

Alcohol, Stress, and the Brain: Implications for PTSD

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Director

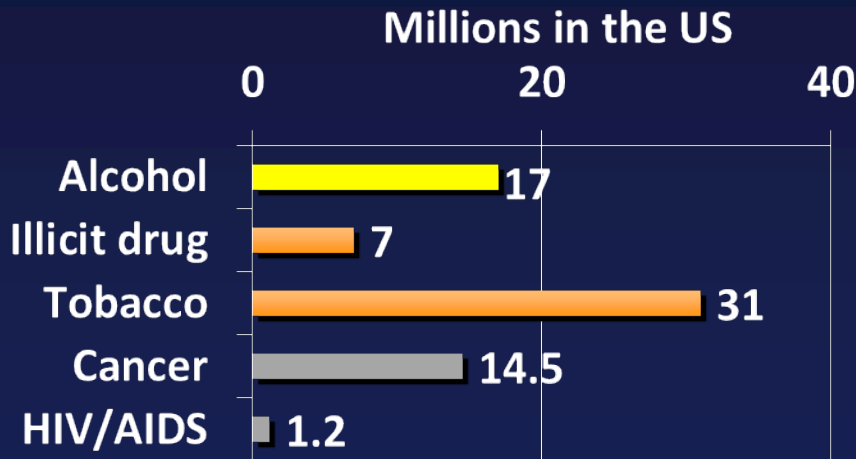
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health



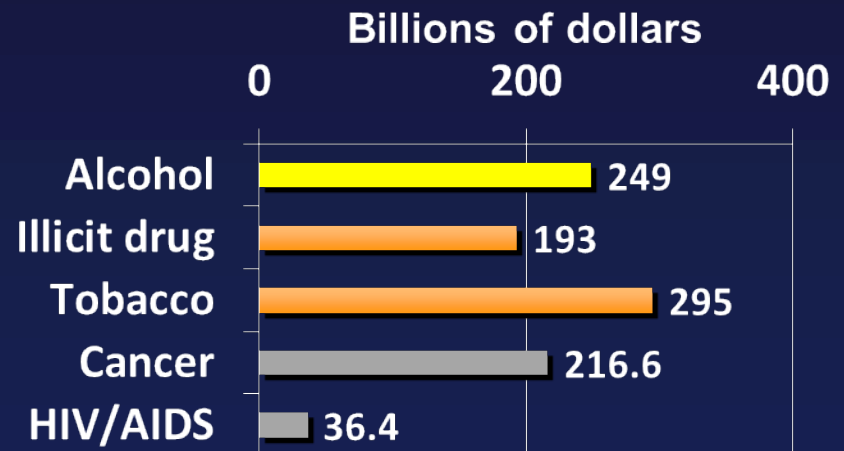
National Institute
on Alcohol Abuse
and Alcoholism

