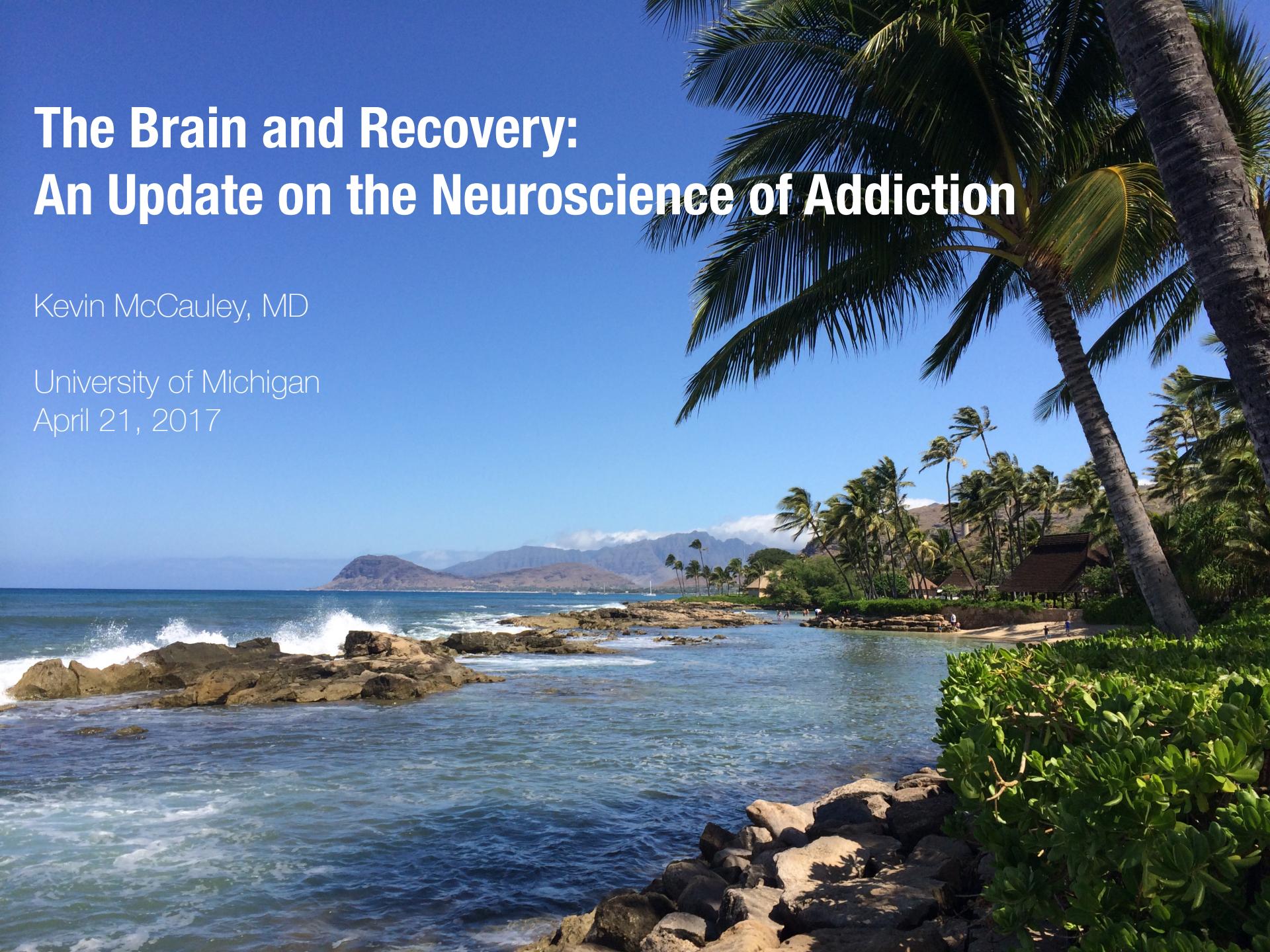


# The Brain and Recovery: An Update on the Neuroscience of Addiction

Kevin McCauley, MD

University of Michigan  
April 21, 2017



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**www.protectingsobriety.com**

# VMFAT-101 Sharpshooters MCAS El Toro, CA



- Naval Flight Surgeon: best time of my life
- Extremely delicate clinical challenge (pilots don't like doctors)
- Patients are charismatic and highly capable heroes (we want them to succeed)
- A “Culture of Safety” is a shared and over-riding value
- We do whatever works; we learn from our mistakes

# *Is Addiction Really a “Disease?”*

*Addiction is a disorder in the brain's hedonic system (pleasure sense) ...*

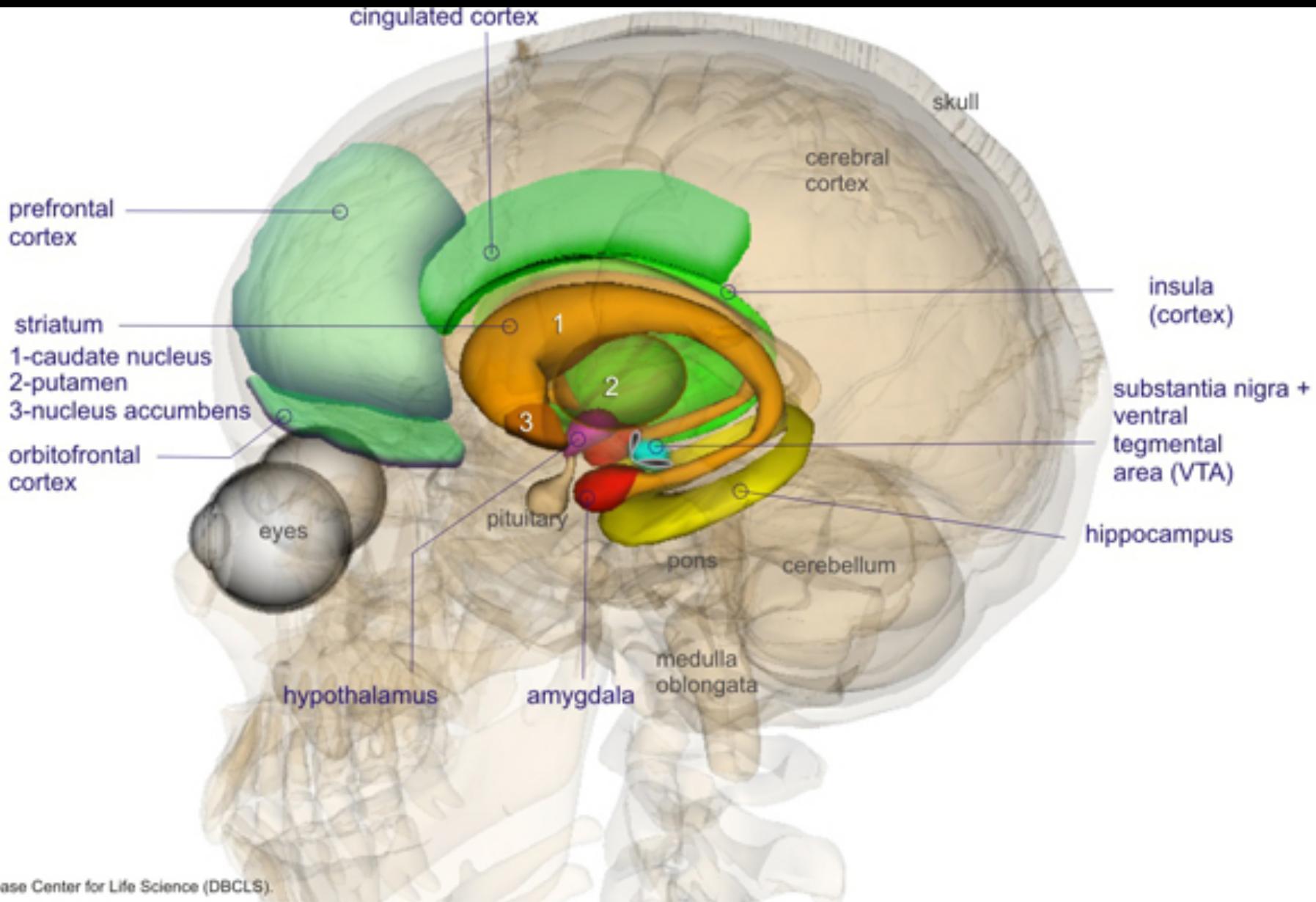


*... resulting in a failure to correctly assess future value and uncertainty (likelihood) ...*



