Relationship Between Stress and Substance Use Disorders: Neurobiologic Interface

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Thanks to My Colleagues and NIH

Traumatic Exposure Common in the Lives of Individuals with SUDs

Clinical Evidence for Stress-Relapse Connection

- Intuitive appeal, but methodologic issues
  - Definition of stressor
  - Causal relationship difficult to establish
- Childhood adverse events strongly associated with SUD's
- PTSD, mood/anxiety disorders strongly associated with SUD's

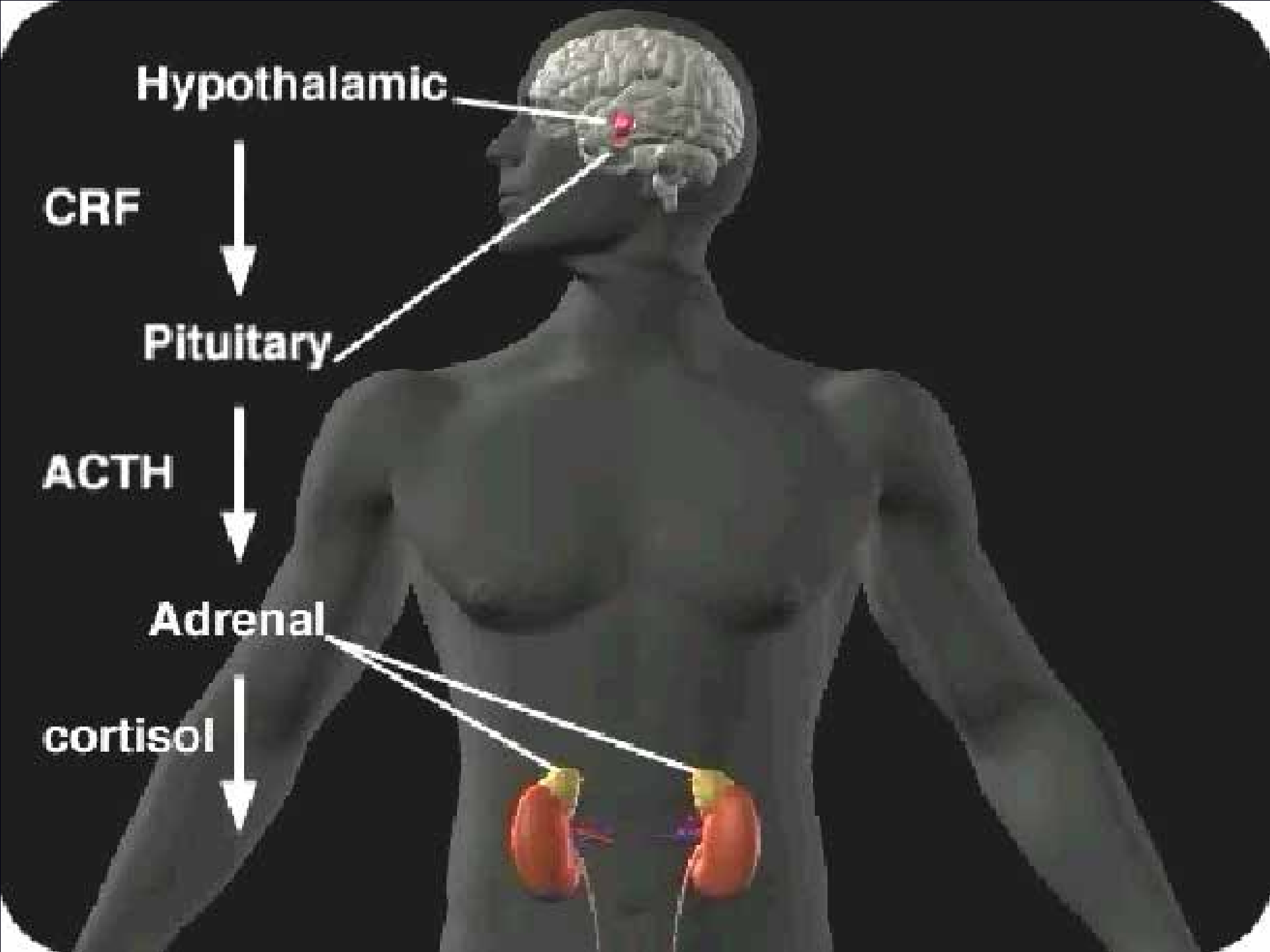
PTSD and Substance Use Disorders

- Treatment seeking individuals
  - PTSD - 30-40 % have substance use disorders
    - maybe higher in combat-related PTSD
  - Substance use samples - 20-60% have PTSD - higher in women, cocaine/opiate users
- Epidemiologic data
  - Significantly increased odds ratios

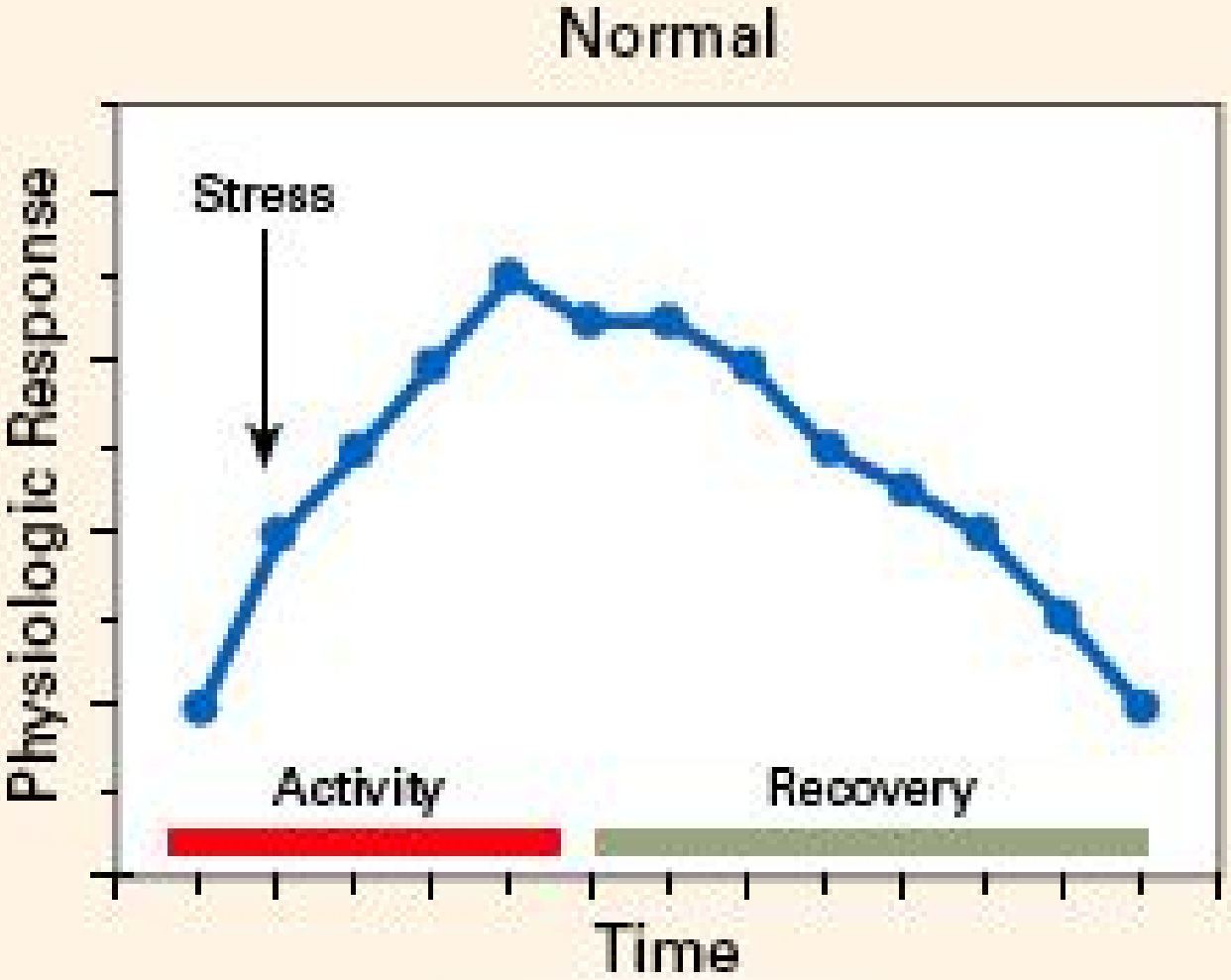
Non-Random Association

Neurochemical Response to Stress

- Hypothalamic-Pituitary-Adrenal axis
- Extra-Hypothalamic CRH systems
- Locus Coeruleus-Norepinephrine
- Dopamine Systems
- Serotonin Systems
- GABA Systems
- Glutamate Systems


Hypothalamic
CRF
Pituitary
ACTH
Adrenal
cortisol

Adaptive Allostatic Response



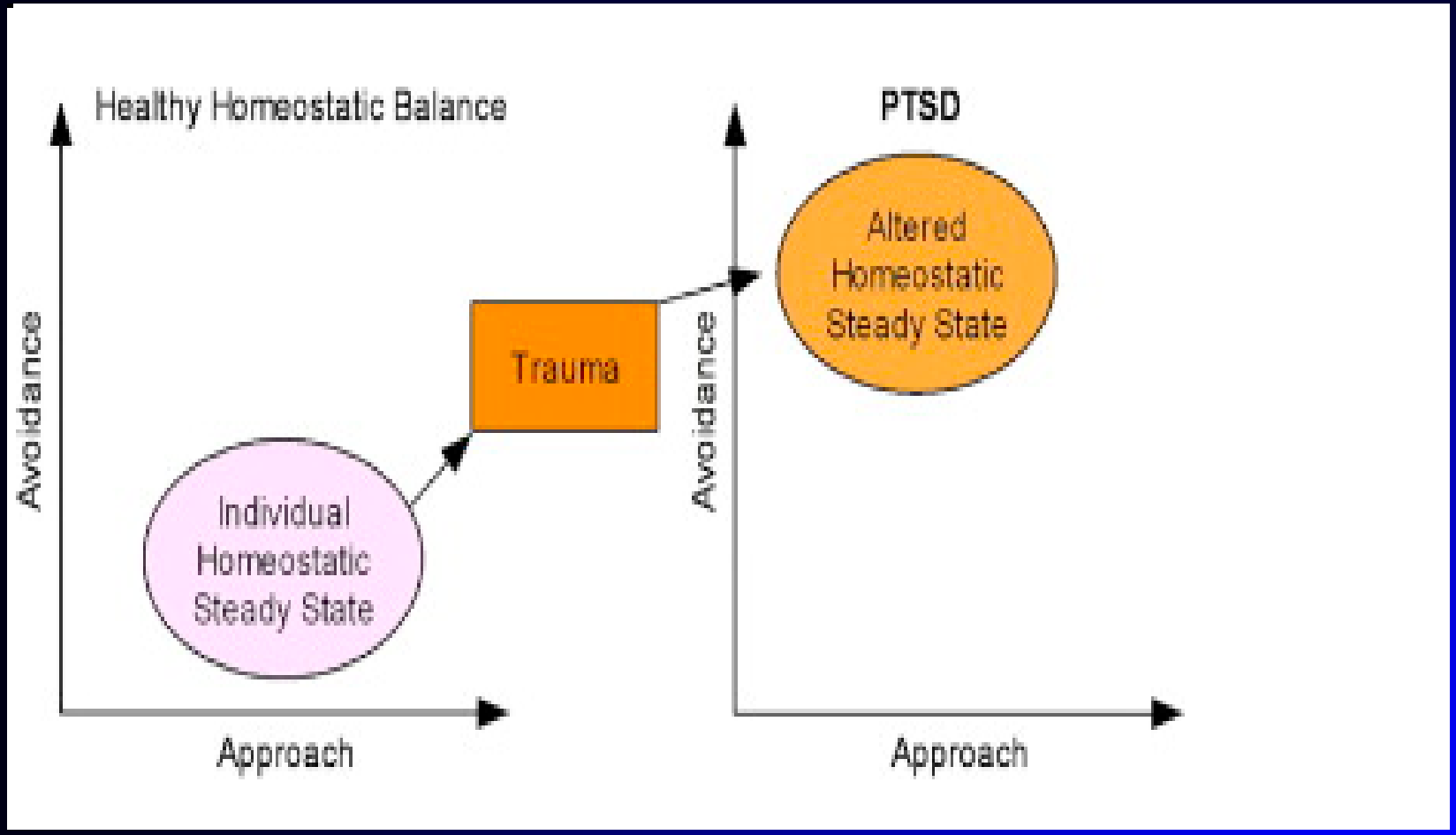
McKewen, B. *NEJM* 1998; 338:171-79

Stress Response
Allostasis vs. Homeostasis

- Homeostasis - tightly controlled physiology parameters
- Allostasis - Adaptive response to stress
  - Recruitment of all available physiological, psychological and behavioral resources

