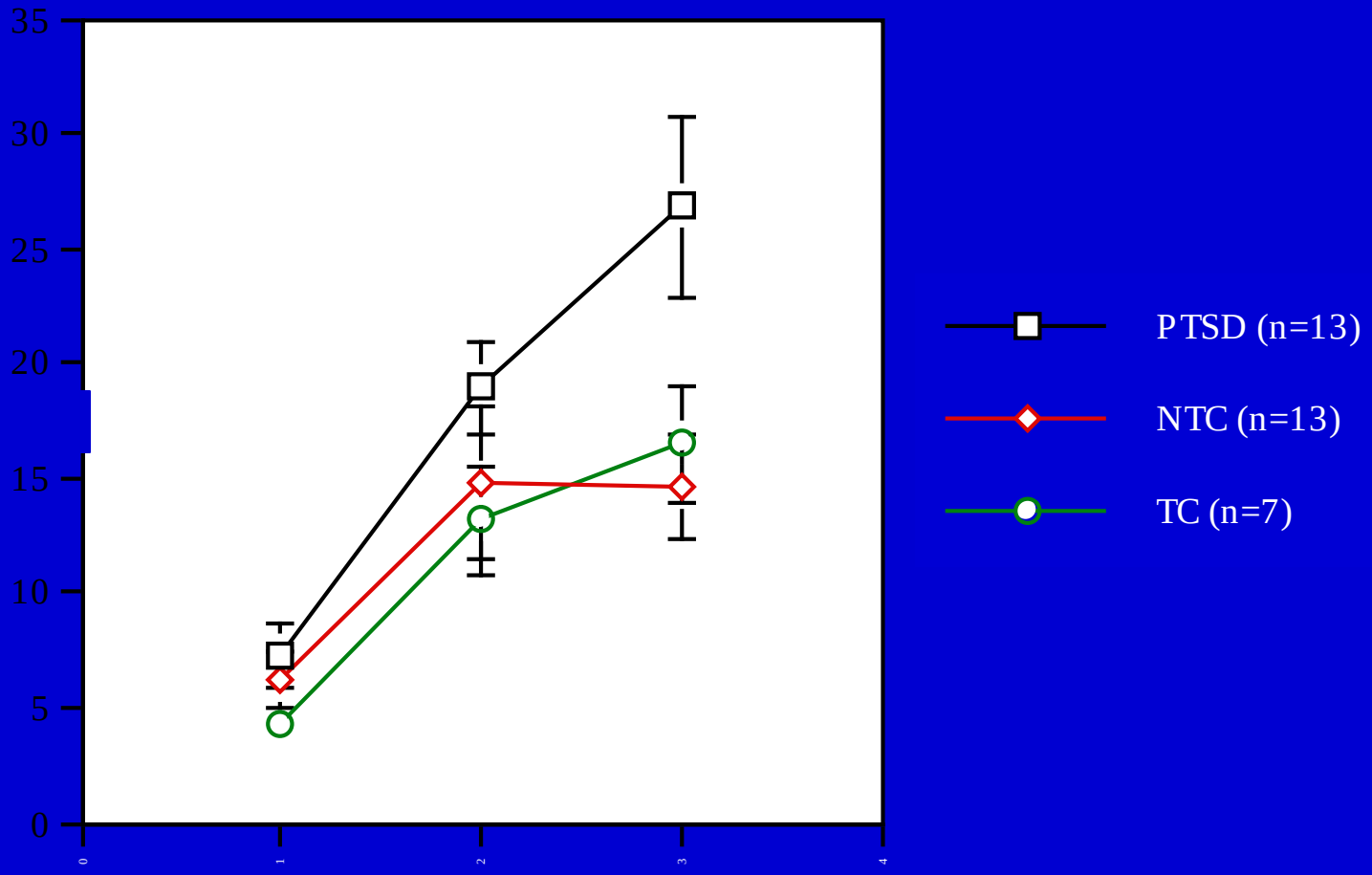
•Reverses decrements in LTP induced by cortisol

•(Kaminska et al 2000)