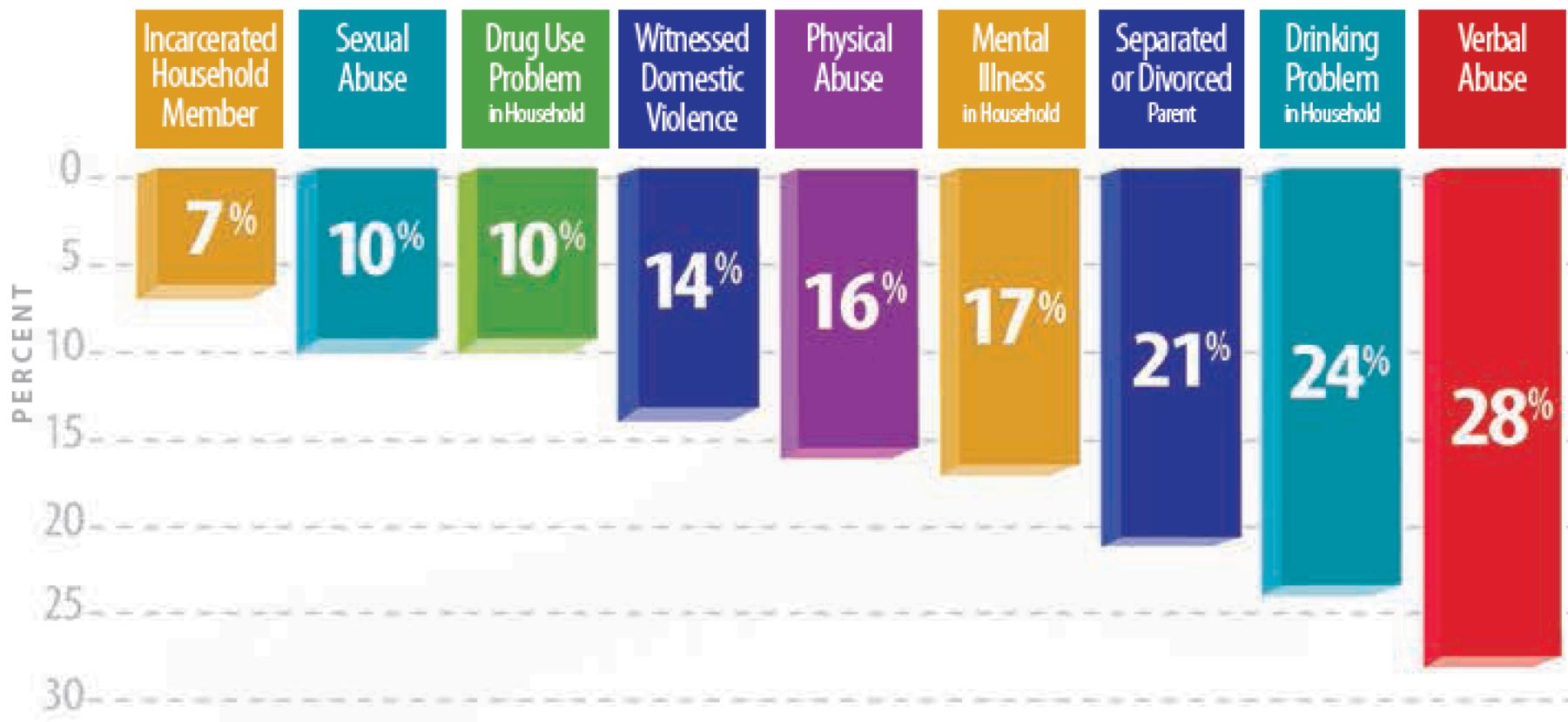
*... undermining the individual's decision-making capacity (choice) and self-awareness (insight).*