McKewen,B. NEJM 1998;338:171-79

Homeostasis versus Allostasis




Old Style
www.jemsmamv.com

Animal Models of Relapse: Reinstatement (Relapse)

- Resumption of previously drug-reinforced behavior by non-contingent exposure to drug or non-drug stimuli
  - Self-administration training
  - Extinction
  - Test for reinstatement under various conditions
    - » deWit and Stewart, 1981;
    - » Psychopharmacology (2003), Volume 168

Reinstatement Models

- Drug-primed reinstatement: low dose drug administration
- Cue-induced reinstatement: environmental cues associated with drug use
- Stress-induced reinstatement: foot shock, forced swim, isolation, immobilization, etc.

Stress-Induced Reinstatement: Pharmacologic and Surgical Manipulation

- Blocked by CRF antagonists
- Induced by CRF agonists
- Blockade of B-receptors in amygdala and BNST blocks stress-induced reinstatement
- Increased by amount of previous drug exposure
- Cue-induced reinstatement increased by stress

Stress Response in Drug Dependent Individuals

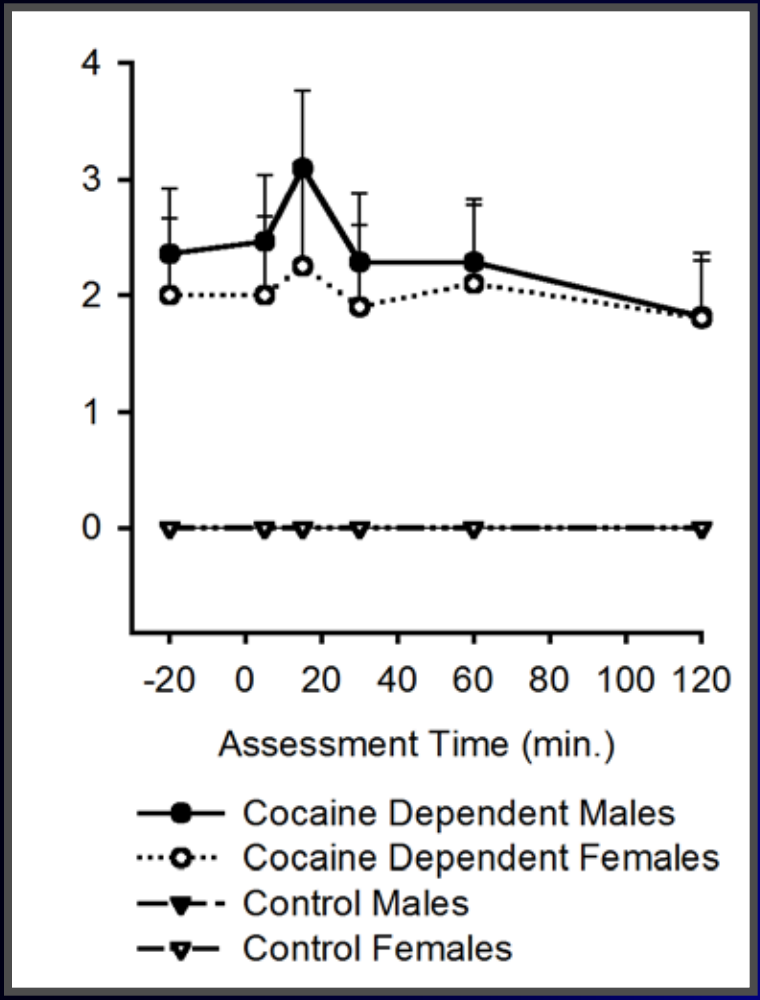
- Acute withdrawal from all drugs of abuse - activation of HPA axis
- Dysregulation of HPA axis/abnormal stress response persists for weeks to months
- ? Dysregulation associated with early life trauma
- ? Role of dysregulation in drug craving/relapse

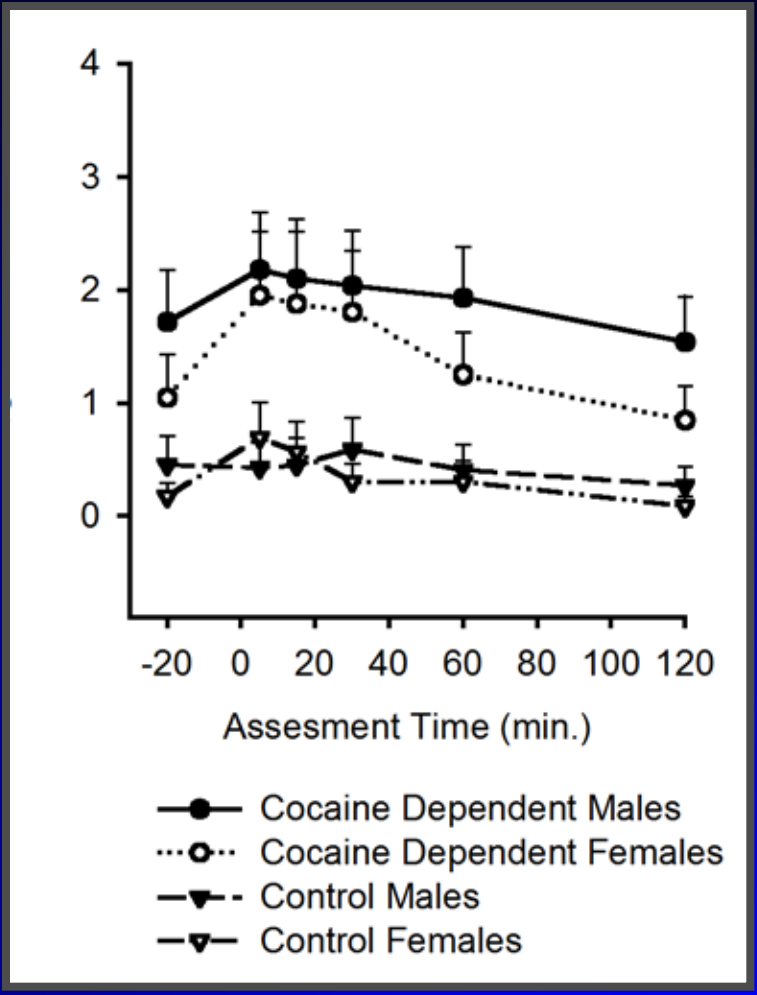
» Kreek and Koob, 2006

Human Laboratory Studies

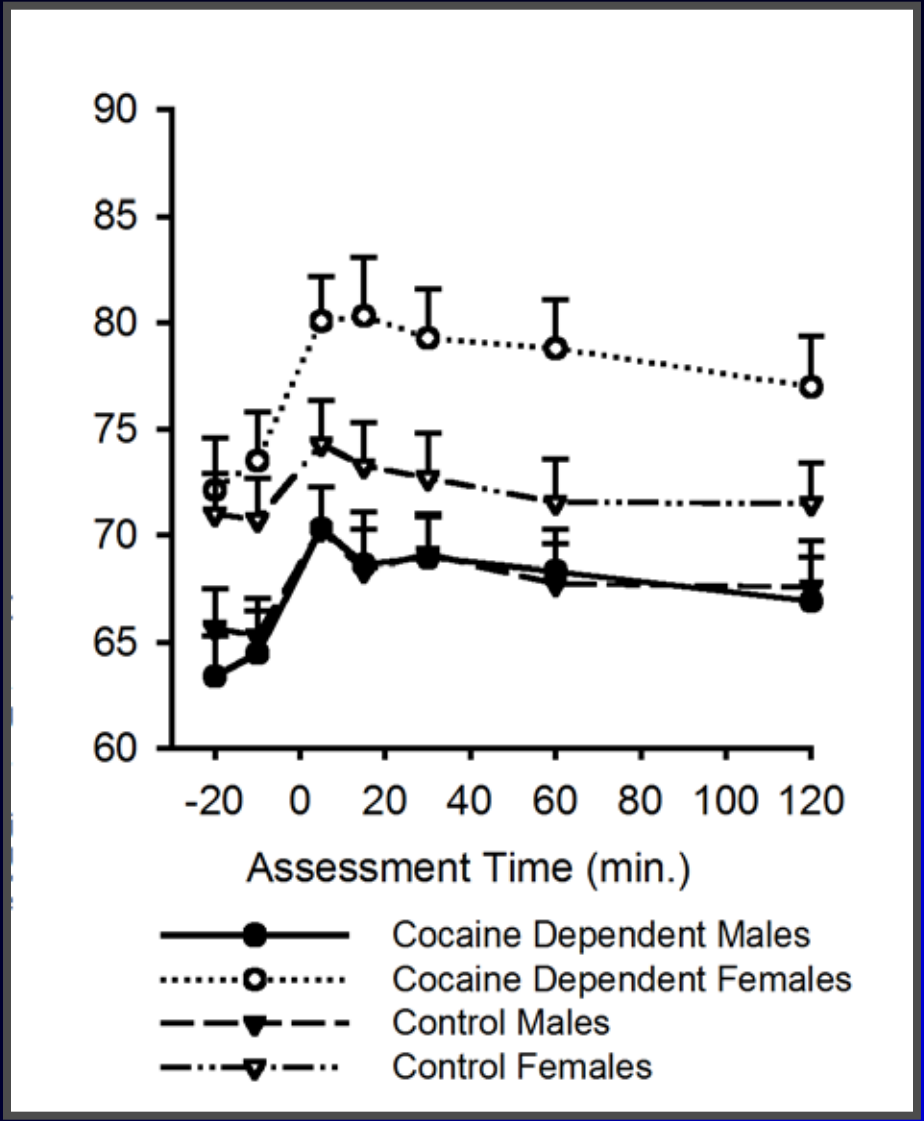
- Stress Exposure
  - Psychological - Trier
  - Physical – Cold Pressor
  - Pharmacologic – CRF, Yohimbine
- Drug-cue Exposure
- Measurement
  - Craving (proxy for use)
  - ACTH/cortisol
  - Physiologic parameters

Craving and Stress Increase in Response to CRF





Heart Rate Responding to CRF



(Cocaine x Gender: $P = 0.05$)