Cost and Scope of Alcohol Related Problems

Prevalence of Use Disorder/Disease



Cost to society



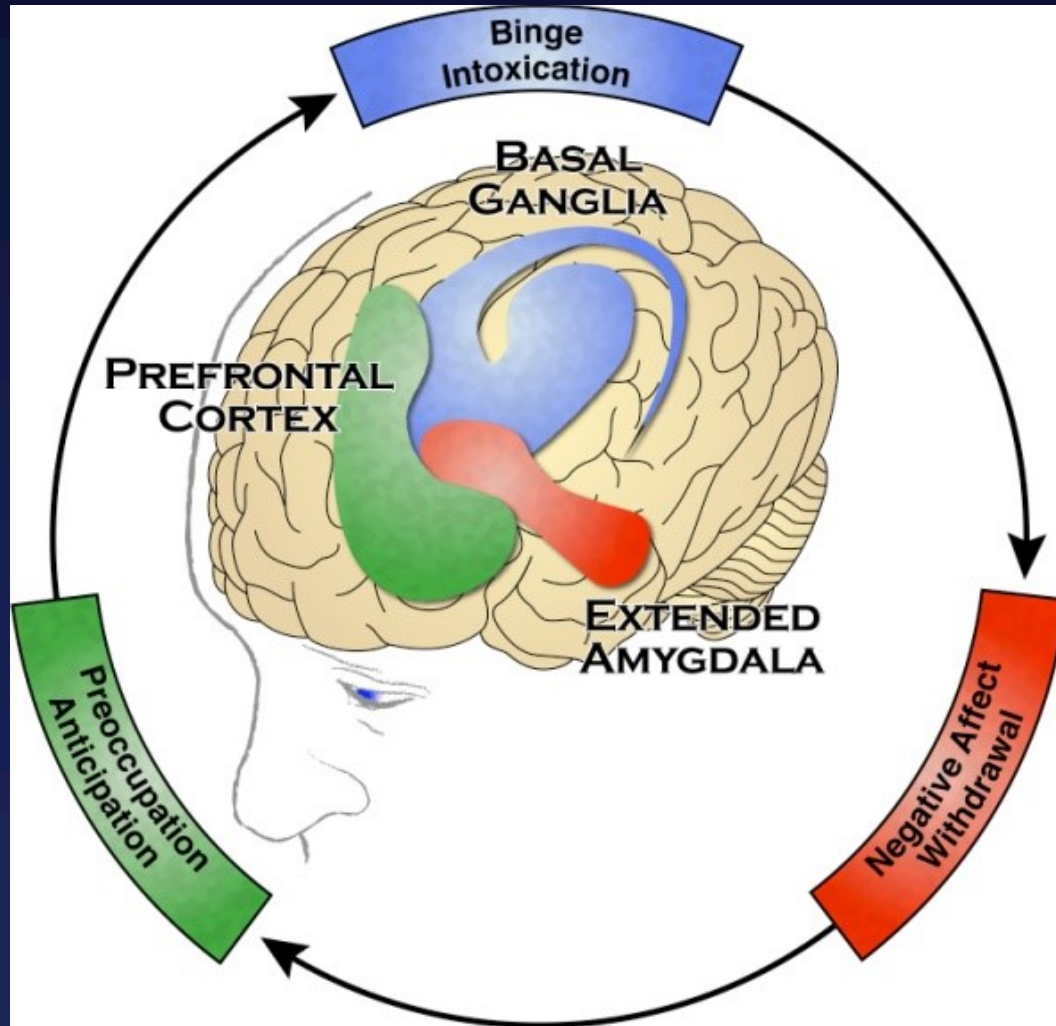
Sources: Prevalence – NSDUH (2014), NCI (2014), CDC (2012); Cost – CDC (2015), National Drug Intelligence Center - National Drug Threat Assessment (2011), 2014 Surgeon General's Report, NHLBI (2012), Hutchinson et. al. 2006.

Alcohol Use Disorder and Addiction

Alcohol Use Disorder (AUD) — The *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* defines AUD as a problematic pattern of alcohol use leading to clinically significant impairment or distress. AUD may be categorized as mild, moderate, or severe depending on the number of diagnostic criteria a patient meets.

Alcohol Addiction — A severe form of AUD, defined as a chronically relapsing disorder that is characterized by a compulsion to seek and drink alcohol, loss of control in limiting intake, and emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) in the absence of alcohol.

3 Stages of the Addiction Cycle



“When people talk about drugs, they assume people take drugs because they enjoy it...But really, it's no different from overeating or watching too much television or drinking too much. **You take drugs to make yourself feel better, to fill a hole.”**

-Ricky Williams, retired Miami Dolphins running back

-Byline Damien Cox, Toronto Star, May 29, 2006

Shift from Impulsive to Compulsive Drinking

Positive Reinforcement —

process by which presentation of a stimulus (alcohol) increases the probability of a response (drinking)

Negative Reinforcement —

process by which removal of an aversive stimulus (negative emotional state of alcohol withdrawal) increases the probability of a response (drinking)

Impulsive drinking
Reward/pleasure
Positive reinforcement

Compulsive drinking
Stress relief
Negative reinforcement



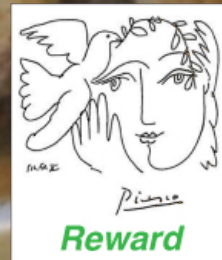
Stress and Reward: The Two Faces of Janus

- Reward and stress resemble the Roman God Janus.
- Janus was the god of doors, passages and transitions and his two faces look to the future and the past.
- Reward and stress represent different components of transitions in our brain emotional systems that lead to and perpetuate addiction.



"**Stress** is anything which causes an alteration of psychological homeostatic processes"
from: Burchfield SR, Psychosom Med, 1979, 41:661-672.