•Regulates programmed cell death (Zhang et al 2002) and promotes neurogenesis (Karishma et al 2002)

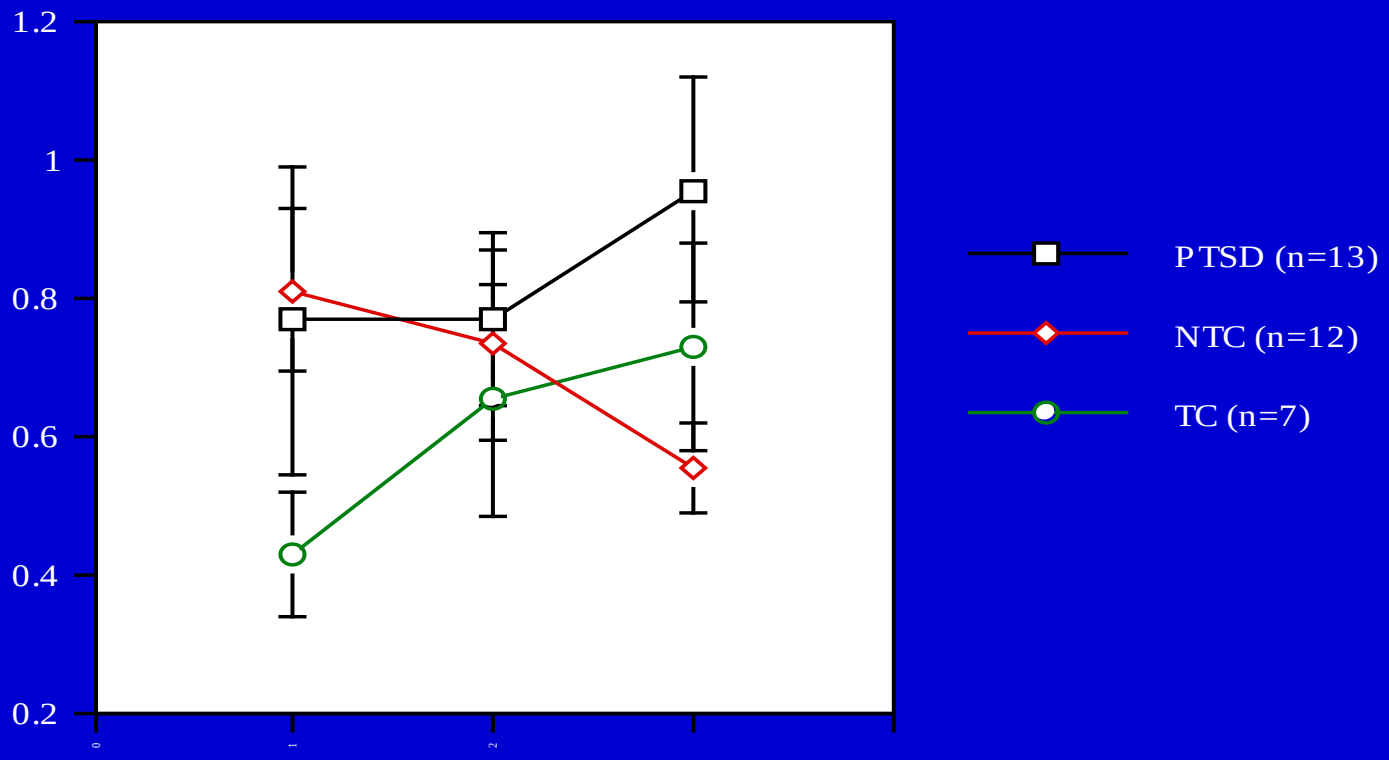
DHEA Response to ACTH $_{1\text{-}24}$

Time x Diagnosis Effect: $F(4,59)=2.96$, $p<0.03$



DHEA/Cortisol Change after ACTH $_{1\text{-}24}$

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

<u>total PTSD symptoms</u>: 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:

$$r = -0.81, p < 0.0009.$$

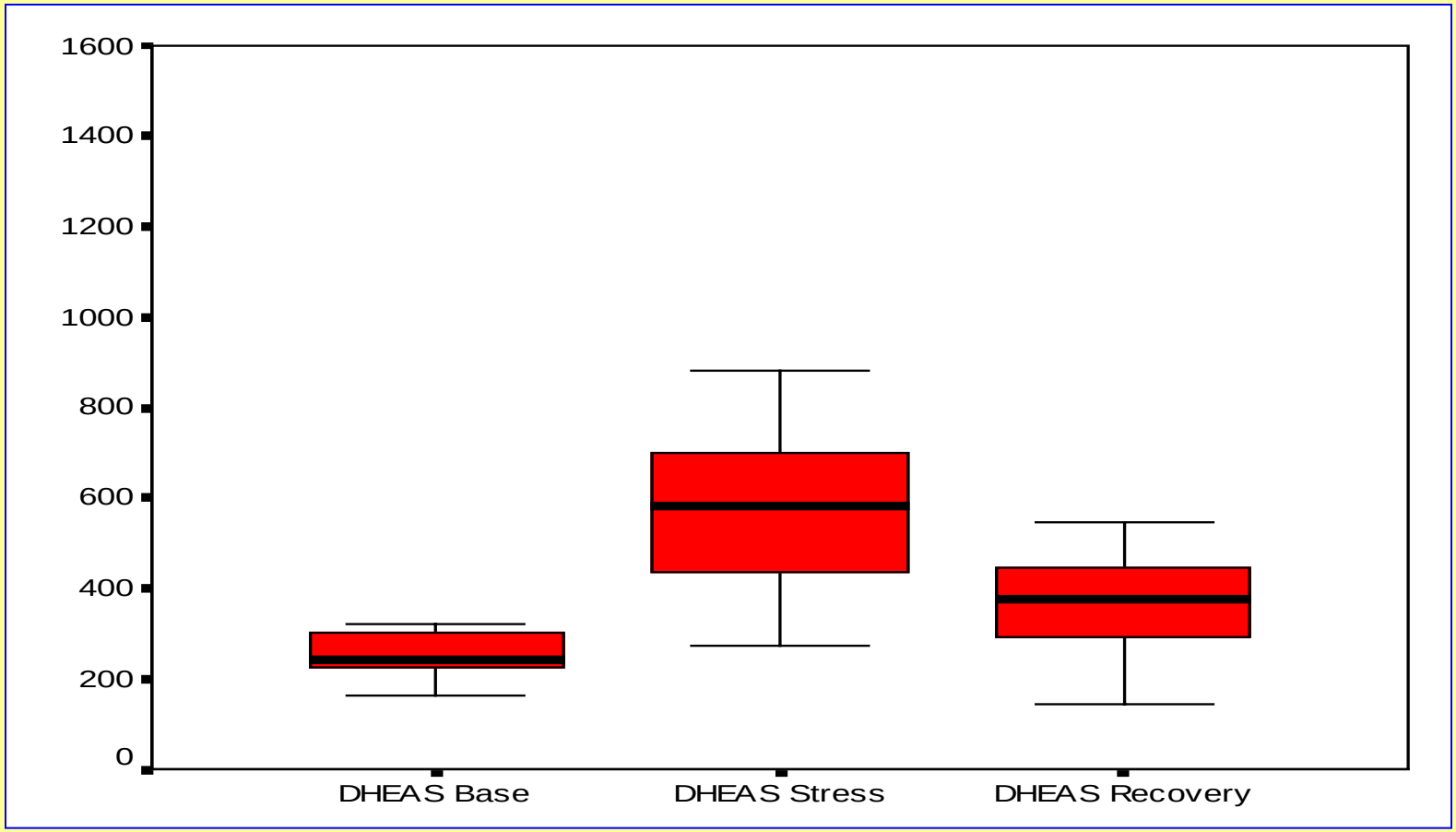
*So even under conditions of sleep deprivation, maladaptive PTSD symptoms are lower in persons with higher DHEA release.