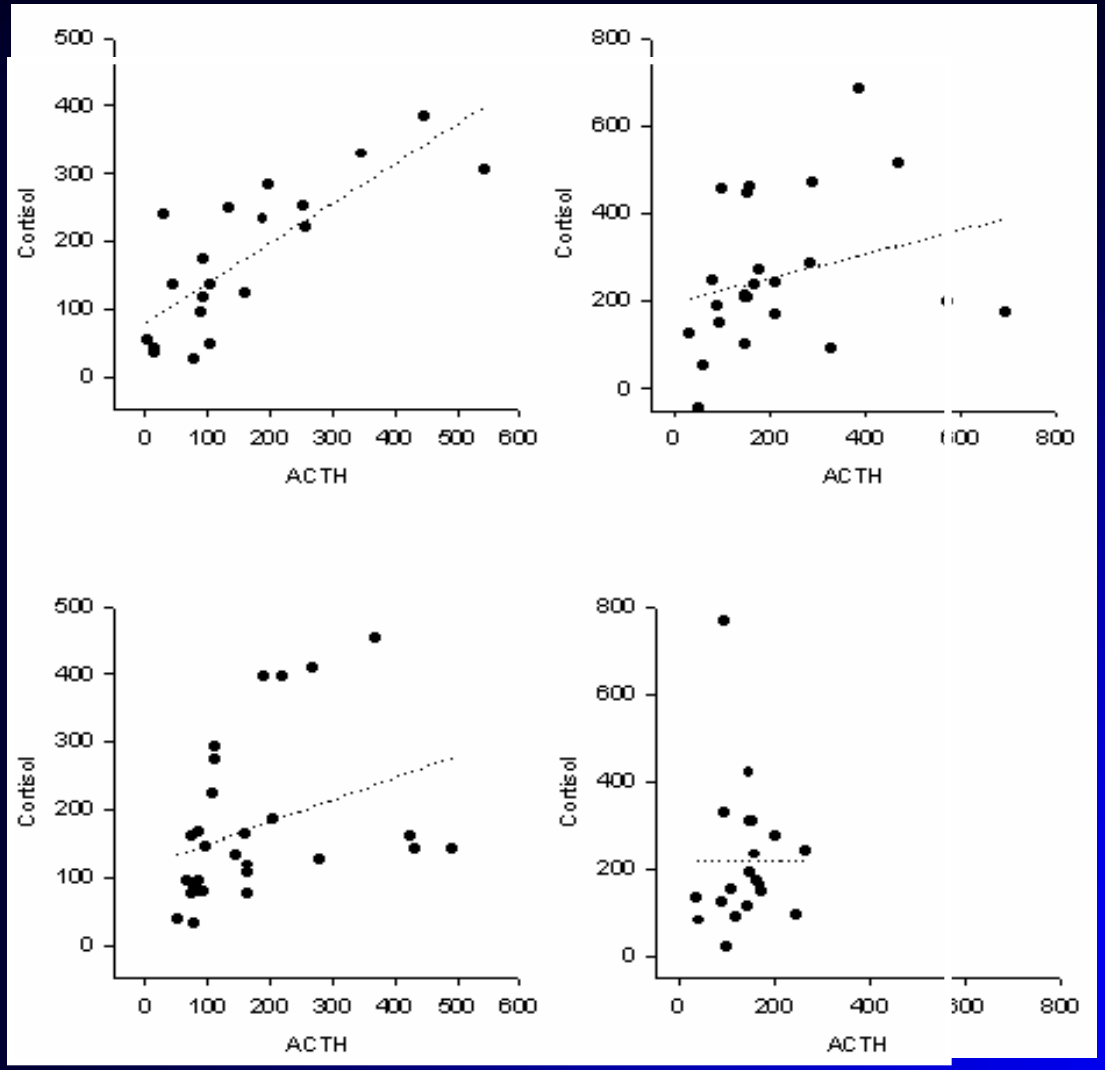
Correlation Between ACTH and Cortisol in Cocaine Dependence

Control Males

Control Females

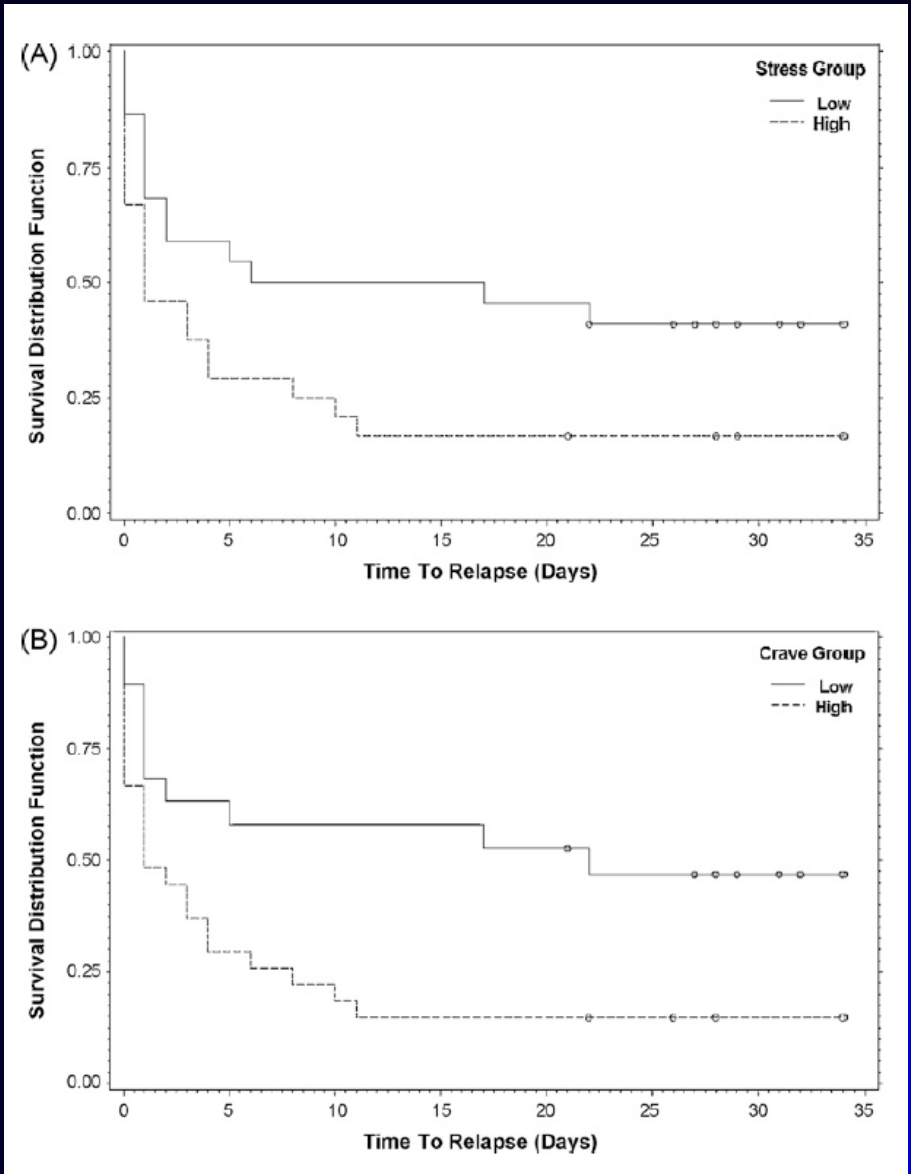
Cocaine Dependent Males

Cocaine Dependent Females



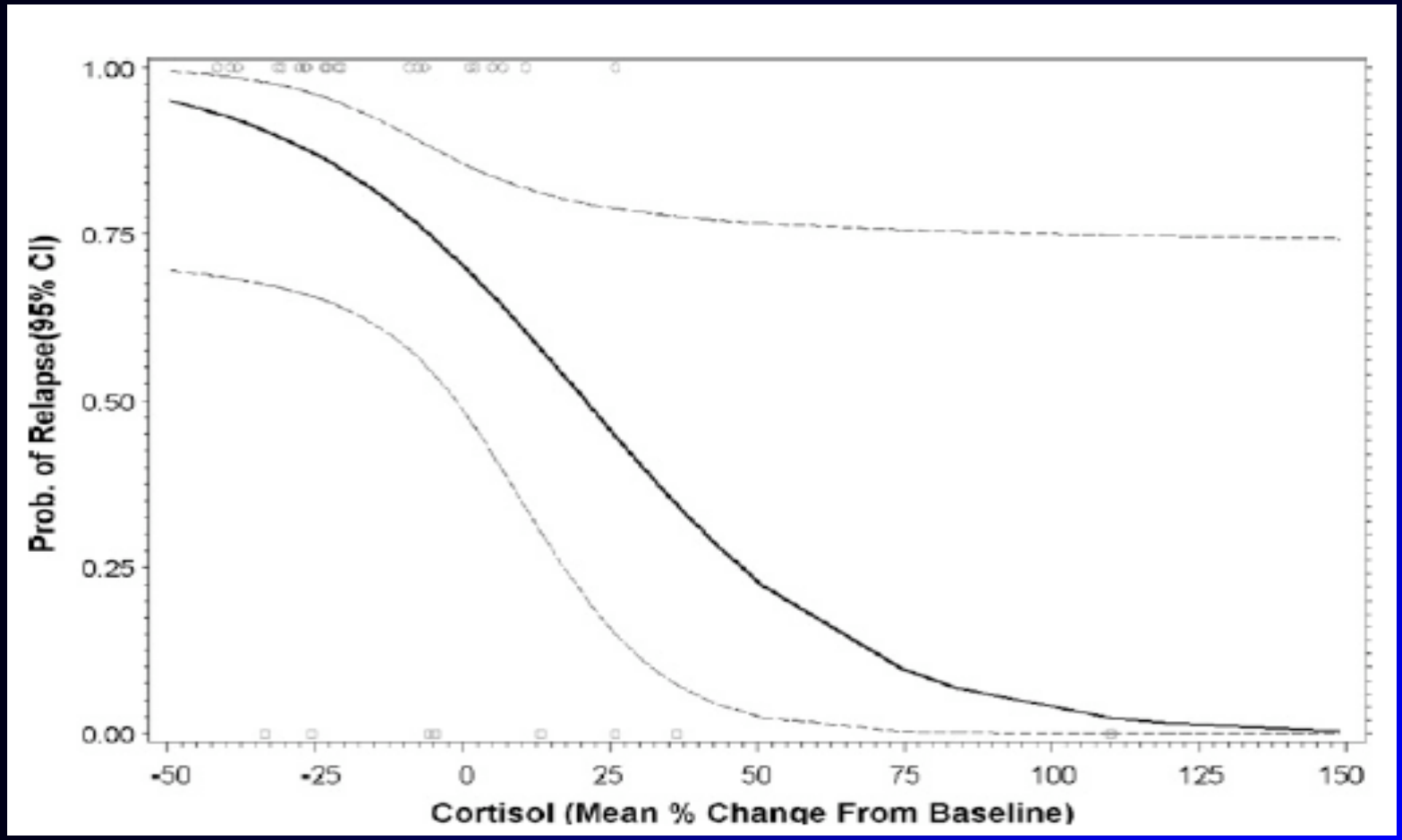
Relationship Between Stress Response and Relapse???