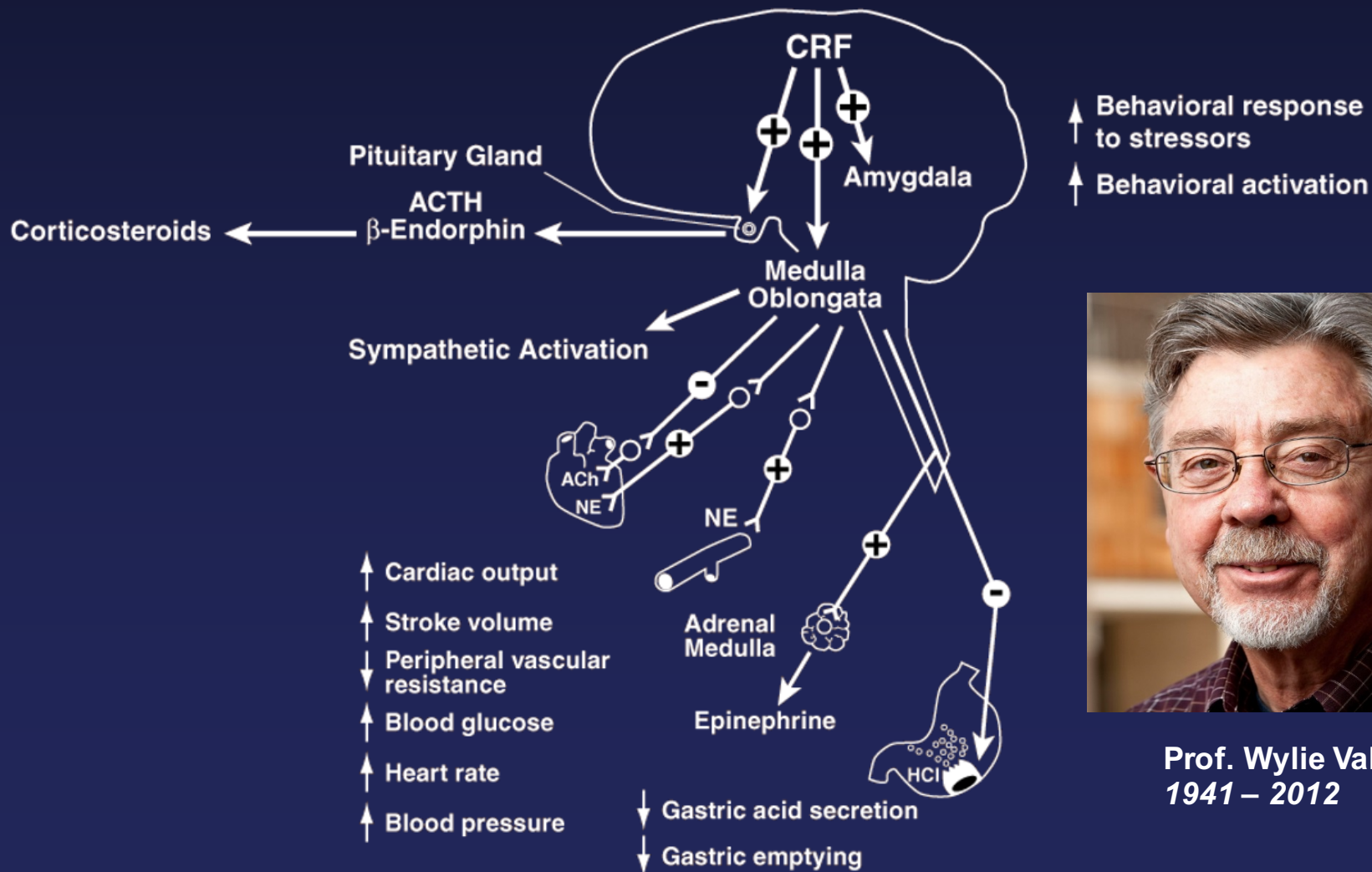
Reward is defined as a stimulus (drug) that increases the probability of a response, but usually includes a positive hedonic connotation



Stress Contributes to Excessive Alcohol Seeking and Relapse in Alcohol Use Disorder