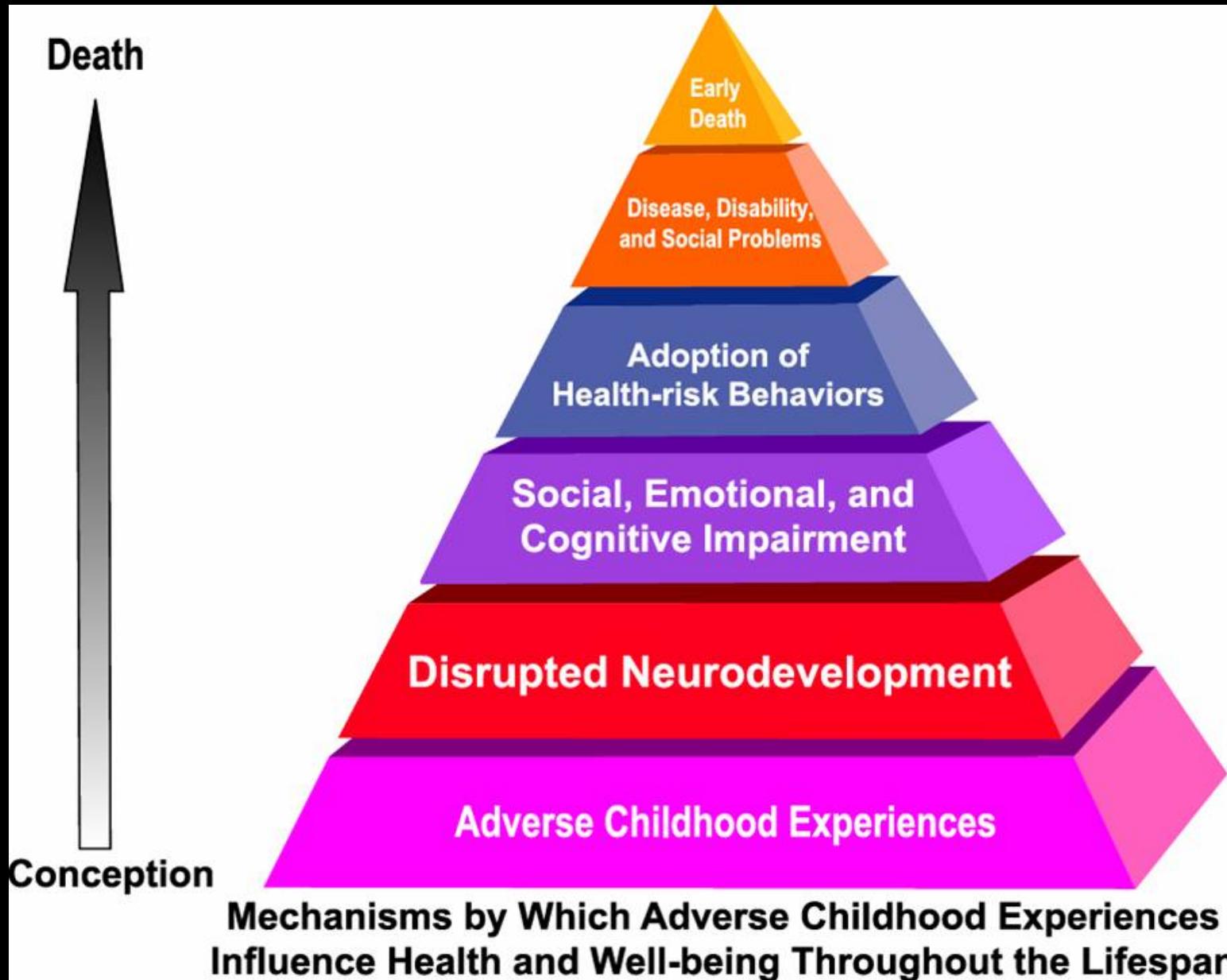




## PREVALENCE OF INDIVIDUAL ACES

MINNESOTA 2011

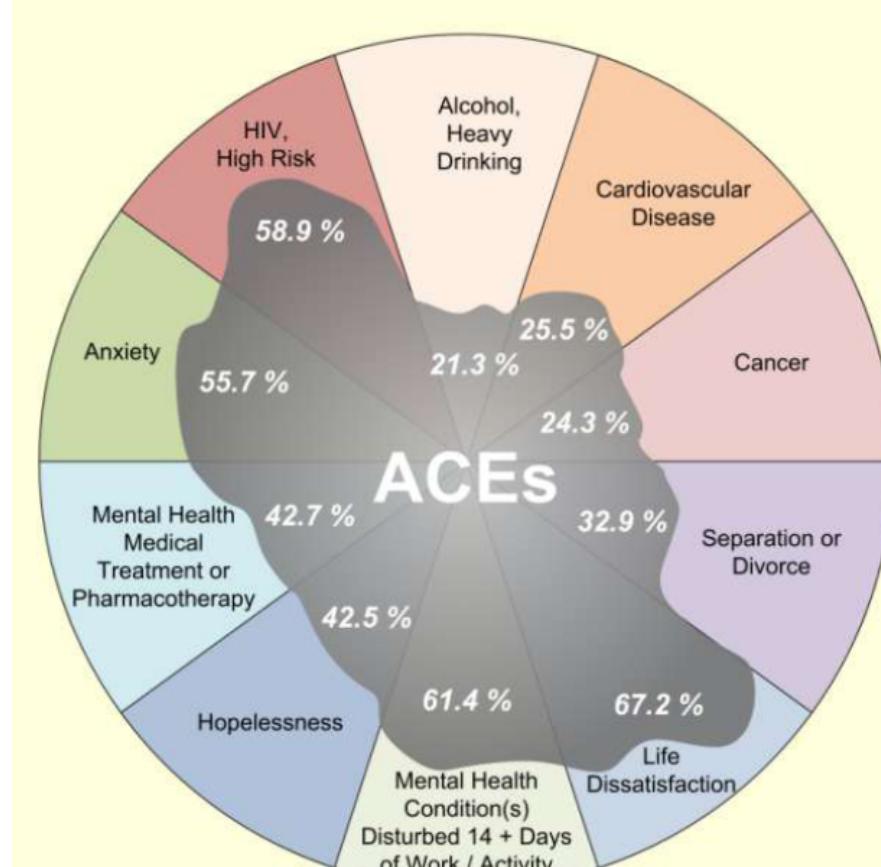




## MAGNITUDE OF THE SOLUTION

ACE reduction  
reliably predicts  
simultaneous  
decrease in all of  
these conditions.

Population  
attributable risk

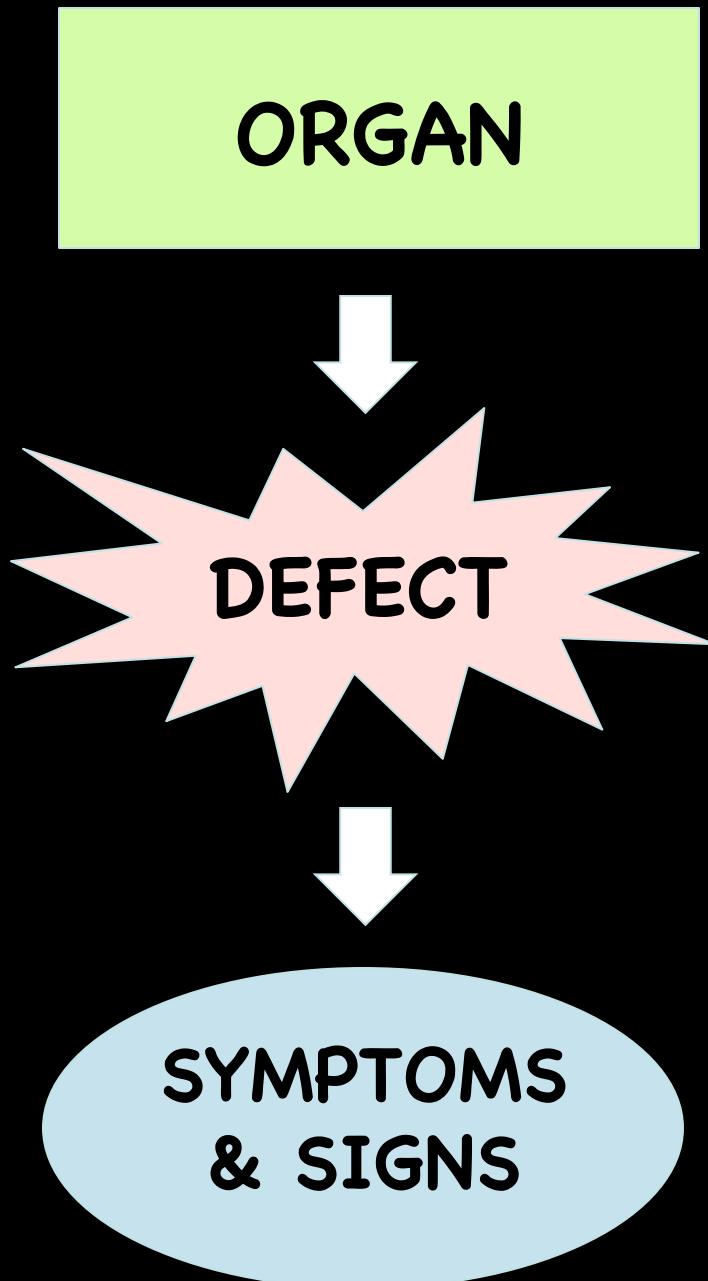


# ASAM Addiction Definition (Aug 2011)

A stress-induced (HPA axis),  
genetically-mediated (polymorphisms, epigenetic mech.)  
primary, chronic and relapsing brain disease  
of reward (nucleus accumbens),  
memory (hippocampus & amygdala),  
motivation and related circuitry (ACC, basal forebrain)  
that alters motivational hierarchies such that addictive  
behaviors supplant healthy, self-care behaviors

# Addiction is a disorder of ...

- |           |                       |                                     |
|-----------|-----------------------|-------------------------------------|
| 5. CHOICE | (motivation, insight) | OFC, ACC, PFC, IC                   |
| 4. STRESS | (anti-reward system)  | HPA axis                            |
| 3. MEMORY | (habits, cues)        | glutamate<br>synaptic remodeling    |
| 2. REWARD | (incentive salience)  | dopamine<br>dopamine receptors      |
| 1. GENES  | (vulnerability)       | polymorphisms<br>epigenetic changes |



# THE DISEASE MODEL

(a powerful  
causal model)

# A “Disease”

# Broken Leg

# Diabetes I

ORGAN

Femur

Pancreas

DEFECT

Fracture

beta cell death  
no insulin

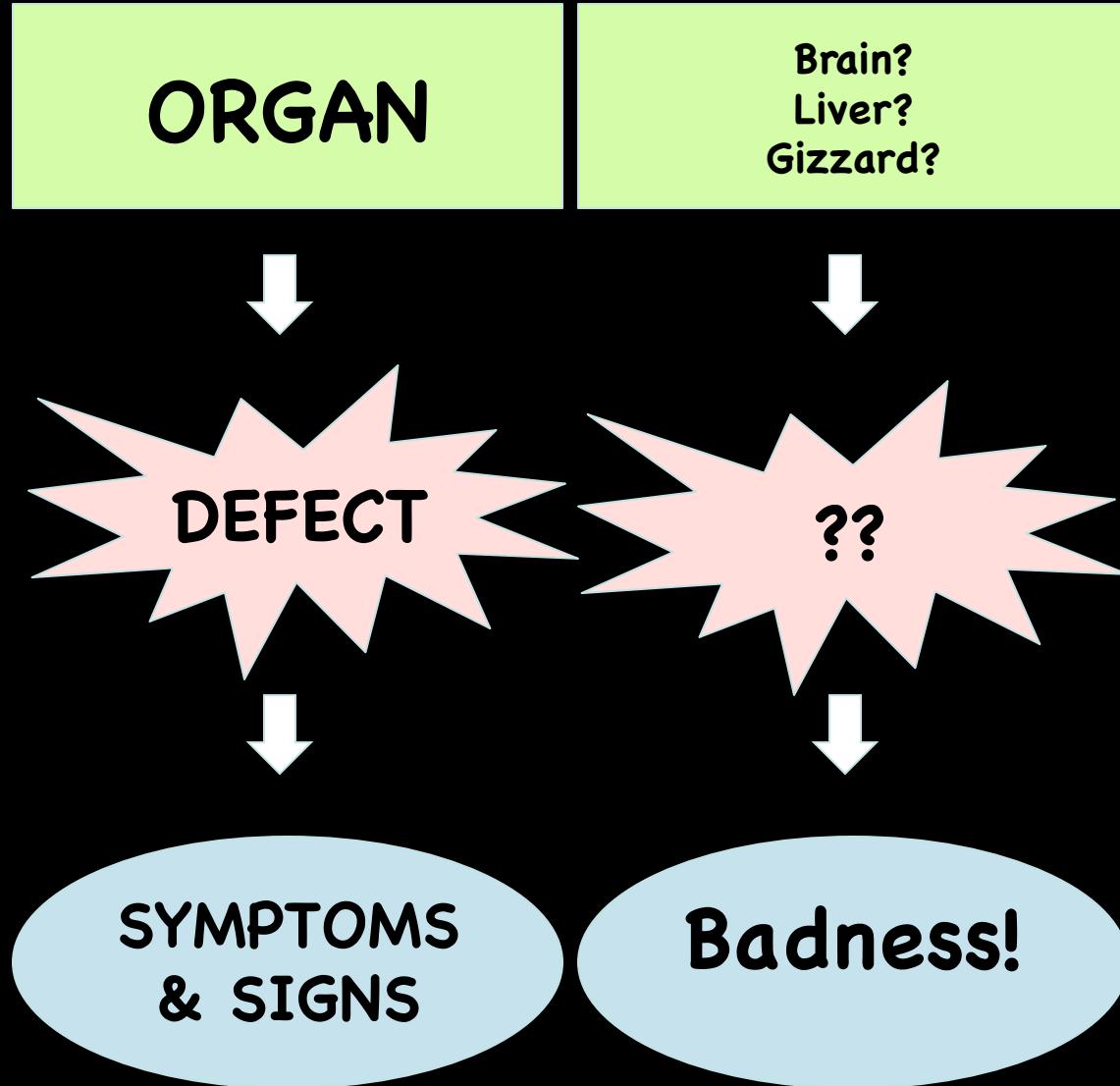
SYMPTOMS  
& SIGNS

Leg Pain  
Leg Swelling  
Can't Walk

1. Polyuria  
2. Poor healing  
3. Blurred Vision  
Etc.

# A “Disease”

# Addiction



If ever we could fit addiction to this model, then it would win admission into "The Disease Club"