Relationship Between CRH-induced Craving/Stress and Relapse



Back et al., 2010

Probability of Relapse Based on % Cortisol Change from Baseline



CONCLUSIONS

- Elevated craving and stress to CRH and drug cues associated with relapse

- Attenuated ACTH/cortisol response to CRH associated with relapse

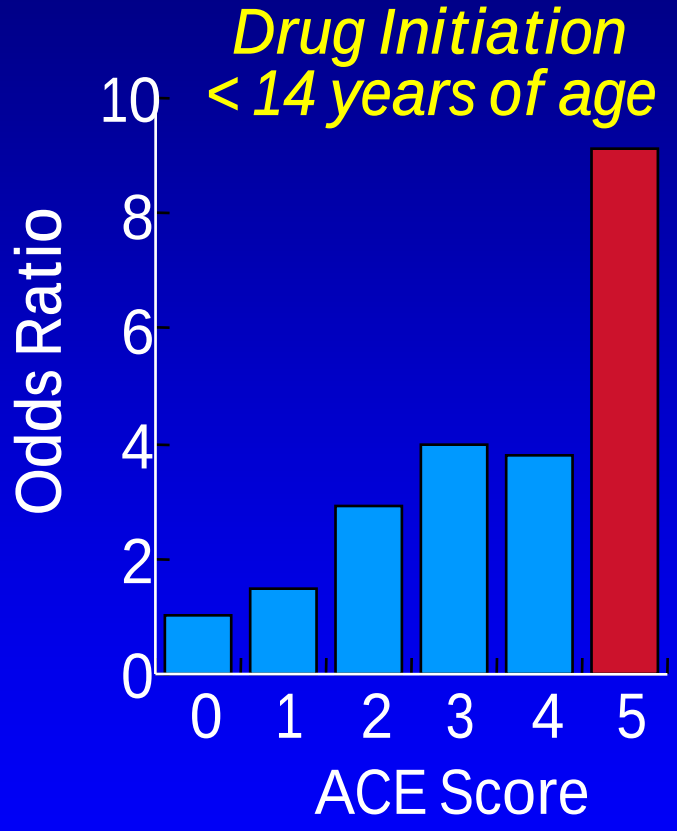
? Impact of Early Trauma on Stress Reactivity/Addiction

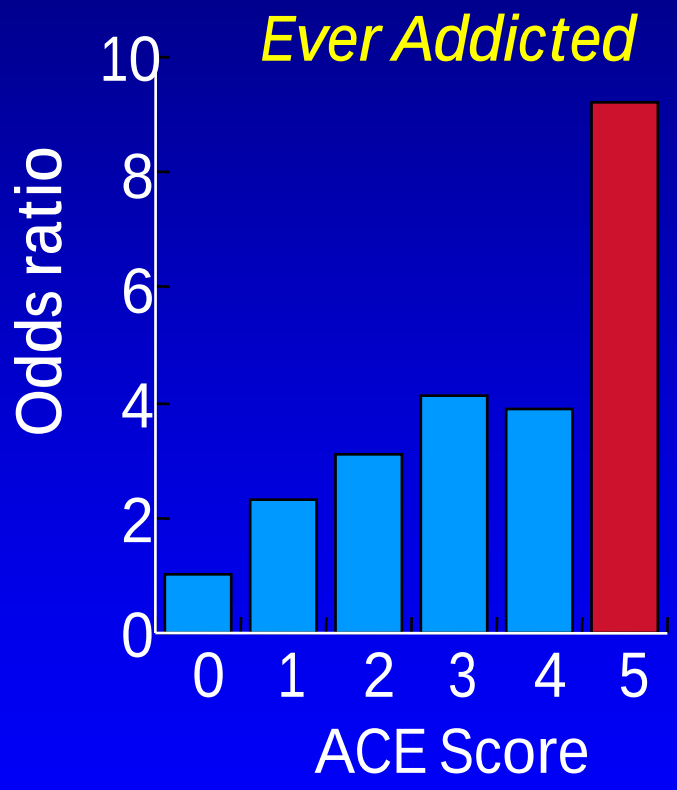
Childhood Sexual Abuse and Psychiatric Disorders in Women

- Abuse positively associated with a number of disorders
- Strongest relationship with alcohol/drug use
- More severe abuse increases risk
- Not explained by background/familial factors

Kendler et. al, 2000

Adverse Childhood Experiences (ACE) and Illicit Drug Use (n = 8603)

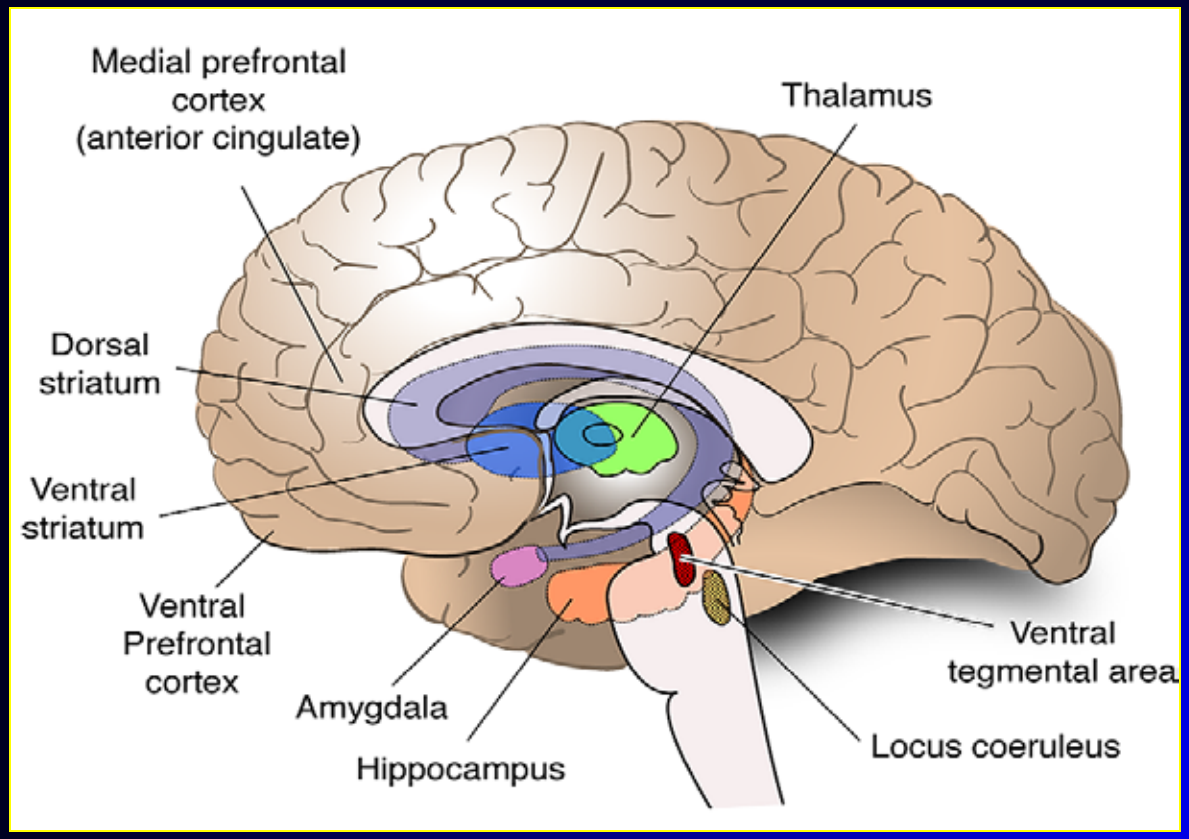




ACE account for one half to two third of serious problems with drug use.

PEDIATRICS 111: 564-572, 2003

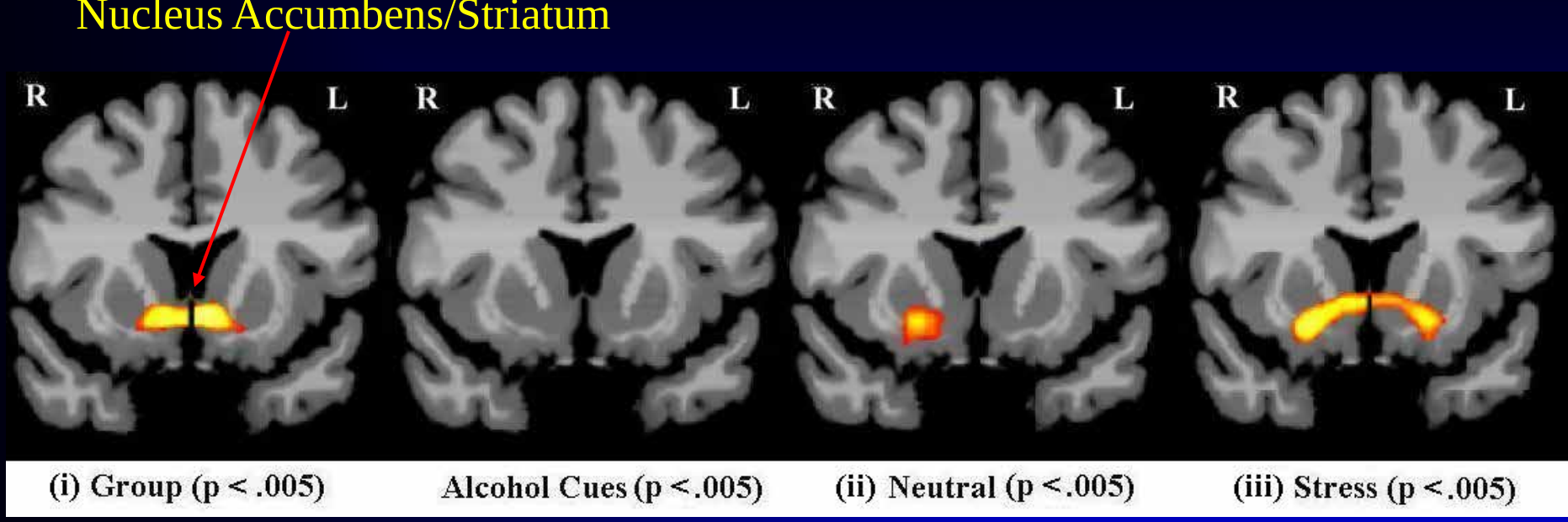
Does Stress Alter Reward Sensitivity before Development of Addiction?



Effects of Childhood Trauma on Reward Sensitivity (Jia et al.)

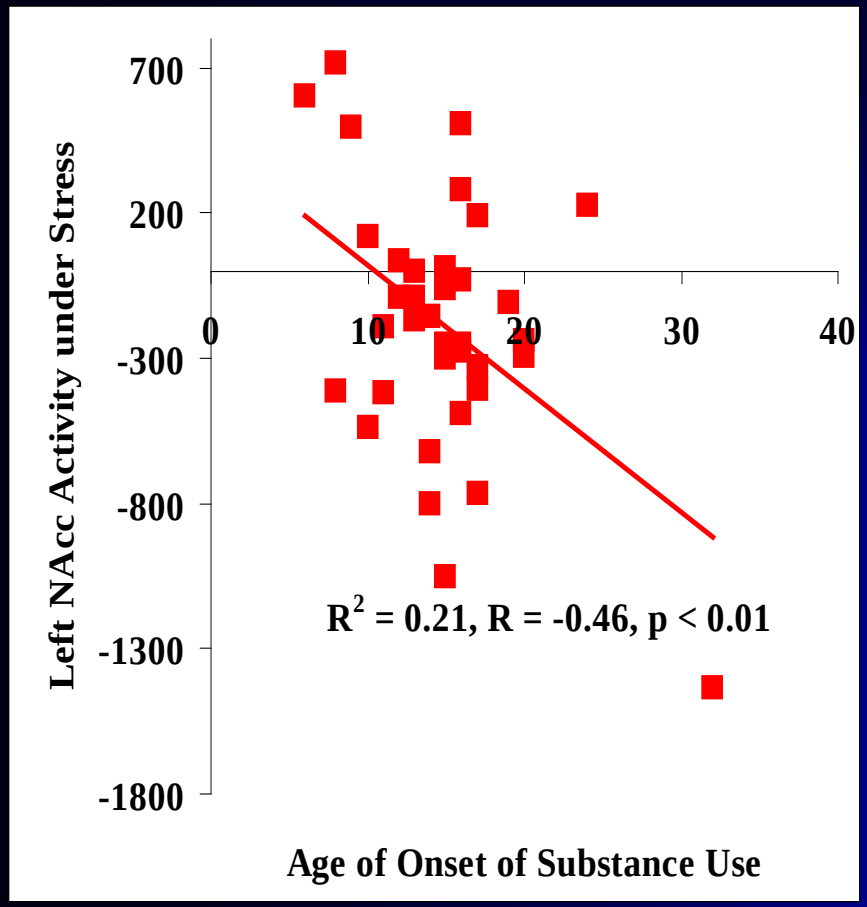
- 36 light to moderate social drinkers.
- Two risk groups (HR vs LR) on the basis of high and low ratings on Childhood Trauma Questionnaire (CTQ, Bernstein et al., 1998).
- Exposed to 2 stress, 2 alcohol cue and 2 neutral relaxed trials presented during fMRI