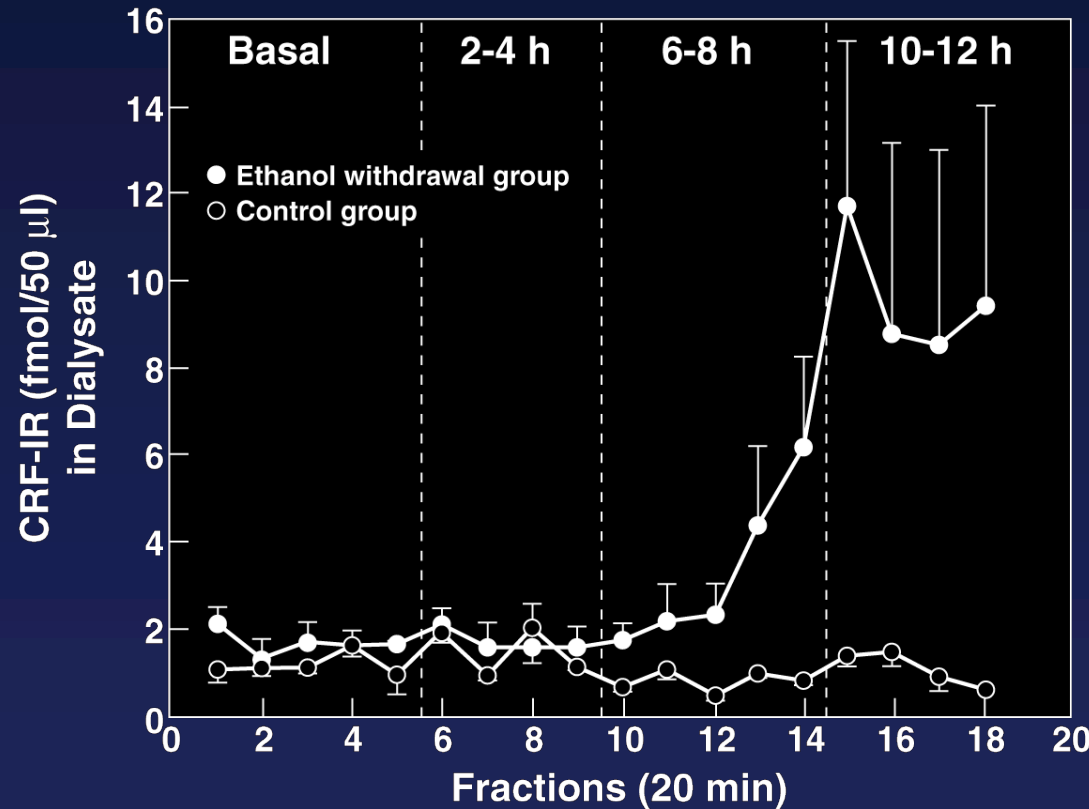
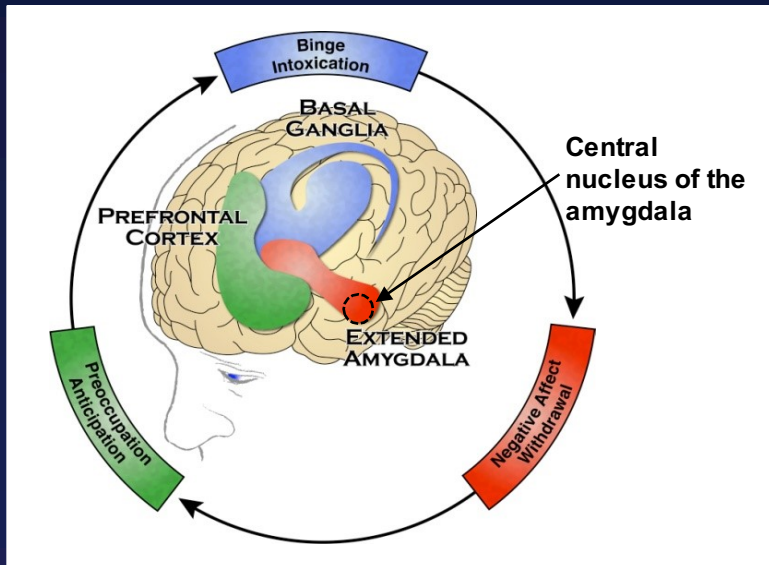
- **Brain stress systems such as corticotropin releasing factor (CRF) are activated during excessive drinking; this activation persists into withdrawal and abstinence**
- **CRF antagonists block excessive drinking in animal models of alcohol addiction**
- **Antagonists of brain stress systems have efficacy in animal models of relapse**
- **Preliminary data suggest that antagonists of brain stress systems attenuate craving and relapse in humans with AUD**

Brain Actions of Corticotropin-Releasing Factor (CRF)