***And now, we finally can ...***

# A “Disease”

# Addiction (SUD)

ORGAN

1. Genetic/Epigenic mech.s
2. Striatum/Limbic Brain
3. HPA Axis
4. Frontal Cortex

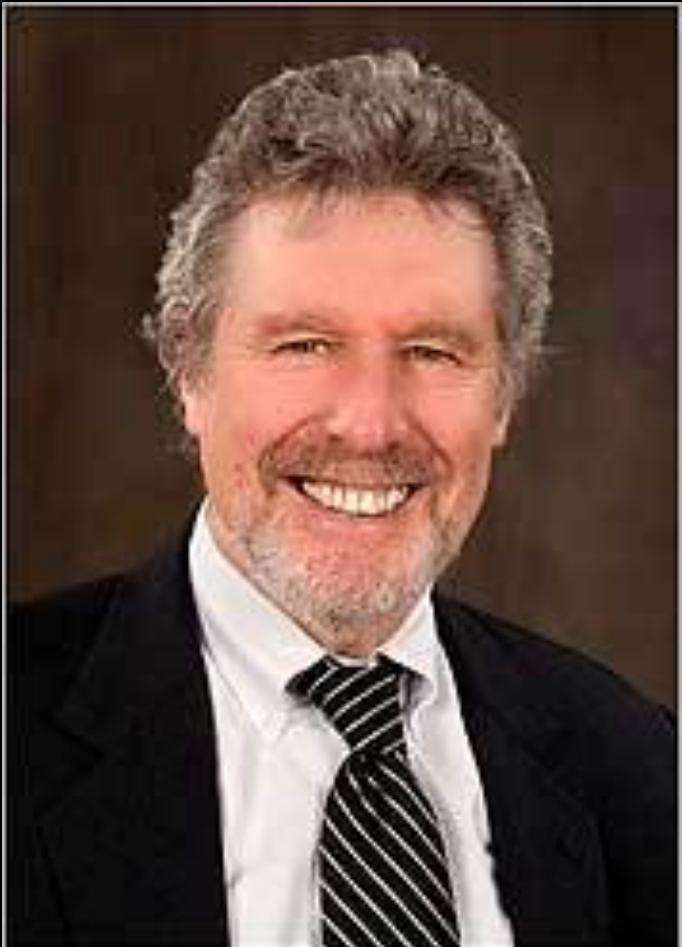
DEFECT

1. Polymorphisms
2. DA/GLU signaling
3. CRF allostatic
4. hypofrontality

SYMPTOMS  
& SIGNS

1. loss of control
2. craving
3. persistent use despite neg. conseq.
4. IDM + LOI

# Gene Heyman, PhD



- **Addiction is not a chronic disease**
- **Most addicts do stop on their own, without treatment, and do not display relapse chronicity**
- **Remission (“maturing out”) is the rule, not the exception**
- **Addicts do not need lifelong treatment**
- **Remission rates lower for legal drugs than illegal drugs**

# **Discrepant findings the Disease Model has to explain ....**

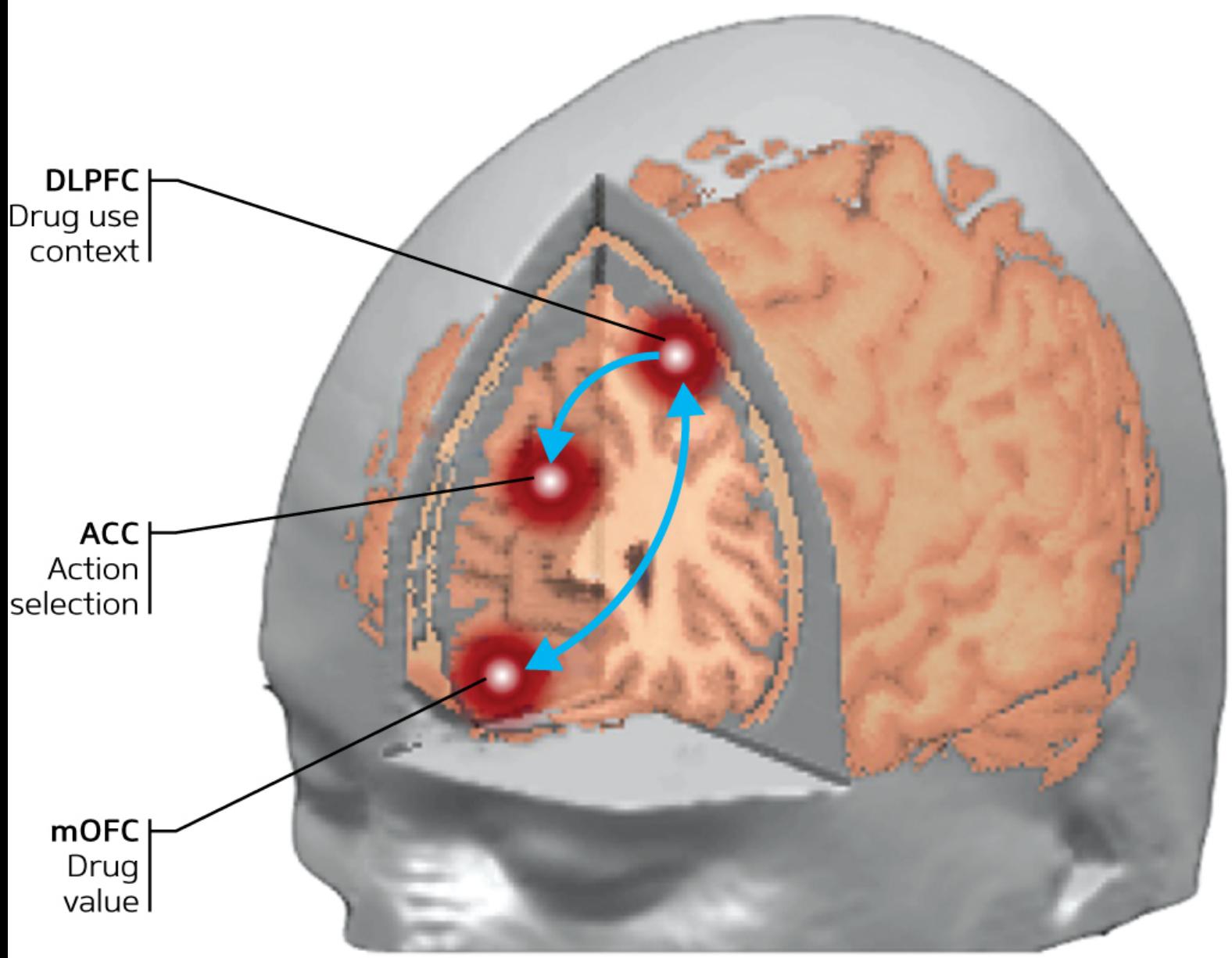
- **Robins (Vietnam Vets): drug use is situational**
- **Alexander (Rat Park): it's not the drug that causes addiction, it's the environment**
- **Heyman: most people with addiction do NOT progress or die – most stop when they get older and start making better choices**
- **Lewis: addiction is a learned habit that can be unlearned; a developmental disorder not a disease**