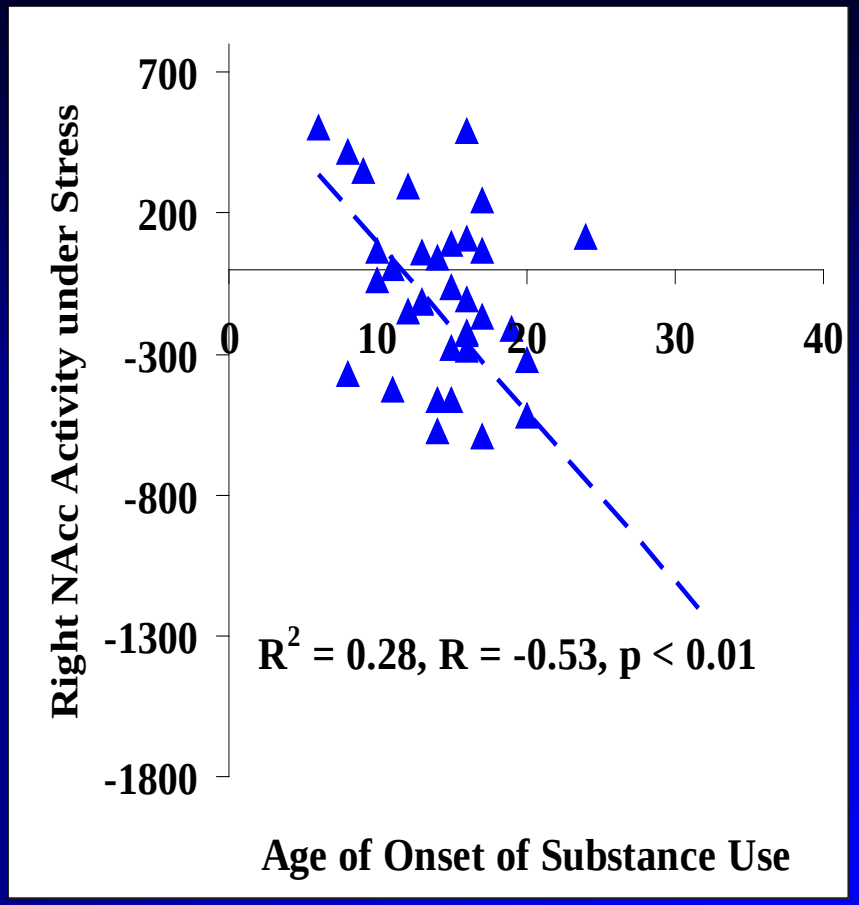
Neural Response to Stress in Healthy Adults with High vs Low Childhood Trauma



Individuals with greater childhood trauma (HR) showed greater nucleus accumbens/striatum (reward) activity with stress and with neutral relaxing stimuli compared to LR group. CTQ scores correlated positively with this NAcc activity ($p<.01$).

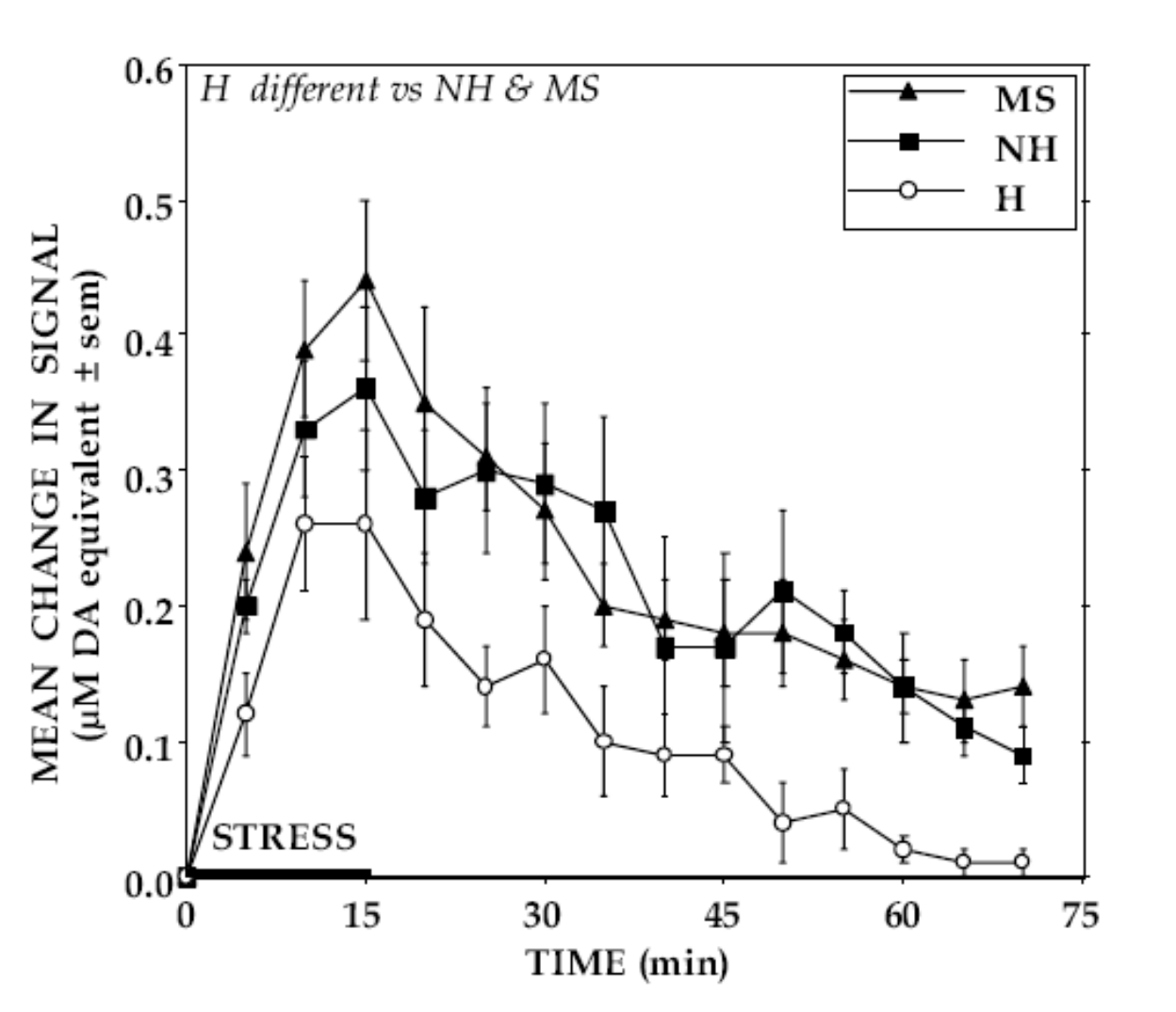
Significant Correlation between NAcc Activity (right) during Stress with Age of First Substance Use



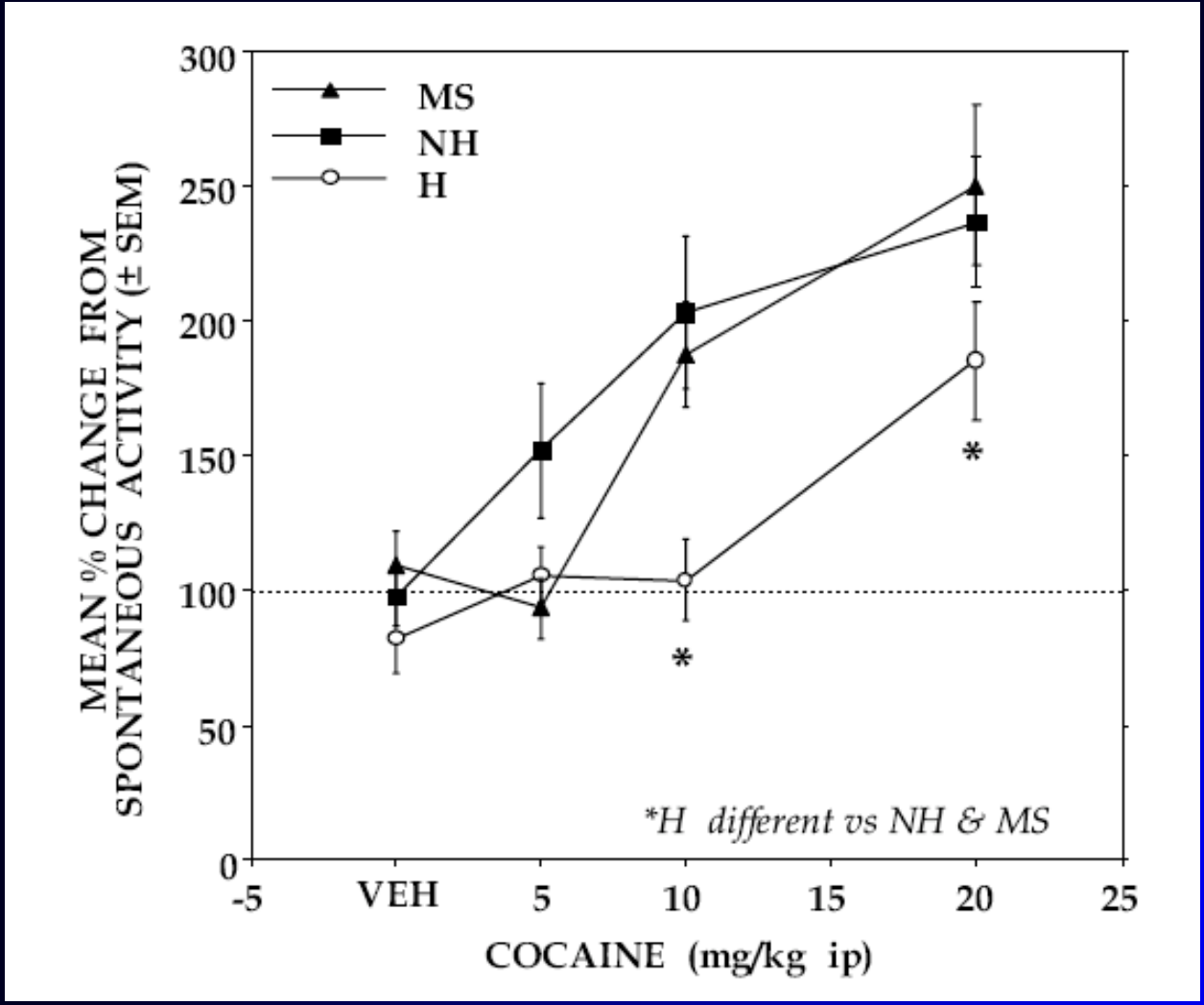


How do early experiences produce long-lasting changes in vulnerability to the development of addictions and other disorders??????