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: $r = -0.63$, $p < 0.04$

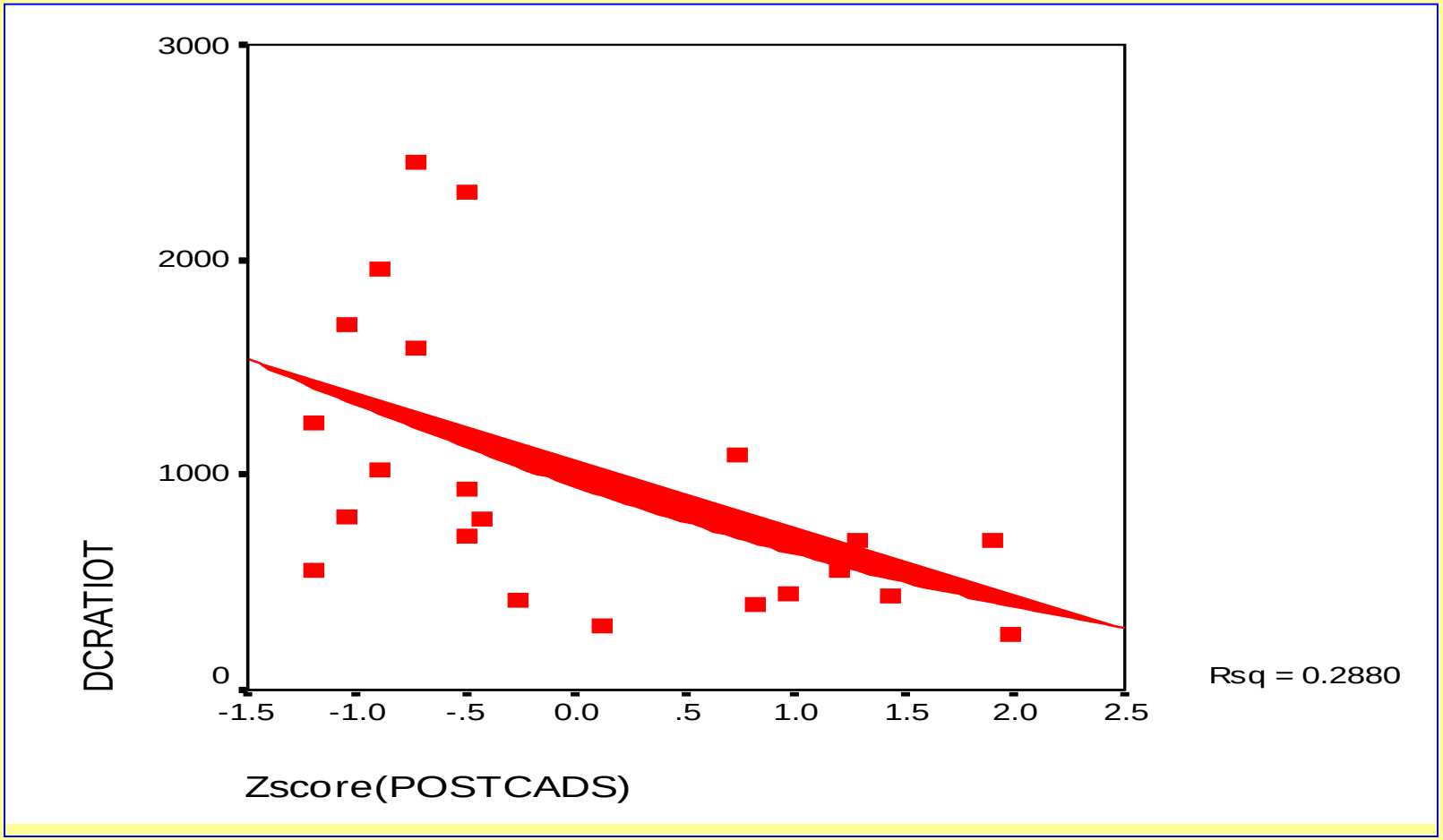
*Laboratory study: ACTH given IV to women with and without PTSD.