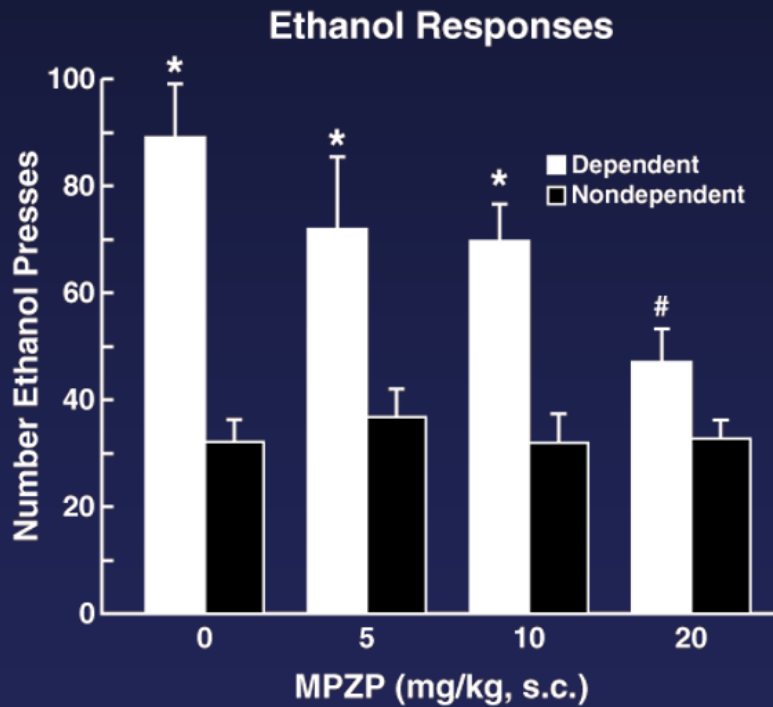


Prof. Wylie Vale
1941 – 2012

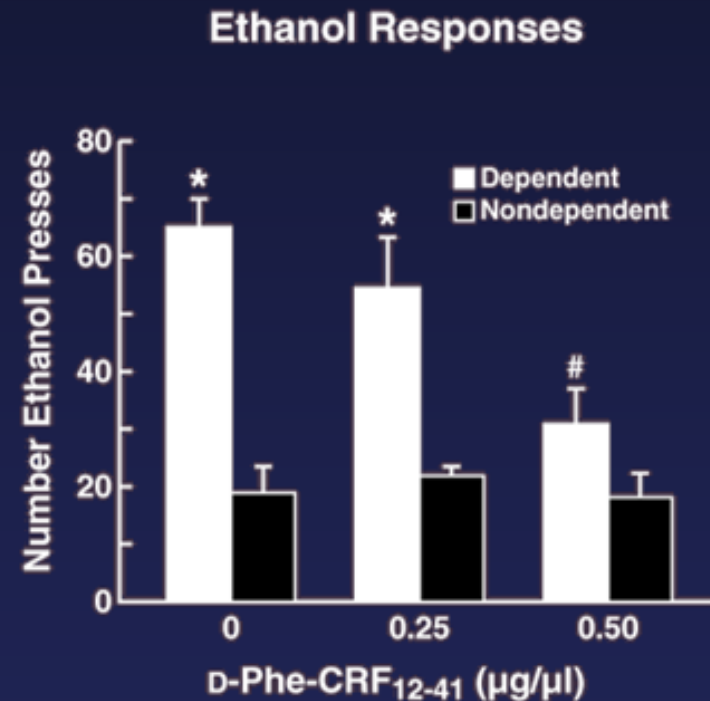
Alcohol Withdrawal Increases Stress Neurotransmitter (CRF) Levels in the Brain (central nucleus of the amygdala)



Blocking the Effects of Stress Neurotransmitters Decreases Excessive Alcohol Consumption In Animal Models



Systemic injection

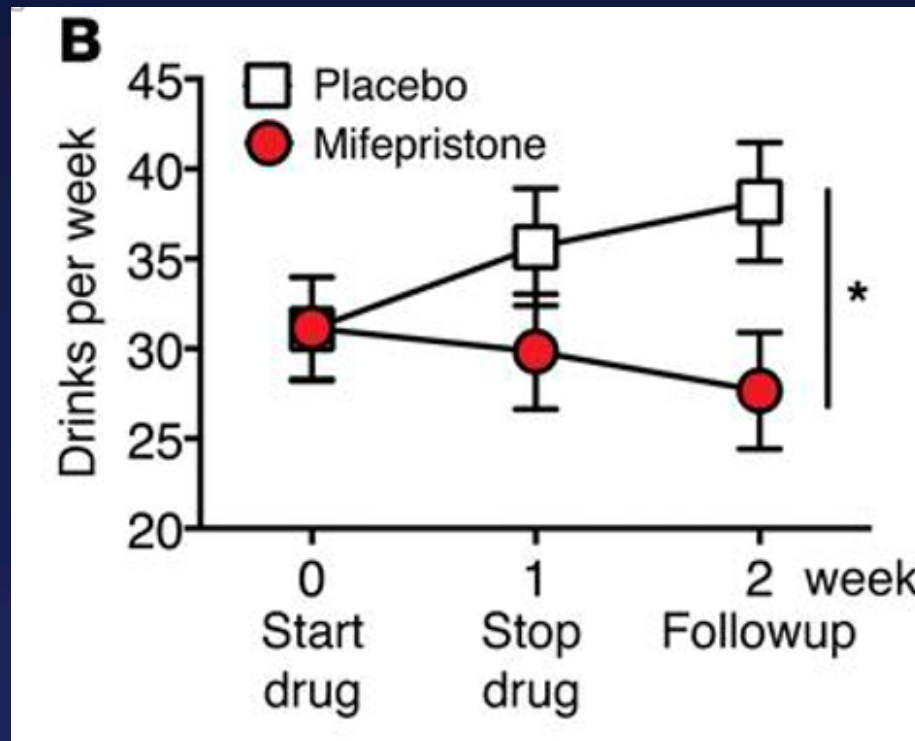


Amygdala injection

From: Funk C, O'Dell LE and Koob GF. *J. Neurosci*, 2006, 26:11324-11332.