Mean Stress-Induced Changes in Dopamine Signals in Core Region of Nucleus Accumbens of Maternally Separated & Handled Animals



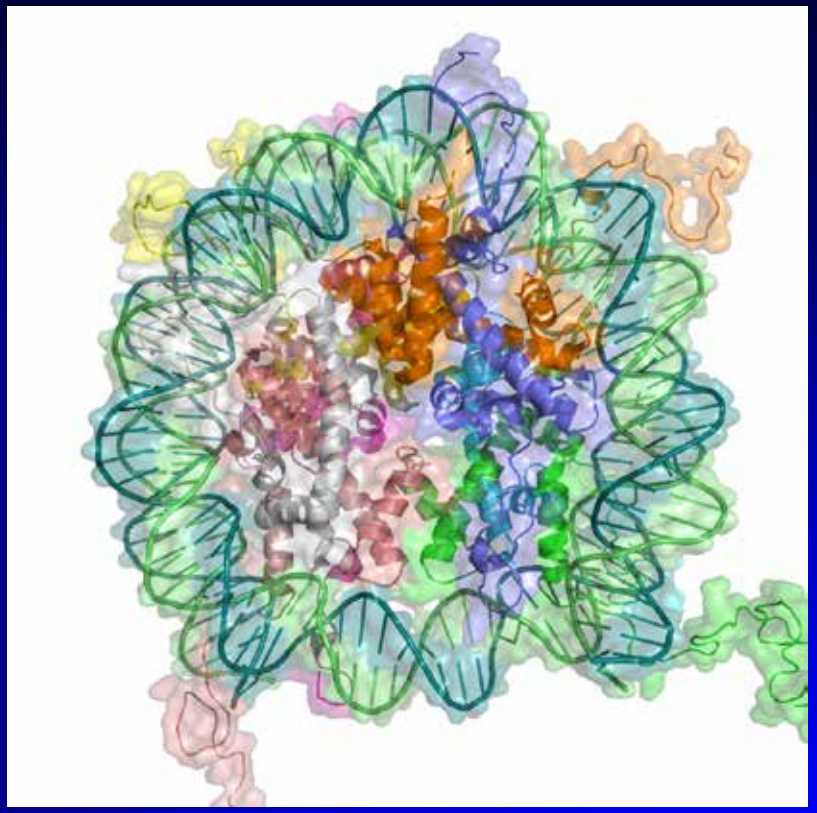
Mean Changes in Locomotor Activity following Injection of Saline or Cocaine



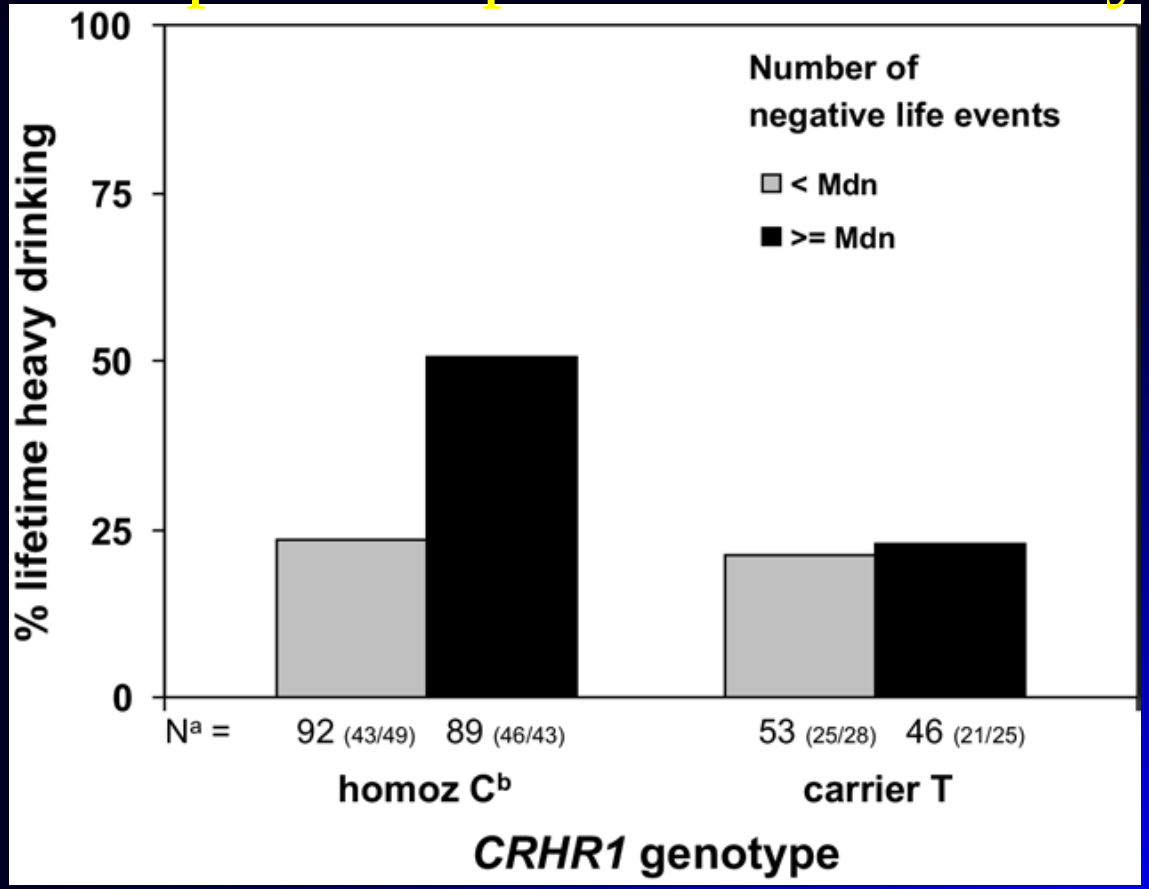
Brake et al.

Epigenetics

- Environmentally-induced changes in DNA expression
- Methylation, acetylation of histones impacts transcription
- Gene-by-environment interactions – CRF polymorphisms



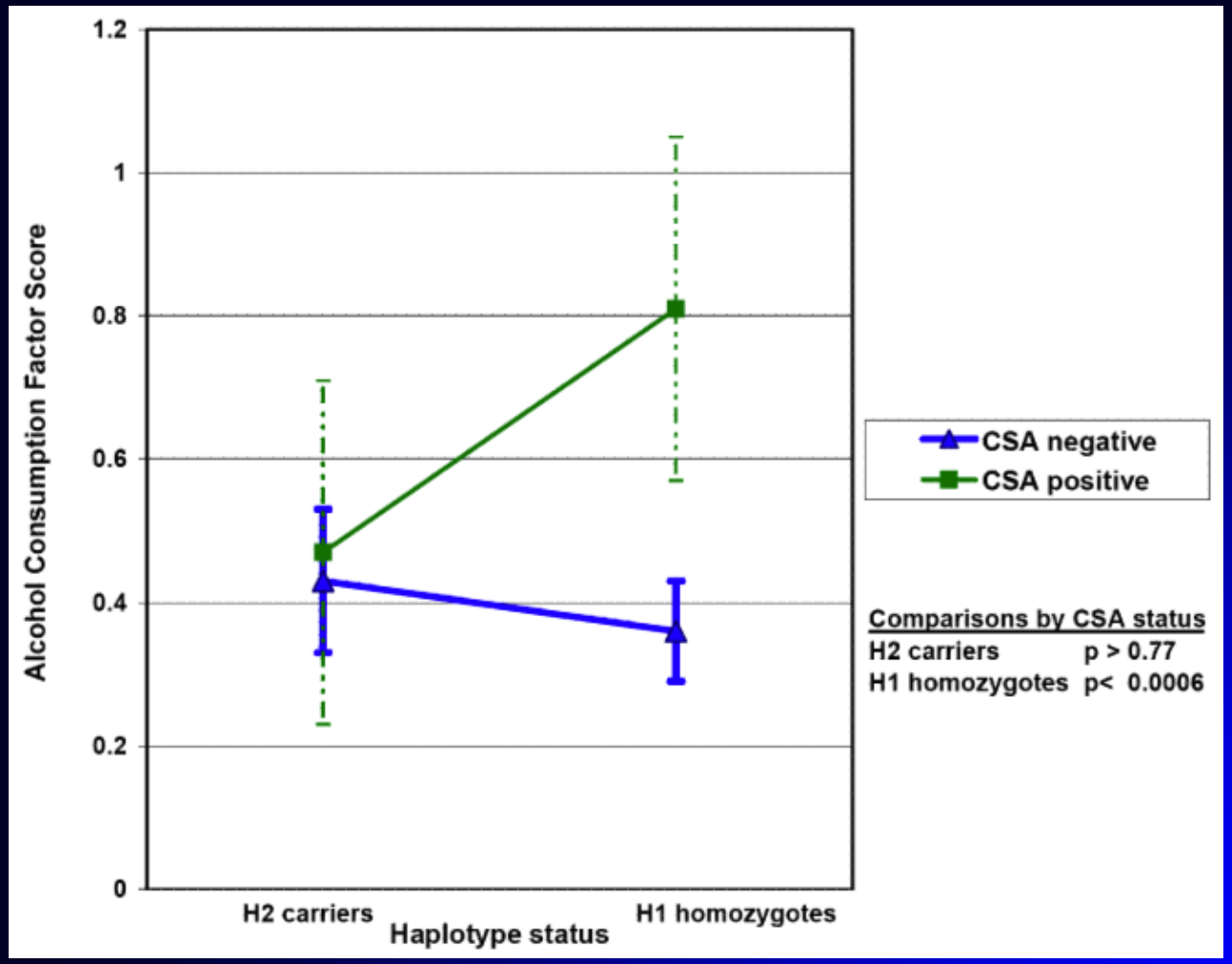
Impact of Negative Life Experience on Alcohol Consumption Depends on CRF Polymorphism



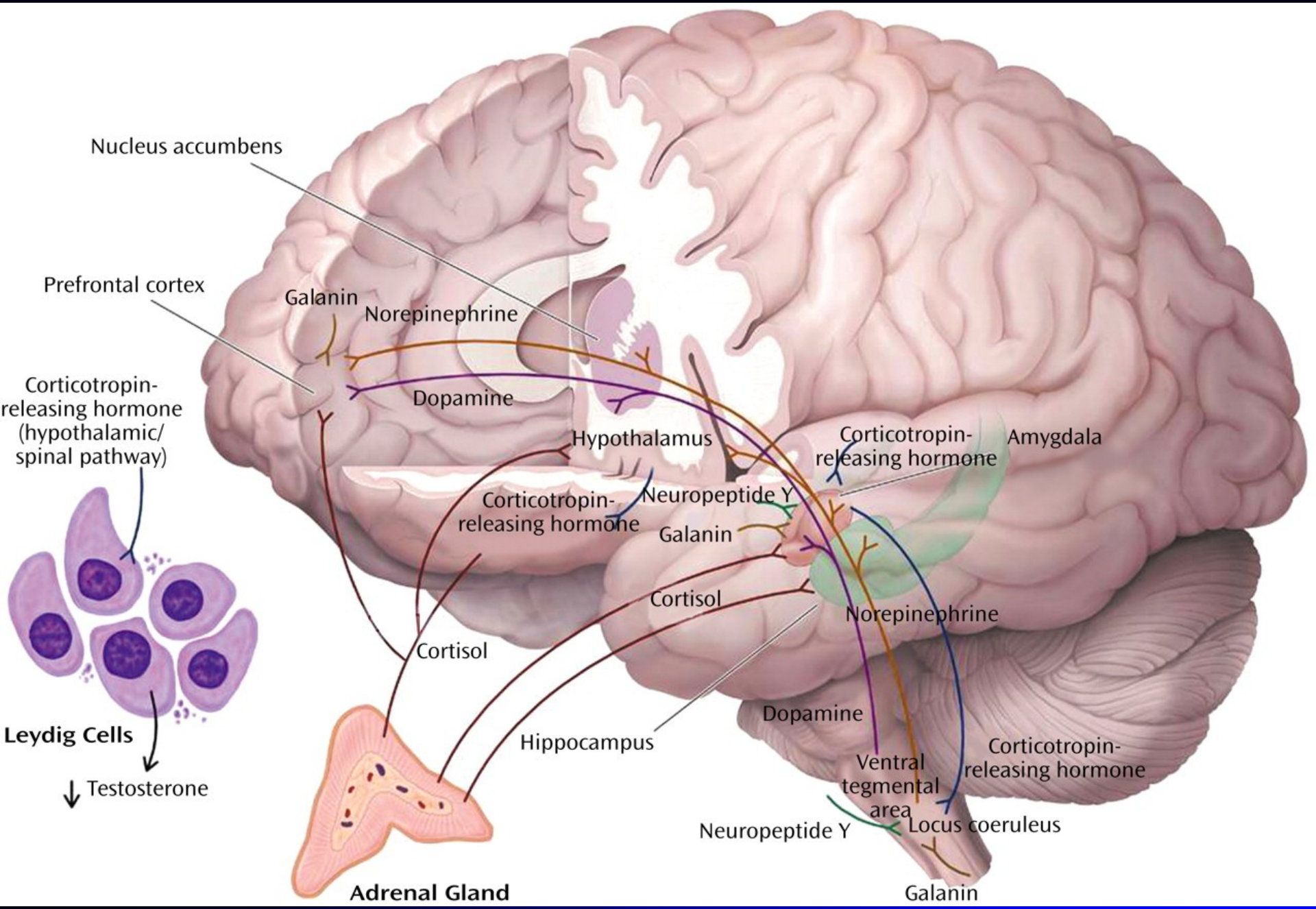
Percentage of lifetime heavy drinking adjusted for sex in adolescents grouped by genotype and exposure to negative life events.