# A “Disease” of Volition

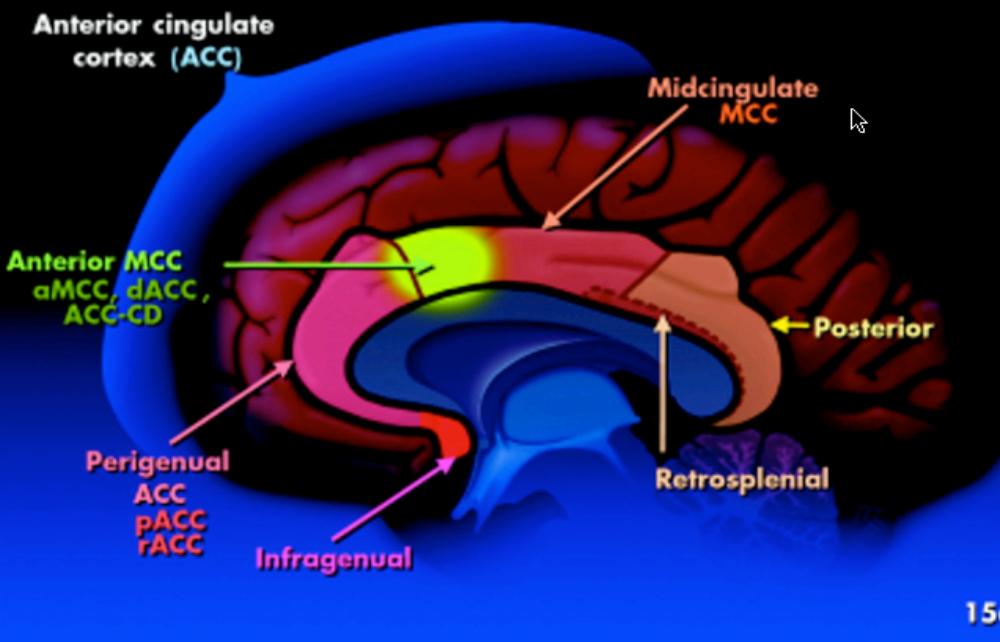
- Could such a thing exist? (ontologic argument)
- What would happen if such a thing existed? (teleologic argument)
- What is the nature of volition/free will/choice?
- Is there something special (non-material) about “choice?”
- If so, what is it?
- If not, how is “choice” realized in the brain?

# What goes into a “choice?”

- Valuation and Framing
- Risk-taking, Novelty-seeking and Impulsivity
- Genetic vulnerability vs resilience
- Empathy vs. Narcissism
- Memory, Stress and Trauma (and Epigenetics)
- Social Status/Social Defeat



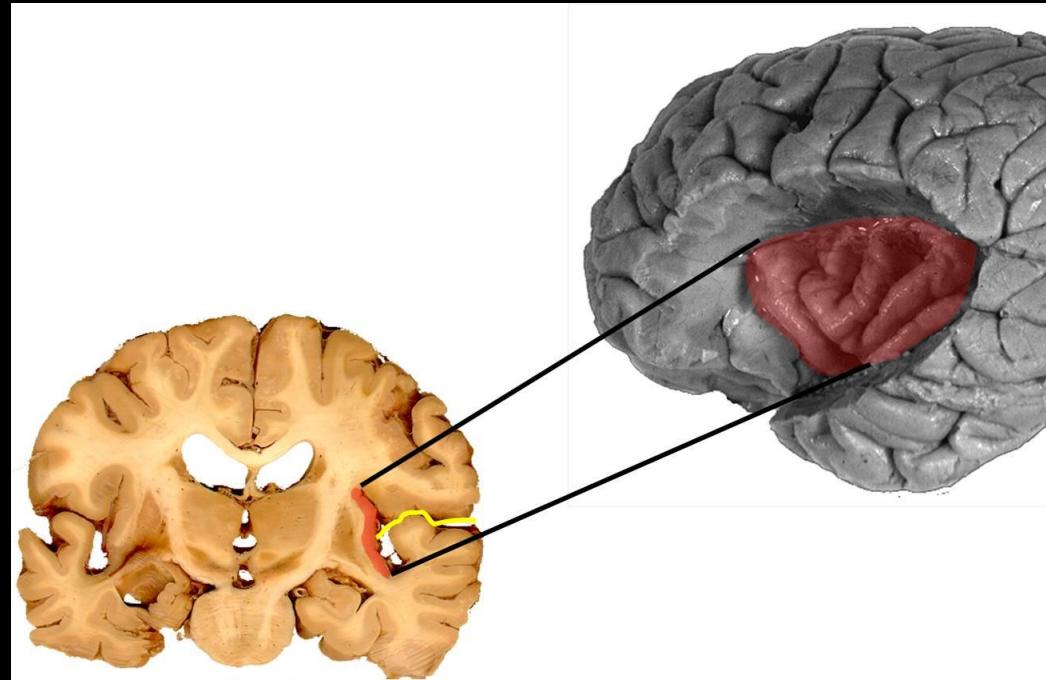
# Anterior Cingulate Cortex (ACC)



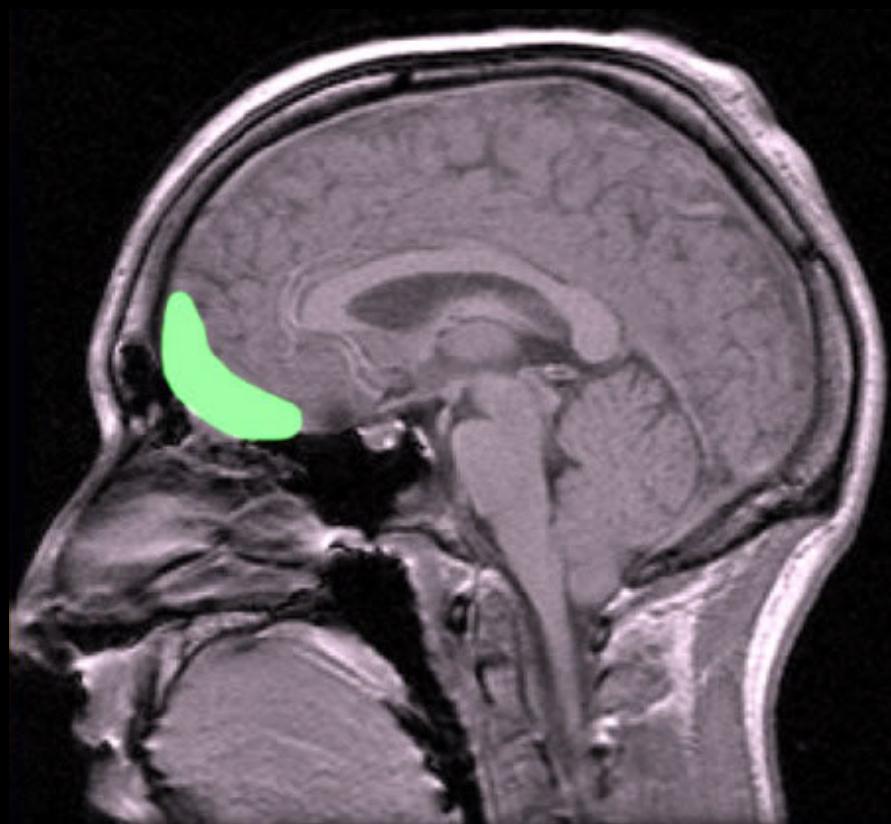
- Works with OFC: decision-making based on reward values
- But also generates new actions based on past rewards/punishments
- Appreciation and valuation of social cues
- MRI: active in tasks requiring empathy and trust

# Insular Cortex (IC)

- Abrupt cigarette smoking cessation with IC lesions (Naqvi et al)
- Important in emotional awareness, empathy, interoceptive representation
- Impairment is one part of craving



# Orbitofrontal Cortex (OFC)



- Decision-making guided by rewards
- Integrates sensory and emotional information from lower limbic structures
- Flexible assignment of value to environmental stimuli to motivate or inhibit choices & actions
- Self-monitoring and social responding

# The Brain is a Bayesian Calculator



Rev. Thomas Bayes (1701 – 1761)

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$







alcoholic

choice

Outcome 1



$$v_1 = x$$
$$p_1 = 1$$

Outcome 2



$$v_2 = y$$
$$p_2 = 1$$

Outcome 3



given



$$v_3 >> v_4$$
$$p_3 >> p_4$$

In addiction,  
the brain's ability to correctly calculate  
1. value  
and  
2. probability  
becomes severely biased

This means that people in early recovery  
have a hard time assessing  
likelihood of future harm

... or RISK

# Addiction is a disorder of ...

- |                  |                              |   |
|------------------|------------------------------|---|
| <b>5. CHOICE</b> | <b>(motivation, insight)</b> | <b>OFC, ACC, PFC, IC</b>                          |
| <b>4. STRESS</b> | <b>(anti-reward system)</b>  | <b>HPA axis</b>                                   |
| <b>3. MEMORY</b> | <b>(habits, cues)</b>        | <b>glutamate</b><br><b>synaptic remodeling</b>    |
| <b>2. REWARD</b> | <b>(incentive salience)</b>  | <b>dopamine</b><br><b>dopamine receptors</b>      |
| <b>1. GENES</b>  | <b>(vulnerability)</b>       | <b>polymorphisms</b><br><b>epigenetic changes</b> |

# Addiction is a disorder of ...

- 5.
- 4.
- 3.
- 2.