DHEA(S) and SERE School Interrogation Stress Exposure

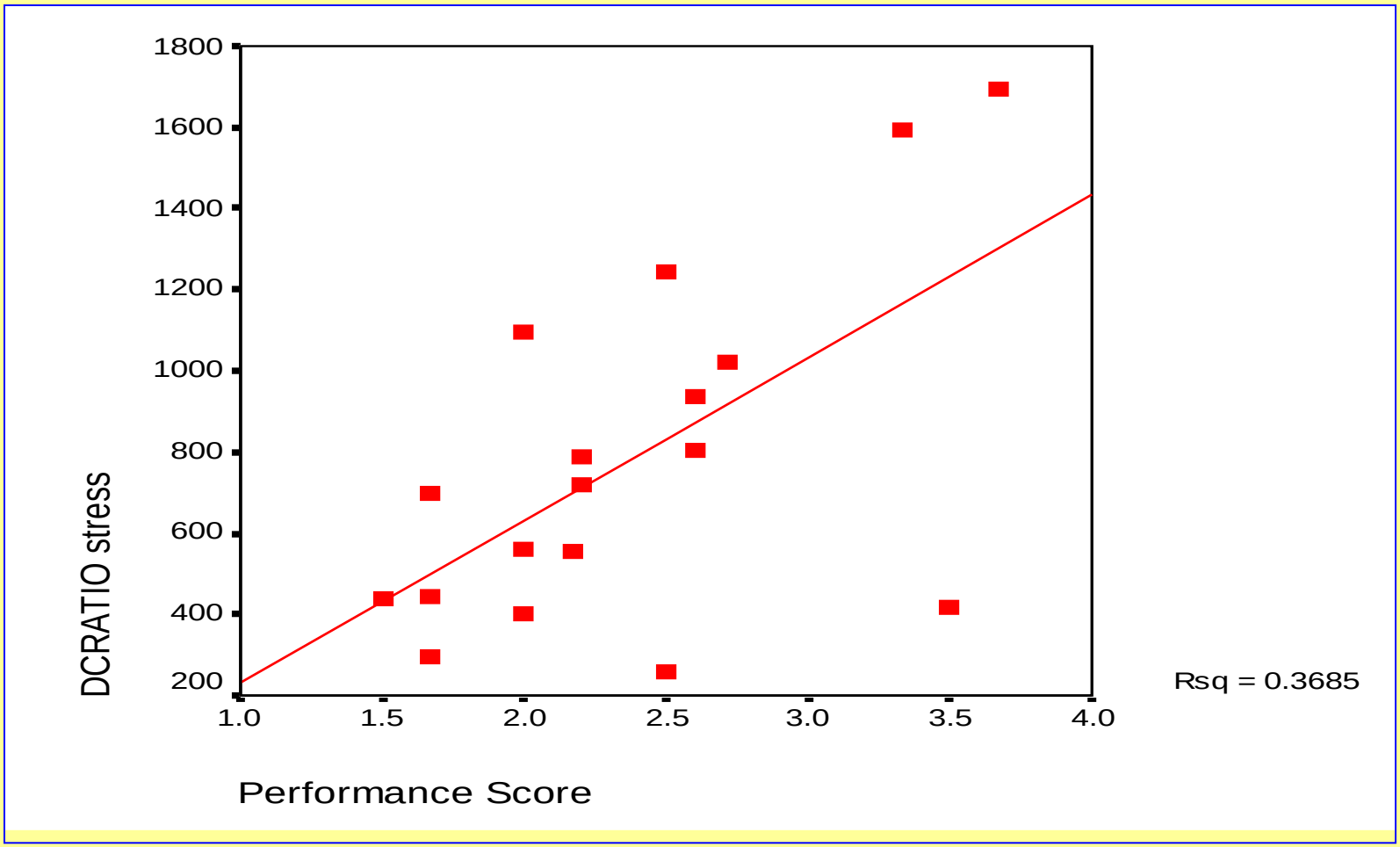


DHEA(S)/Cortisol Ratio and Symptoms of Dissociation in Response to Interrogation Stress