Blomeyer, et al., 2008
Biol Psychiatry

Mean Alcohol Consumption by H1/H2 haplotype and CSA status



Nelson et al., 2010
Addict Biol



Charney, *Am J Psychiatry*, 2002

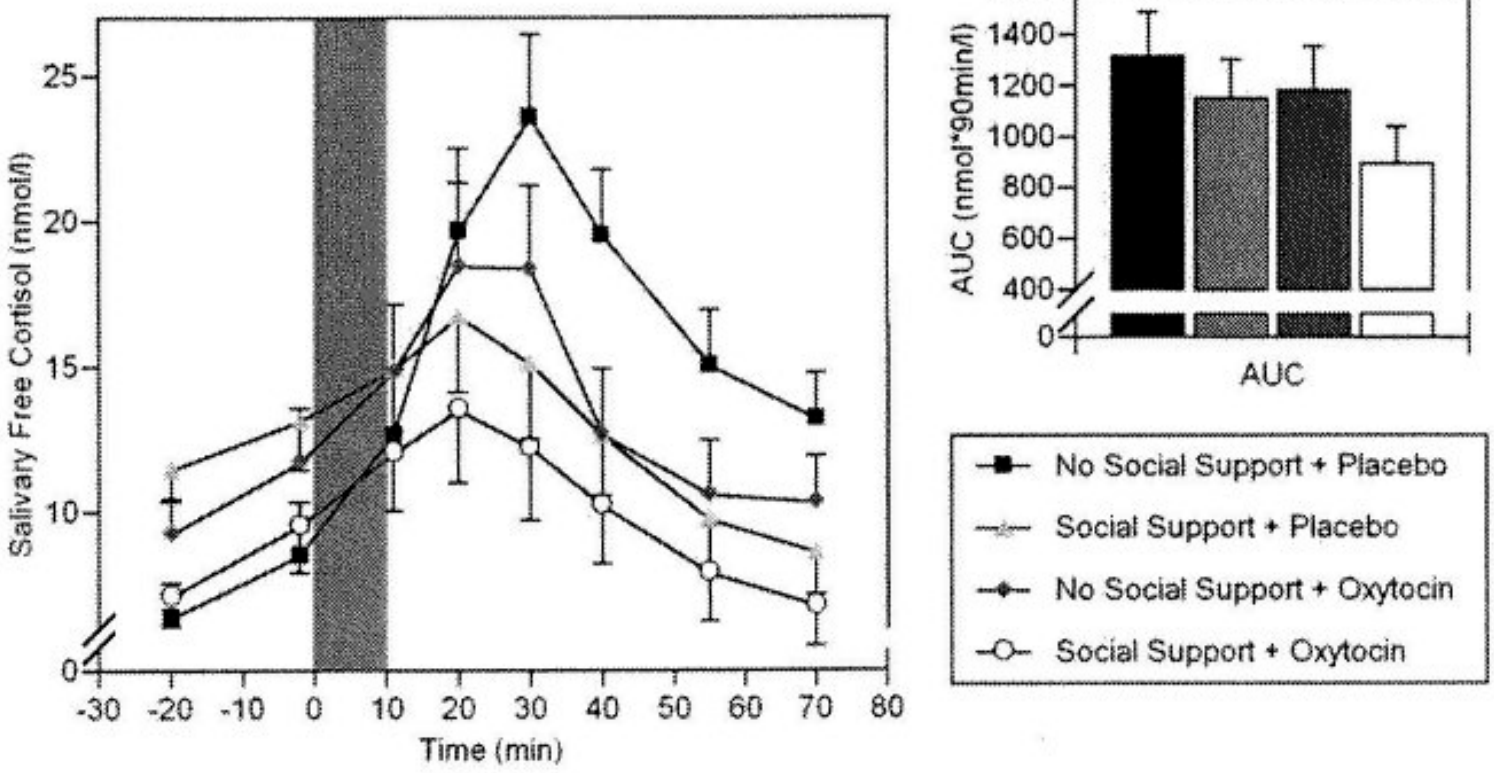
OXYTOCIN

- Regulates lactation
- Promotes affiliative behavior
- Anxiolytic, released in response to stress
- Decreases HPA and “fight or flight” response

Interaction of Social Support and Oxytocin on Stress Response

- 37 healthy males
- Trier Social Stress Test
- Social support from friend during preparation
- Intranasal oxytocin (24 IU) before task
- Measure cortisol, subjective effects
  - » Heinrichs et al., 2003

Social Support and Oxytocin in Psychosocial Stress Task



Heinrichs et al., 2003

OXYTOCIN AND MARIJUANA/COCAINE CRAVING

- Pilot human laboratory studies
- Intranasal administration of oxytocin versus placebo
- Trier Social Stress Task
  - Decreased cortisol
  - Decreased stress response
  - Decreased craving

Mcrae et al, in press

PTSD and SUBSTANCE USE DISORDERS

Little empirical evidence to guide treatment:

- Traditional substance use programs defer treatment of trauma related issues

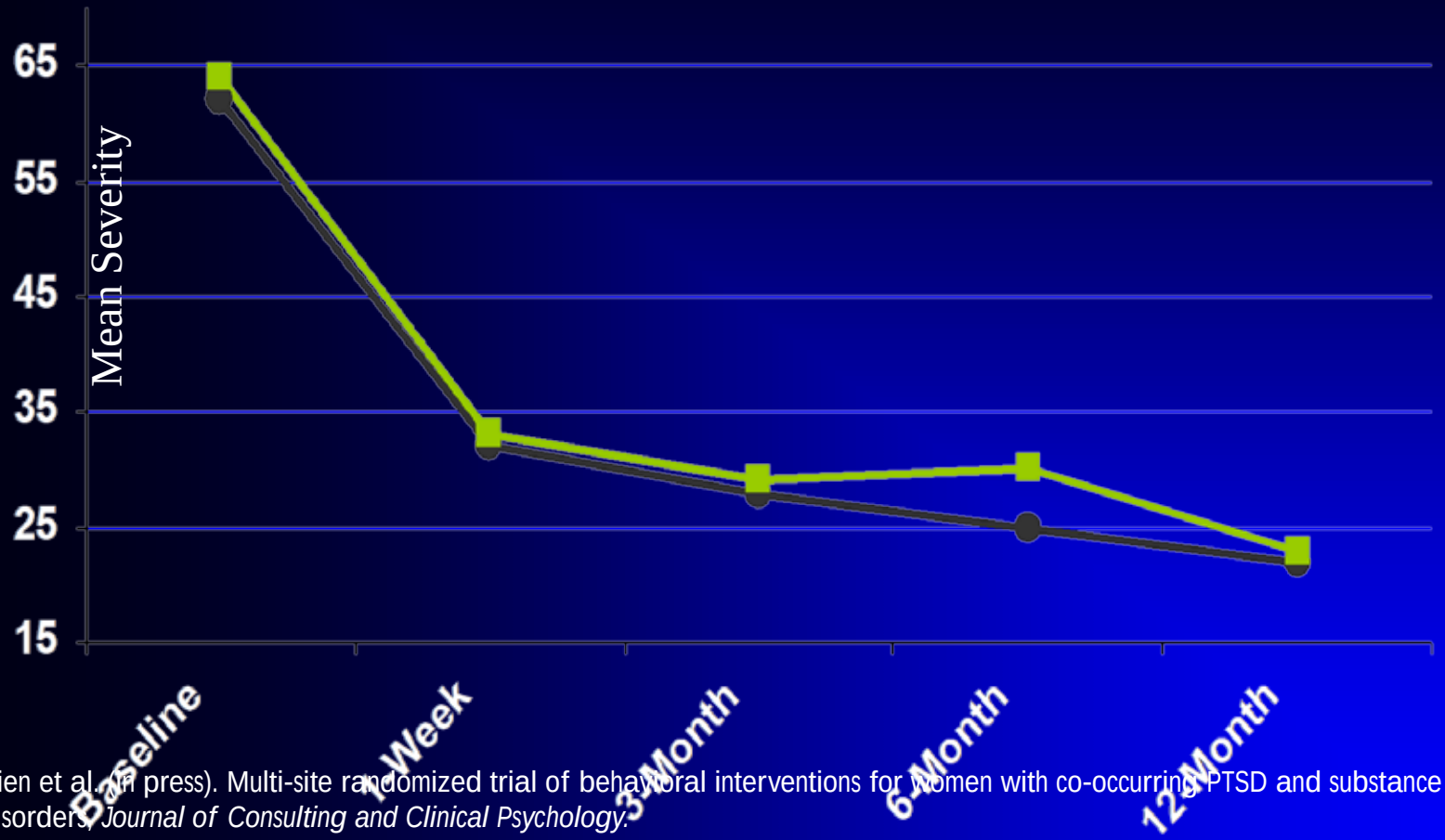
- PTSD programs don't accept individuals with active substance use disorders

Psychotherapeutic Treatments

- Cognitive-behavioral therapies efficacious in both PTSD and substance use disorders

- Manualized integrated treatments promising
  - Relapse prevention + stress inoculation + exposure (Triffleman et al., 1999)
  - Imaginal exposure + relapse prevention (Brady et al., 2002)
  - Education + relapse prevention + coping skills ("Seeking Safety", Najavits et al, 2002)

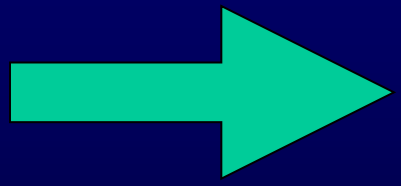
Seeking Safety in CTN:Trauma Severity (N=353)



Hien et al. (in press). Multi-site randomized trial of behavioral interventions for women with co-occurring PTSD and substance use disorders. *Journal of Consulting and Clinical Psychology.*

Temporal Course of Improvement in PTSD/SUD

- Investigate relationship between improvements in PTSD and substance use during 12 week treatment phase

- PTSD improve  SUD improve

- SUD improvement not associated with PTSD improvement

» Hein et al, 2010

Concurrent Treatment with Prolonged Exposure (COPE)