Richardson HN, Zhao Y, Fekete EM, Funk CK, Wirsching P, Janda KD, Zorrilla EP and Koob GF, *Pharmacol Biochem Behav*, 2008, 88:497-510.

Blocking The Effects of Stress Neurotransmitters Decreases Alcohol Use in Individuals with AUD



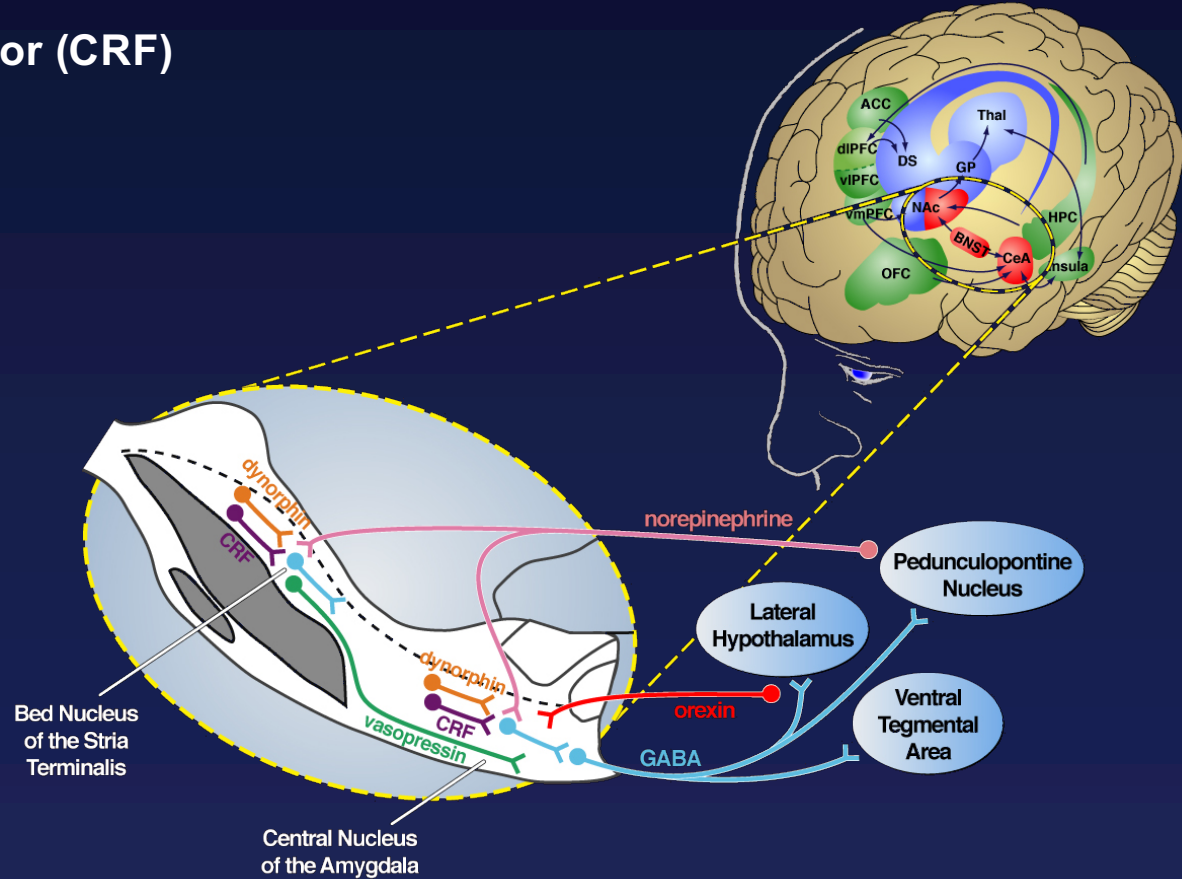
Extended Amygdala: Interface of Stress and Addiction

Stress Neurotransmitters

- ☒ Corticotropin-releasing factor (CRF)
- ☒ Norepinephrine
- ☒ Dynorphin
- ☒ Vasopressin
- ☒ Orexin (hypocretin)
- ☒ Substance P
- ☒ Glucocorticoids
- ☒ Neuroimmune factors

Anti-stress neurotransmitters

- ♪ Neuropeptide Y
- ♪ Nociceptin (orphanin FQ)
- ♪ Endocannabinoids
- ♪ Oxytocin



From: Koob, GF 2008 Neuron 59:11-34 and George O, Koob GF. Proc Natl Acad Sci USA, 2013, 110:4165-4166.