Morgan et al., Arch Gen Psychiatry, 2004



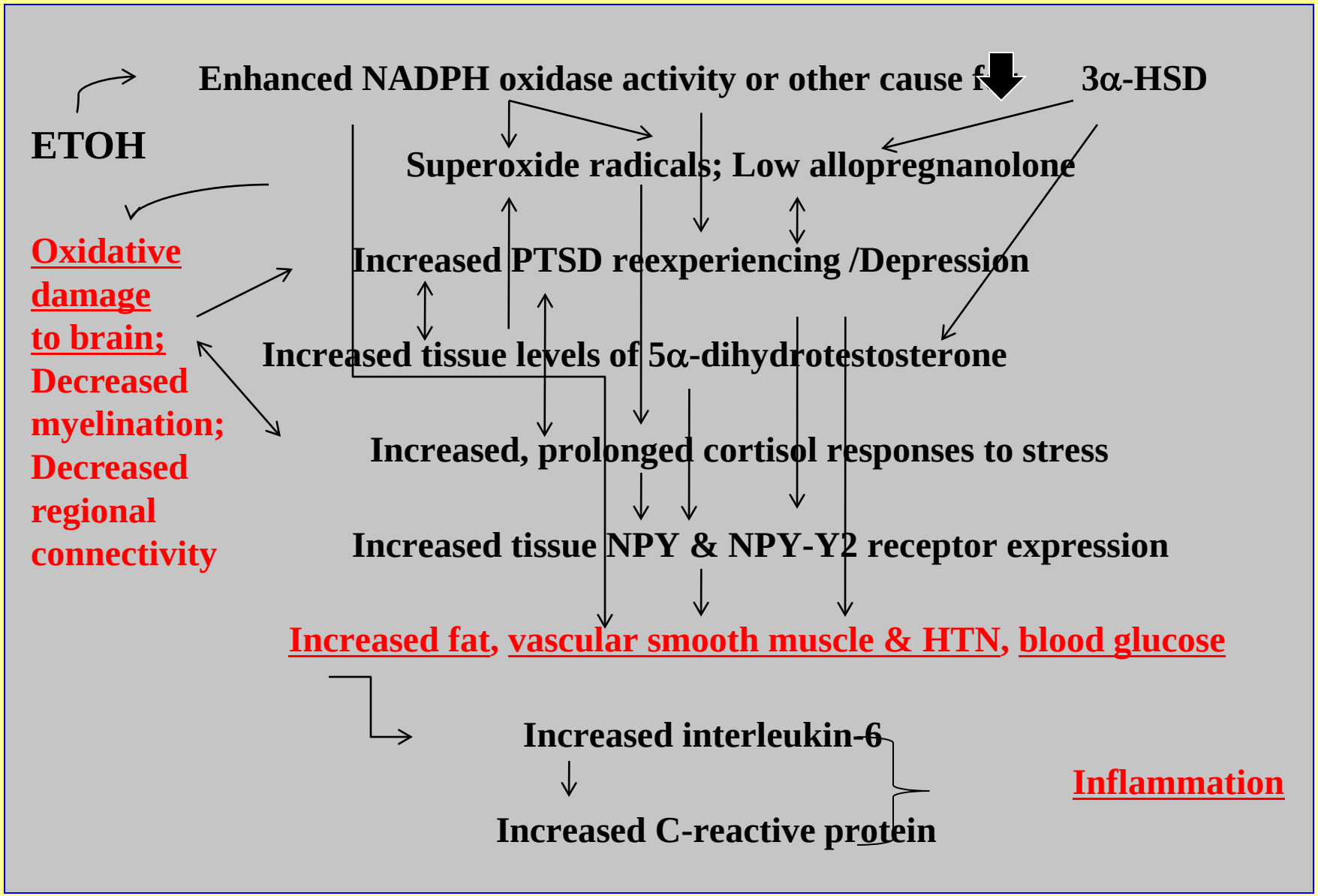
DHEA(S)/Cortisol Ratio and Objective Military Performance



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



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.

General take home from past 15 years of research. . .