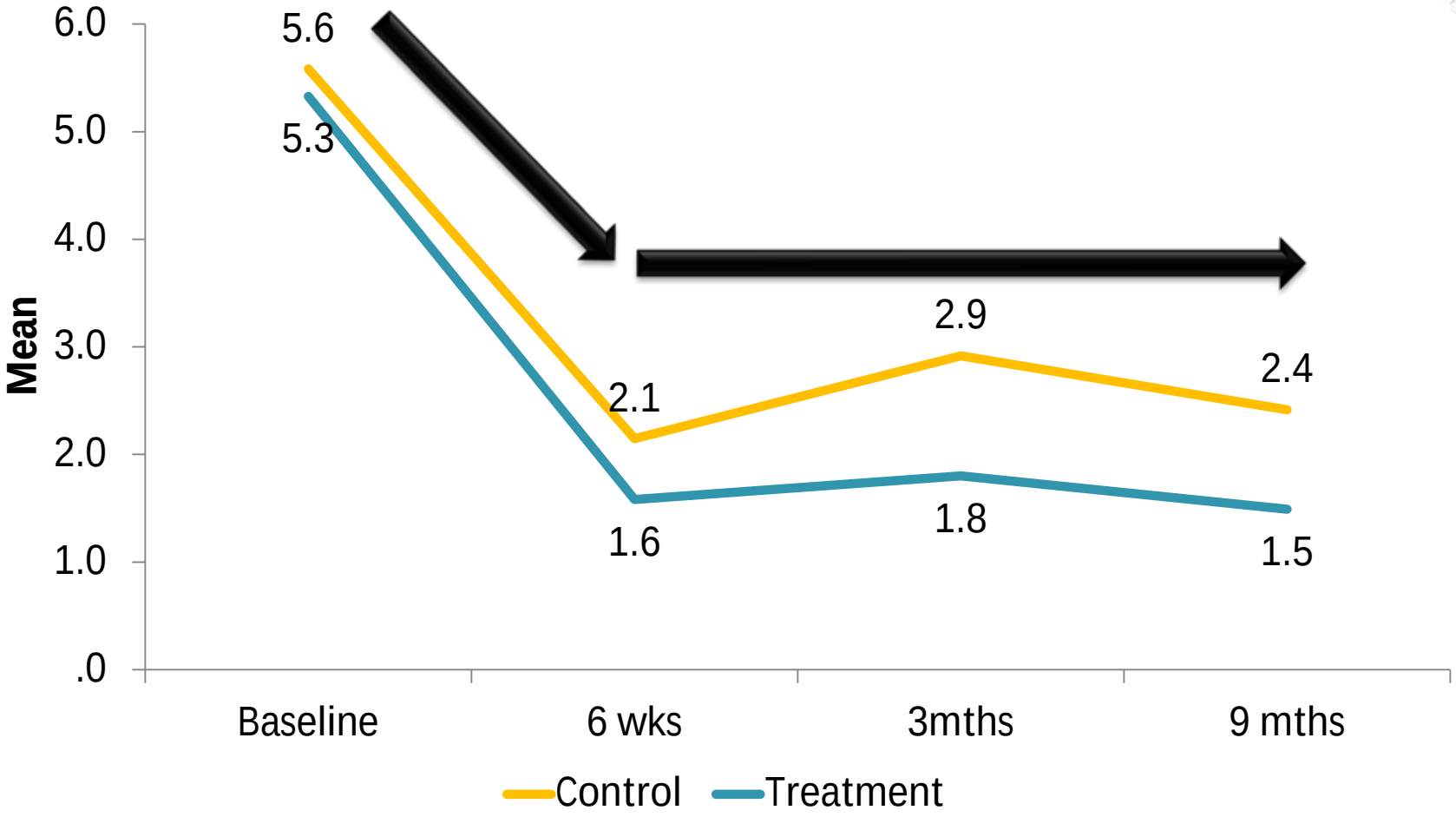
- 12 sessions, manual guided, individual therapy
- First 4 sessions CBT for cocaine - education re: trauma response/ PTSD
- Sessions 5-12 exposure

Brady, Back, Foa, Carroll

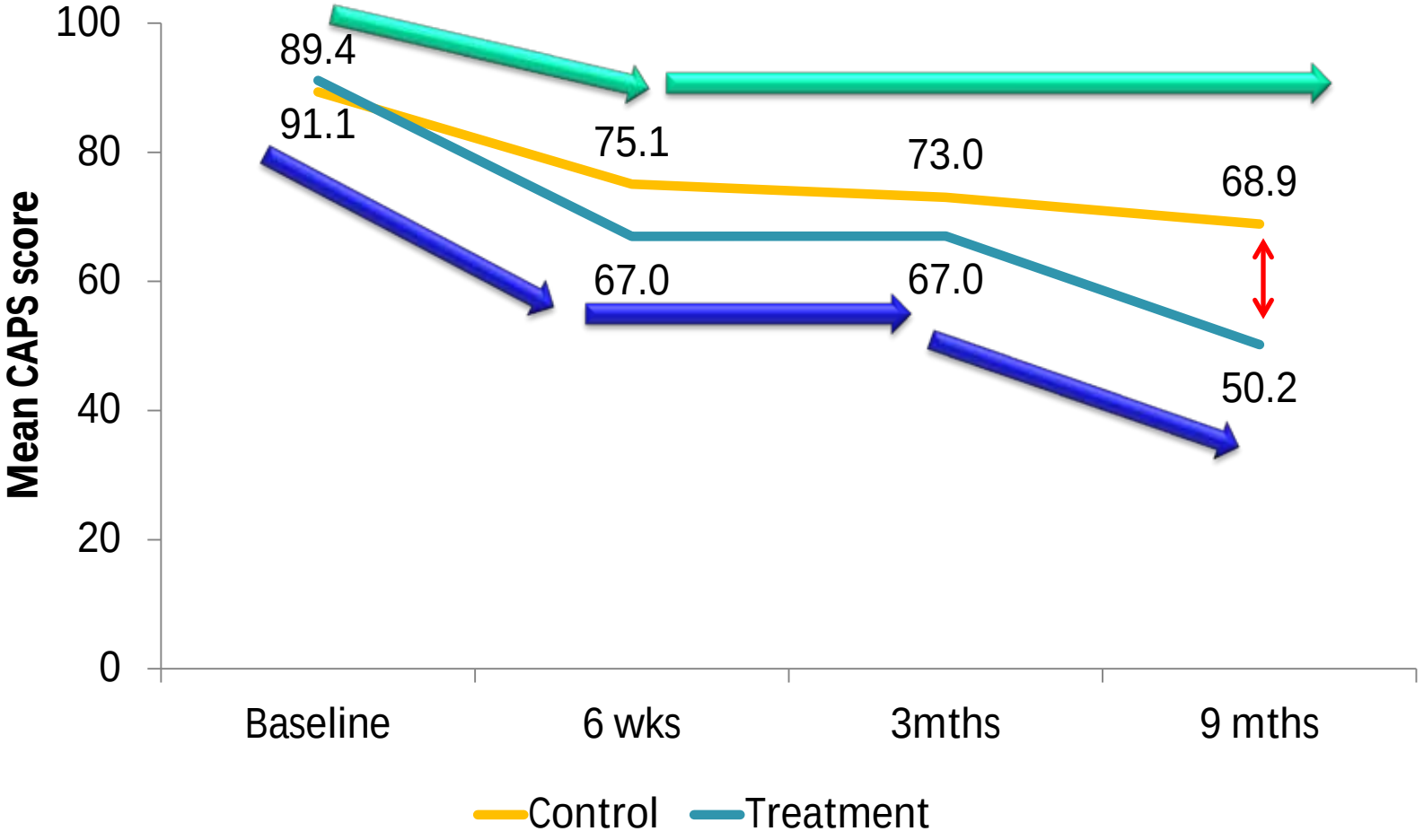
COPE Clinical Trials

- University of New South Wales: 120 individuals with drug dependence/PTSD, compared to treatment as usual
- Columbia University: 120 individuals, compared with Relapse Prevention CBT
- MUSC: OEF/OIF Veterans

Severity of dependence



Severity of PTSD symptoms

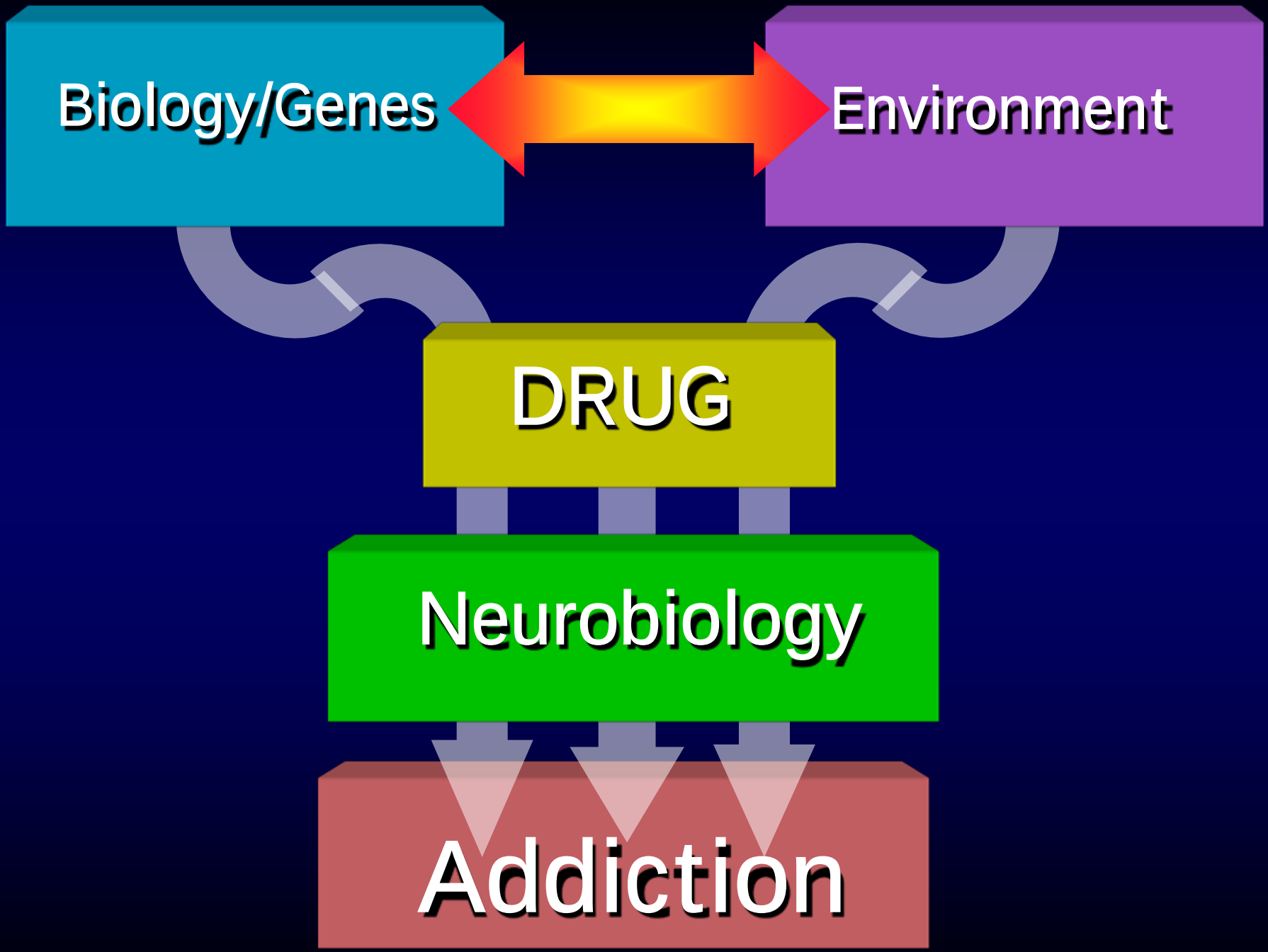


Effects of Stress/Trauma On Substance Use Disorders

1. Facilitate initiation

2. Increase risk of developing addiction after initiation

3. Trigger relapse


Biology/Genes
Environment
DRUG
Neurobiology
Addiction

Stress and Substance Use Disorders: Clinical Considerations

- Careful assessment/aggressive treatment of co-occurring stress sensitive disorders
- Importance of social support in mediating effects of stress
- Careful attention to environmental factors – ongoing stress/abuse
- Coping Skills/Stress Management Techniques

CONCLUSIONS

- Relationship between stress and substance use/relapse, development of dependence
- Mechanistic studies important
- Identification of new avenues for treatment development