1. GENES (vulnerability)

polymorphisms  
epigenetic changes

# Heritability of Addiction

(from twin studies)

**Alcohol:** 48 – 66%

**Cannabis:** 51 – 59%

**Cocaine:** 42 – 79%

**Opioids:** 23 – 49%

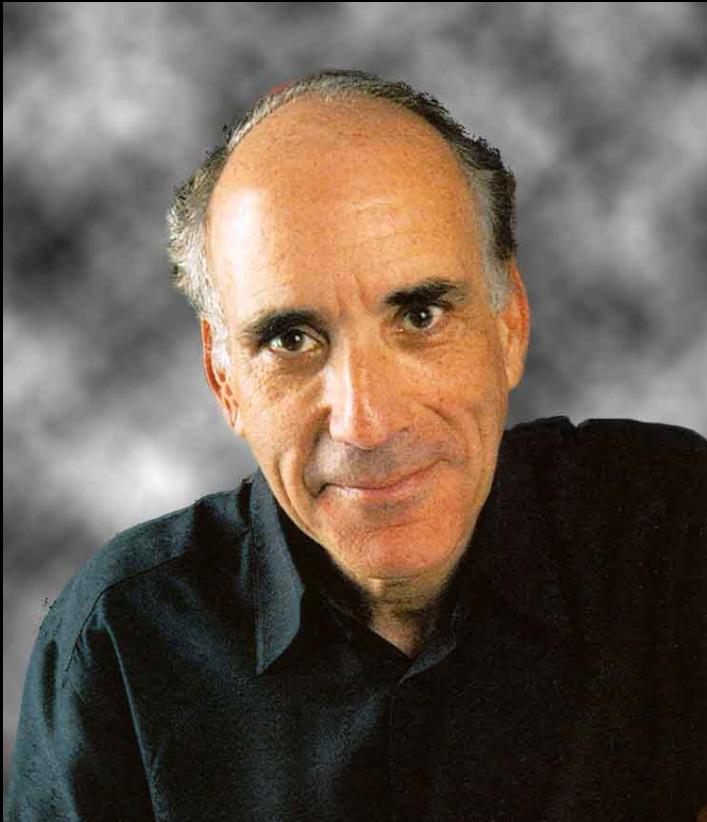
**Nicotine:** 33 – 71%

shifts from adolescence (environment)  
to young adulthood (genetics)

**Gambling:** 49%

- Heritability: an aggregate measure of the variability of a characteristic due to genetics vs environment (the risk due to genes – “risk genes”)
- First-order family members of a person with SUD have a 4 – 8 x increased risk of developing SUD
- Applies to populations, not individuals (that would be *inheritance*)
- Probabalistic, not deterministic

# *Genetic Vulnerability vs Resilience*



Mark Schuckit, MD  
U.C. San Diego

- Genetic difference determine “low responders” vs. “high responders” to the effects of alcohol (low responders are more likely to become alcoholics)
- There are genetic differences in how people respond to methylphenidate (Ritalin) injections (some like it, some don’t care) implying different vulnerabilities
- For addicts, drugs really do “feel” different than they do to non-addicts

# Common pharmacogenetic polymorphisms

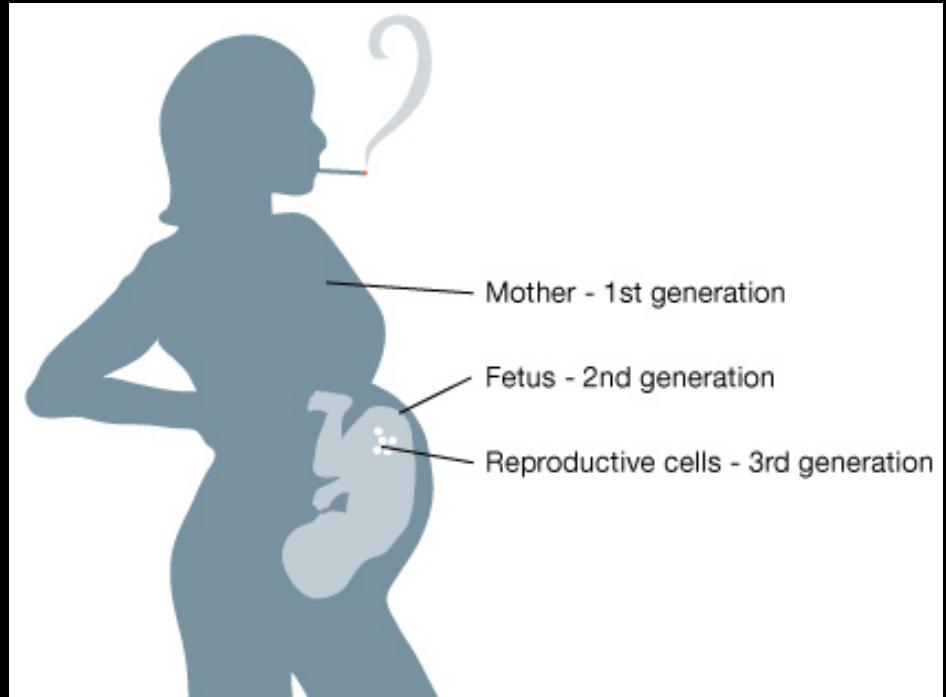
Cytochrome P450	Phenotype	Frequency in ethnic groups	Total # drugs	Examples
CYP2D6	Poor metabolizer	White 6% AA 2% Asian 1%	>100	codeine, nortriptyline, dextro- methorphan fluoxetine propranolol
	Ultra-rapid	Ethiopian 20%, Spanish 7%, Scand 1.5%		
CYP2C9	Reduced activity		>60	tolbutamide, diazepam, ibuprofen, warfarin
CYP2C19	Poor metabolizer	Asian 23% White 4%	>50	omeprazole, plaquenil,
N-Acetyl transferase	Poor metabolizer	White 60% AA 60% Asian 20% Intuit 5%	>15	isoniazid, procainamide, hydralazine

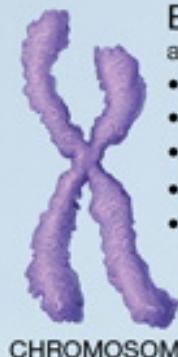
# Epigenetics

- **Modifications (DNA methylation, Histone acetylation) that effect gene expression**
- **Tells the cell what genes to express**
- **Heritable (but reversible) changes in gene expression due to environmental factors**
- **Allows passage of information from generation to generation that is not encoded in DNA**
- **Inheritance without DNA sequence change**

# Epigenetics

- Overkalix study: Starvation during adolescence increased the prevalence of diabetes in *grandchildren*
- Holocaust survivors with PTSD: their children also had PTSD without having been exposed to trauma
- A mechanism exists to transmit environmental exposure information from one generation to the next to the next





## EPIGENETIC MECHANISMS

are affected by these factors and processes:

- Development (in utero, childhood)
- Environmental chemicals
- Drugs/Pharmaceuticals
- Aging
- Diet

DNA

METHYL GROUP

CHROMATIN

### DNA methylation

Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

GENE

HISTONE

HISTONE TAIL

DNA inaccessible, gene inactive

Histones are proteins around which DNA can wind for compaction and gene regulation.

## HEALTH ENDPOINTS

- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

PICTURE OF EPIGENETIC FACTOR

HISTONE TAIL

DNA accessible, gene active

### Histone modification

The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

# **Strategies to deal with the GENETIC (VULNERABILITY) component of addiction**

- Careful framing (vulnerability > adaptation)
- Adaptive strategies
- Risk assessment and stratification for all future medications
- Pharmacogenomics

# Addiction is a disorder of ...

5.  
4.  
3.