Drugs Targeting the Extended Amygdala Alter Stress and Addiction

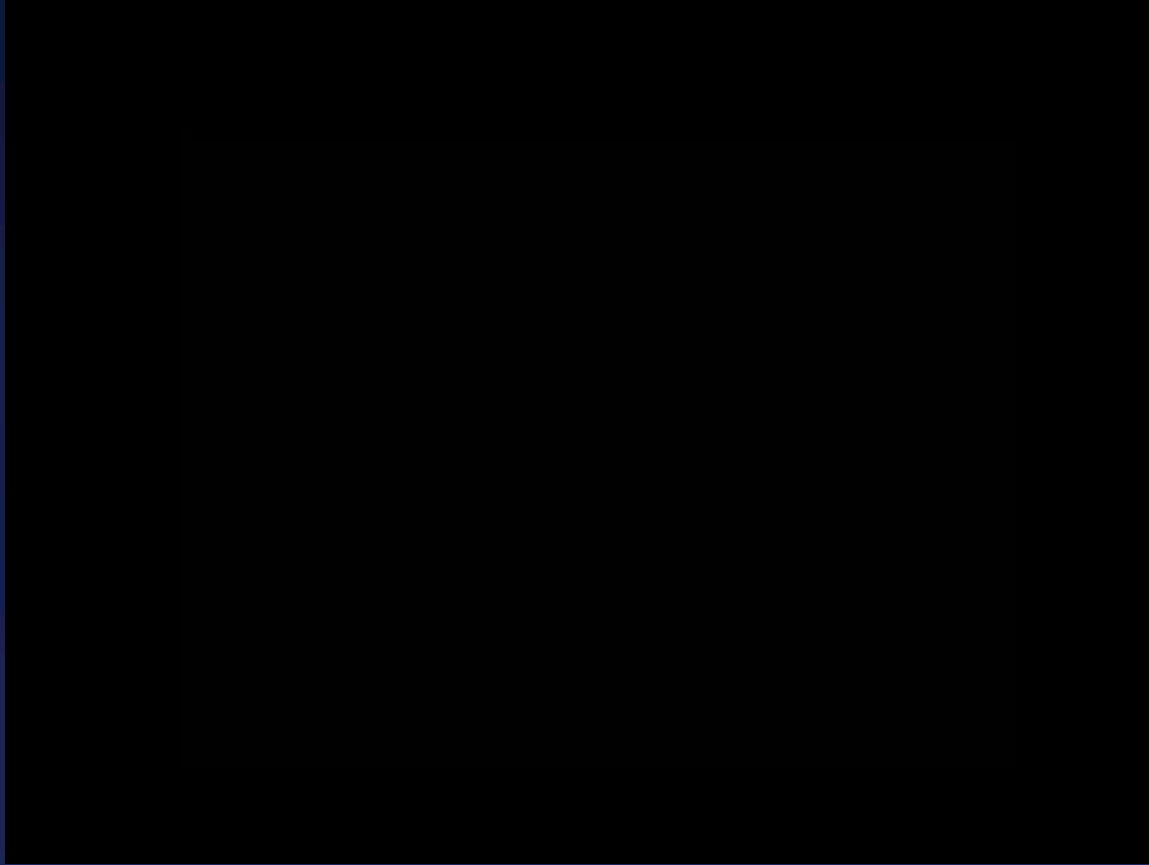
- **Corticotropin-releasing factor (CRF) antagonists**
- **Dynorphin – kappa receptor antagonists**
- **Vasopressin antagonists**
- **Norepinephrine antagonists**
- **Glucocorticoid antagonists**
- **Endocannabinoids**

What is Posttraumatic Stress Disorder?

- PTSD can develop after exposure to a traumatic event
- Traumatic events are beyond typical stressors—they may include violent personal assaults, disasters, serious accidents, military combat
- Individuals with PTSD may have persistent, frightening thoughts and memories of the event(s), experience sleep problems, feel detached or numb, or may be easily startled
- PTSD can severely impair a person's ability to function at work, at home, and socially
- PTSD is especially prevalent among our nation's military personnel, veterans, and victims of violence, including sexual assault



What Does PTSD Feel Like?