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)

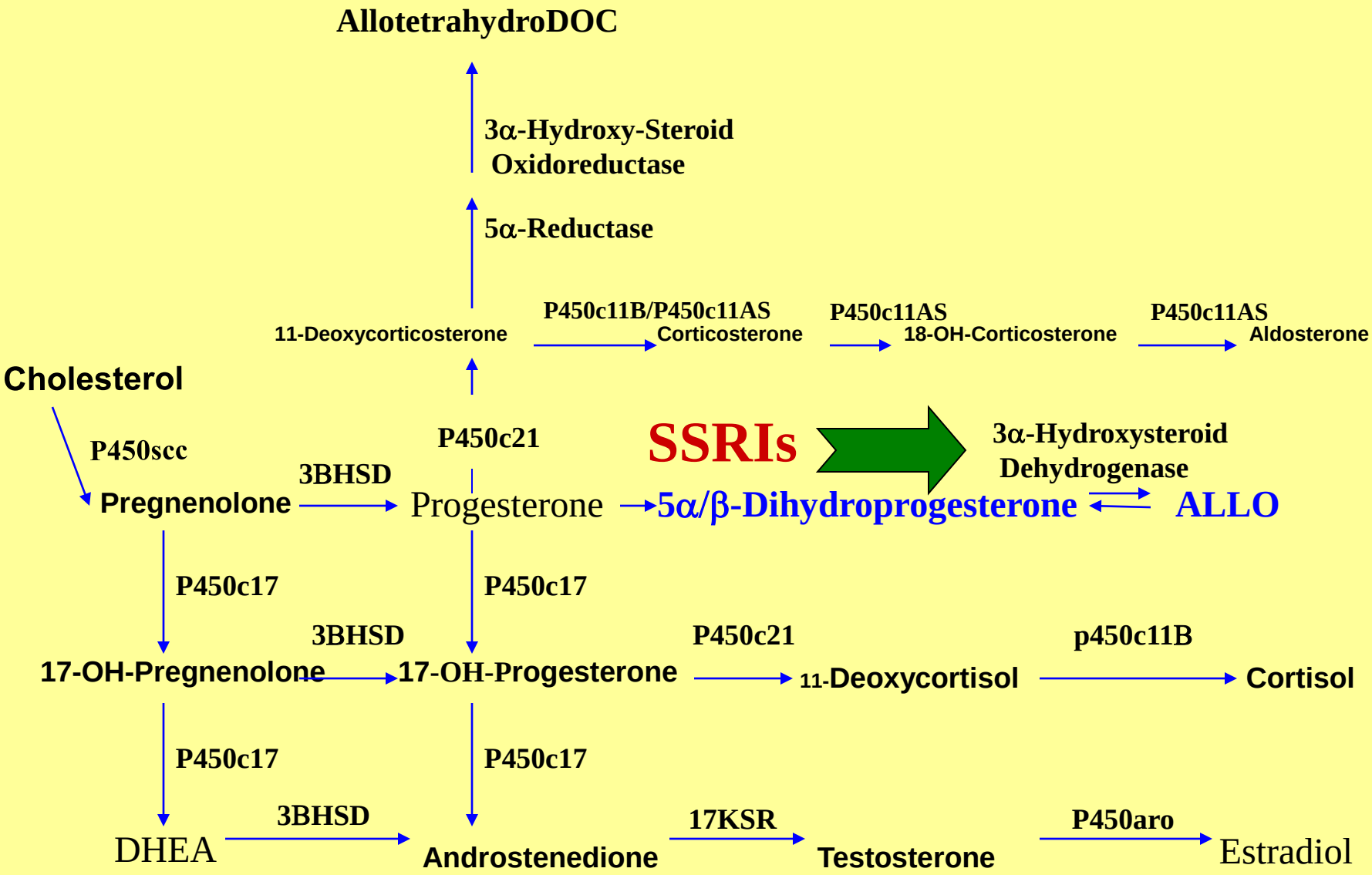
a) Genetic studies should look at genes in context of mechanistic systems (e.g., high output NPY gene polymorphism could be effectively countered by a particular NPY-Y2 receptor gene with regard to risk for metabolic syndrome. Such could account for the contradictory genetic studies that abound.