2. REWARD (incentive salience)

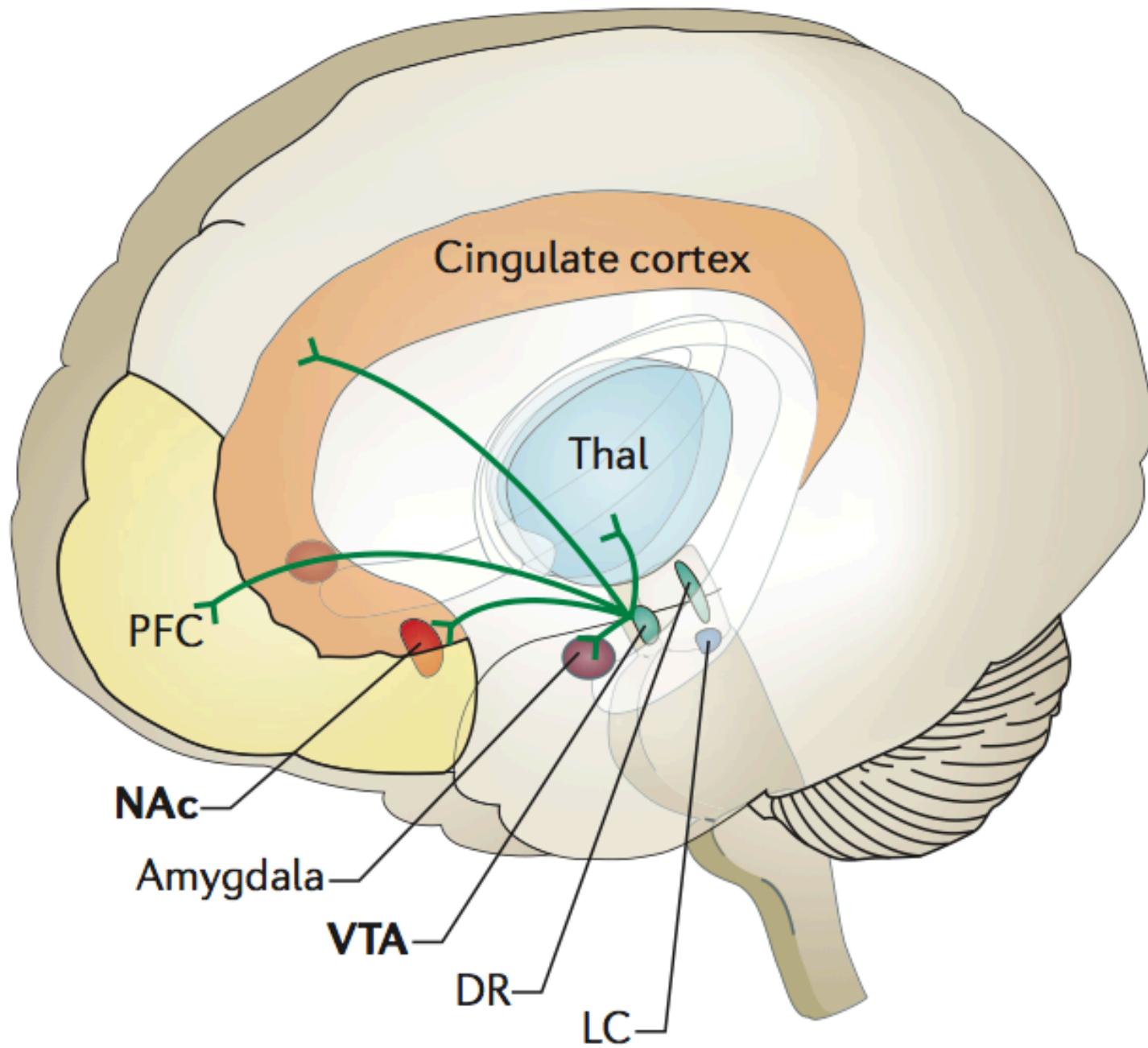
dopamine

dopamine receptors

1. GENES (vulnerability)

polymorphisms

epigenetic changes



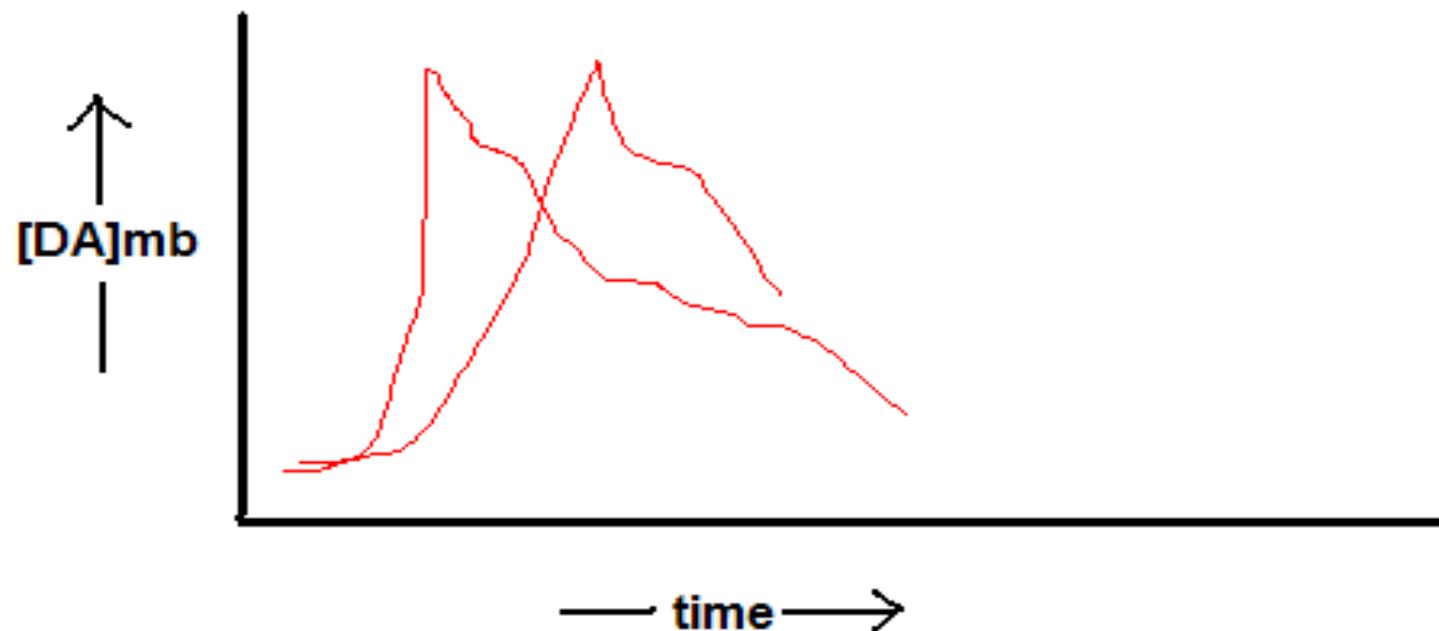
# Addiction Neurochemical #1: Dopamine

- All drugs of abuse and potential compulsive behaviors release Dopamine
- Dopamine is the first chemical in the cascade of chemicals that generate a rewarding experience
- DA is the chemical of salience (survival importance)
- DA is more about “wanting” than “liking”
- DA is more about expectation than consummation
- DA signals reward prediction error - it tells the brain when something is “better than expected”

# **DA NAc neurons do more than encode receipt of reward**

- **Expectancy of reward**
- **Amount of reward**
- **Delay of reward**
- **Errors in reward prediction**
- **Motivation for drug seeking**
- **Contribute to synaptic neuroplasticity that underlies the acquisition of addictive behaviors**