PTSD and AUD Frequently Co-Occur

- 30-60% of patients seeking treatment for AUD meet criteria for PTSD
- 1/3 of people who have experienced PTSD have experienced AUD at some point in their lives
- 20% of veterans who received treatment for PTSD at a VA medical center have a substance use disorder
- Comorbidity is associated with greater health and behavioral problems and results in reduced treatment success and higher rates of relapse

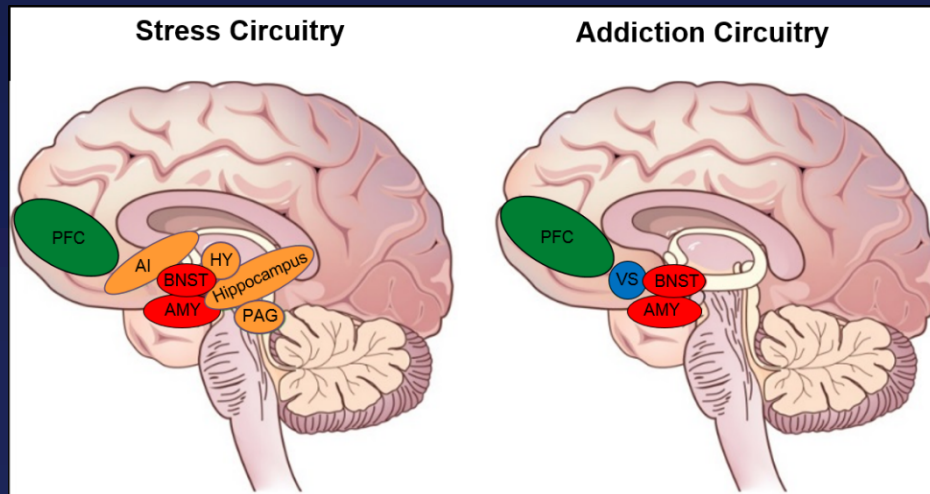


PTSD and AUD Frequently Co-Occur

- PTSD symptoms generally precede and predict onset of AUD or other substance use disorders
- AUD can increase risk for later development of PTSD
- Alcohol use by people with PTSD has been ascribed to self medication
- Alcohol use can affect:
 - hyperarousal symptoms
 - intrusive traumatic memories
 - acute symptom relief
- Alcohol use exacerbates PTSD

Overlapping Neurobiology of PTSD and AUD

- Both conditions are linked to dysregulation of brain stress systems
 - Increased CRF in PTSD and alcohol dependence
 - Altered HPA-axis (i.e., stress system) function
 - Improvement of PTSD symptoms and reduction in drinking with administration of mifepristone (CRF antagonist)
- Increased neuroimmune activation in PTSD and alcohol dependence
- Research suggests that alcohol use may increase PTSD risk by altering the brain's ability to recover from traumatic experiences



Overlapping Genetic Risk of PTSD and AUD

Gene variants implicated in PTSD and AUD risk:

DRD2	dopamine receptor D2
HTR2A	serotonin receptor 2A
CRFR1	CRF receptor type 1
GABRA2	GABA receptor type A alpha 2
COMT	neurotransmitter metabolizing enzyme
CHRNA2	cholinergic receptor nicotinic alpha 2 subunit
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells

Suggests that there may be **shared vulnerabilities** for these disorders

Treating Co-occurring PTSD and Substance Use Disorders (SUDs)

1. Sequential Model

- SUD first, PTSD later

2. Parallel Model

- SUD and PTSD treated at same time by different clinicians

3. Integrated Model

- Treat the SUD and PTSD concurrently, same clinician

Treating Co-occurring PTSD and AUD

- Behavioral interventions for co-occurring AUD and PTSD have been developed; however, they are not effective for all people
- There are currently no FDA-approved medications for co-occurring AUD and PTSD
- There are FDA-approved medications for people with either PTSD or AUD, but it is unclear how effective they are for people diagnosed with both disorders

NIAAA Research Goals

- **Develop a deeper understanding of the relationship between AUD and stress, including PTSD**
 - Underlying neurobiological and behavioral mechanisms
 - Role of stress in relapse and recovery
- **Develop interventions to treat stress-triggered alcohol consumption**
- **Identify risk factors for PTSD-AUD comorbidity**
- **Develop interventions to prevent and treat co-occurring AUD and stress-related disorders, including PTSD**
 - Behavioral treatments
 - Medications
- **Partner with DoD, VA, and other federal agencies to accelerate the development of PTSD treatments**



The Dark Side of Alcohol Addiction



Don't judge people who drink alcohol and end up in National Health Services (NHS).

“I have met many people from all walks of life in my career. Alcohol is often an emotional prop, a way of coping with pain, harm, sexual assault, traumatic events, inability to find the words to talk about stress, coping with financial pressure, family life, parenting pressure, death. Individuals who hear voices use alcohol to self-medicate. So next time you look at the person getting drunk, should you be so smug as to judge them as wasting NHS resources? Or should you think differently? Our culture promotes drinking for fun and we need to work on that. But let's look a little bit deeper and consider this more.”

*Sarah Johnson, The impact of alcohol on the NHS: 'We get the drunks in 24/7,'
The Guardian, January 22, 2016.*