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.

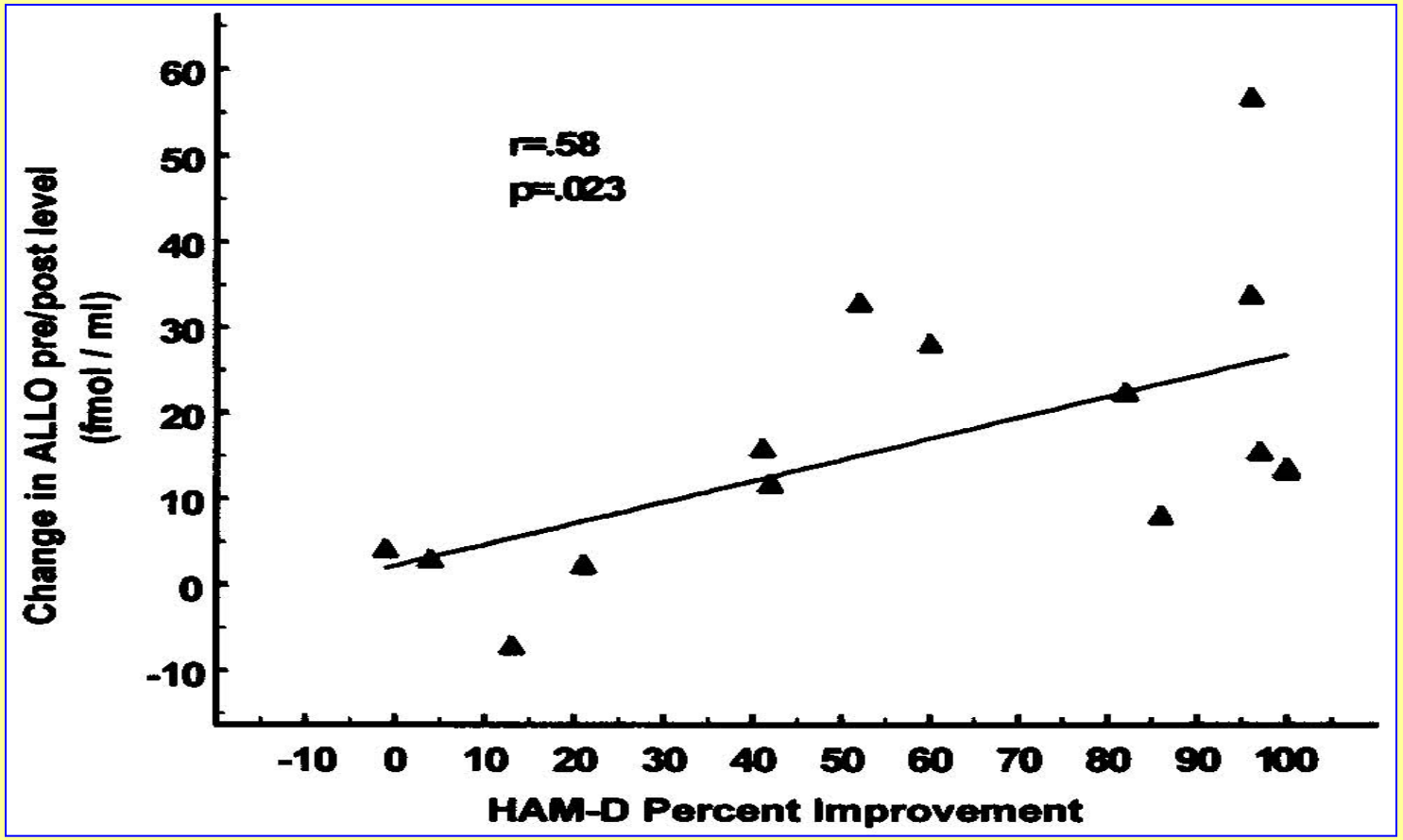
b) Towards gender-based, individualized medicine . . .

Neuroactive Steroid Synthetic Pathways



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.