# *Drugs cause Dopamine Surges in the midbrain reward system*



# *Dopamine-Releasing Chemicals*

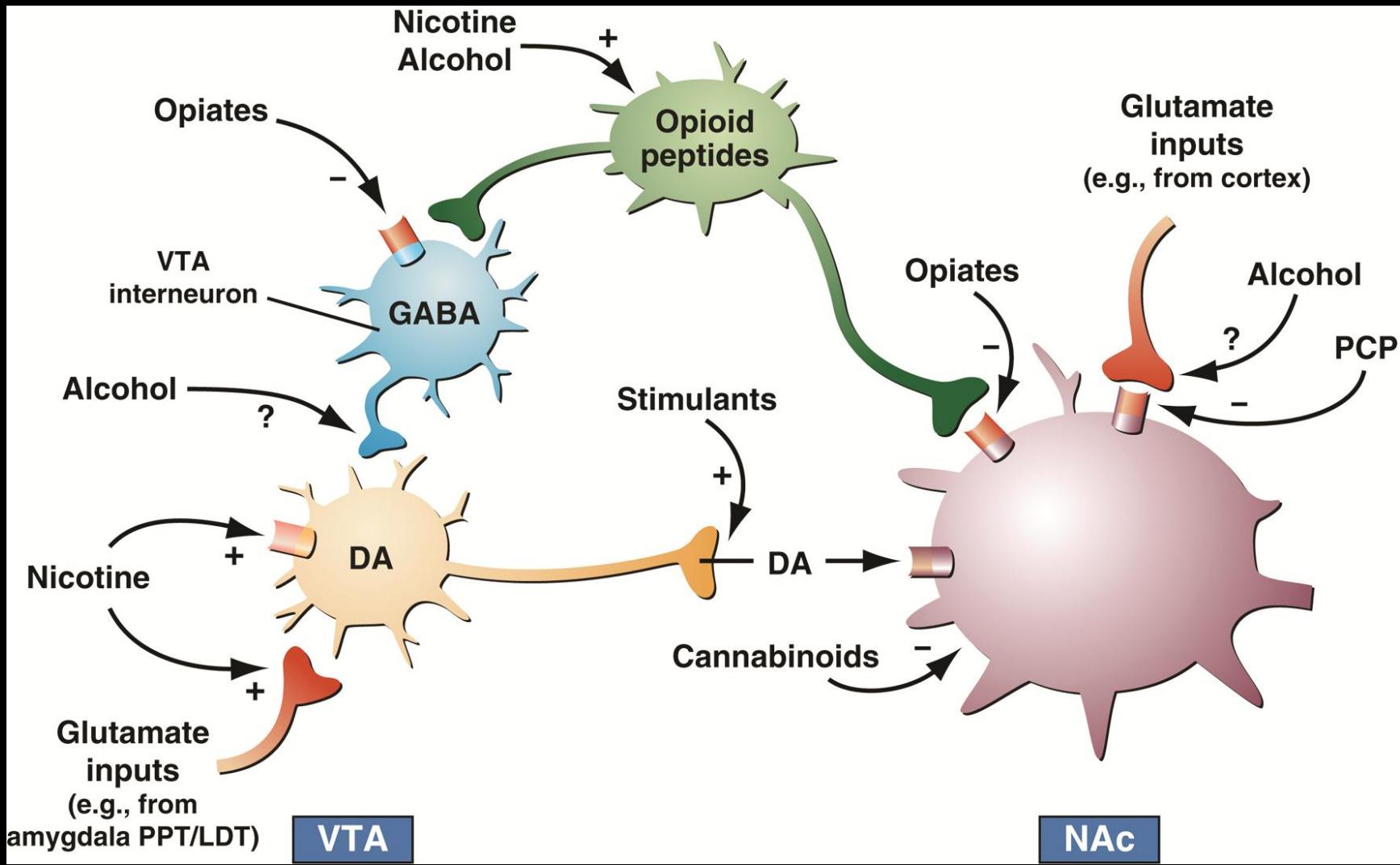
- Alcohol & Sedative/Hypnotics
- Opiates/Opioids
- Cocaine
- Amphetamines
- Entactogens (MDMA)
- Entheogens/Hallucinogens
- Dissociants (PCP, Ketamine)
- Cannabinoids
- Inhalants
- Nicotine
- Caffeine
- Anabolic-Androgenic Steroids

# *Dopamine-Releasing Behaviors*

- Food (Bulimia & Binge Eating)
- Sex
- Relationships
- Other People  
("Codependency," Control)
- Gambling
- Cults
- Performance  
("Work-aholism")
- Collection/Accumulation  
("Shop-aholism")
- Rage/Violence
- Media/Entertainment

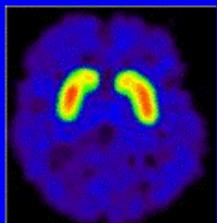
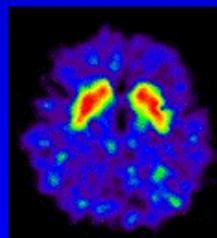
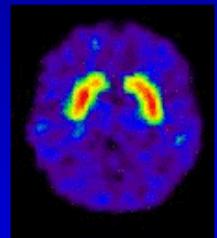
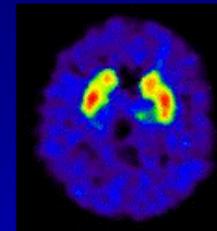
# *The Full Spectrum of Addiction*

- Alcohol & Sedative/Hypnotics
- Opiates/Opioids
- Cocaine
- Amphetamines
- Entactogens (MDMA)
- Entheogens/Hallucinogens
- Dissociants (PCP, Ketamine)
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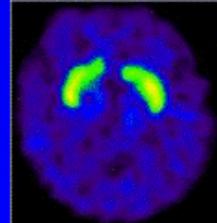
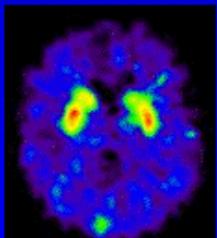
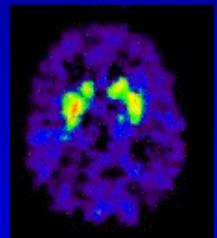
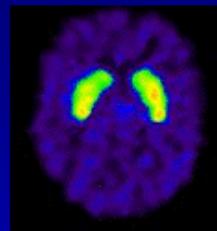


*Functionally...*

## Dopamine D2 Receptors are Decreased by Addiction



Control

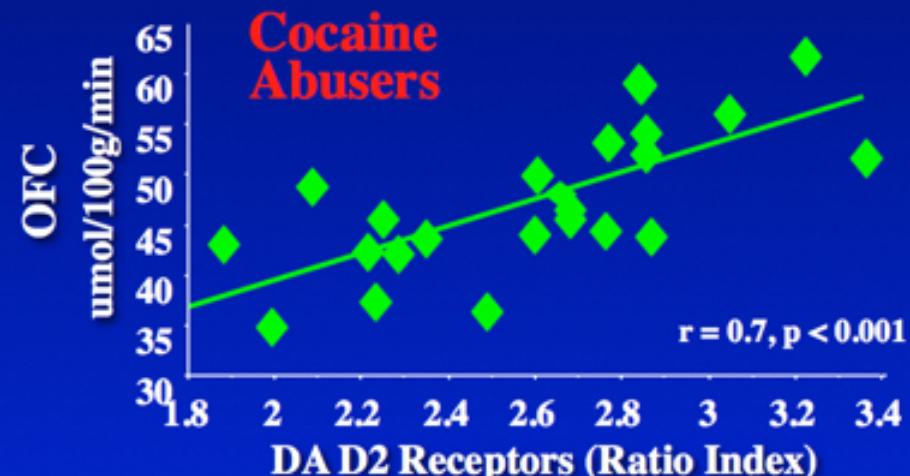
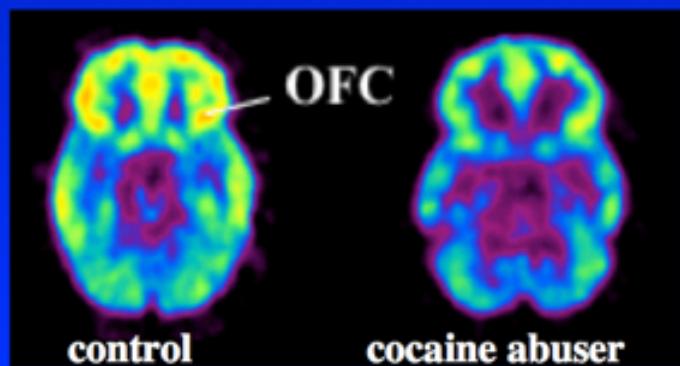
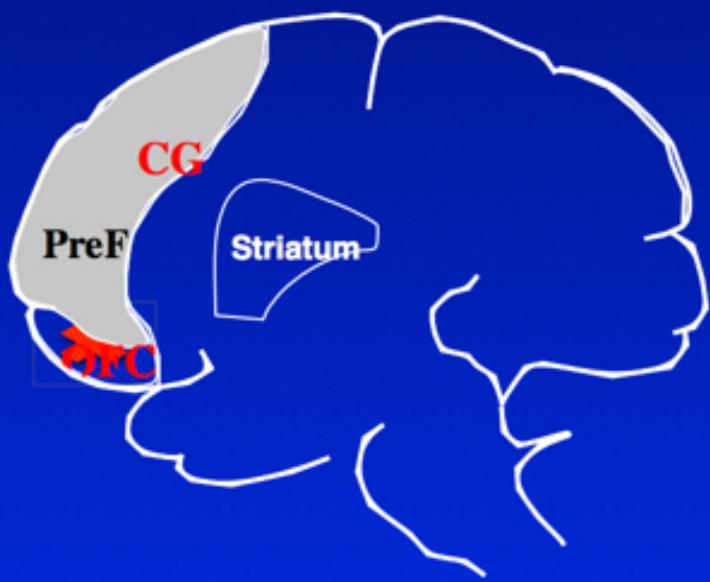


Addicted

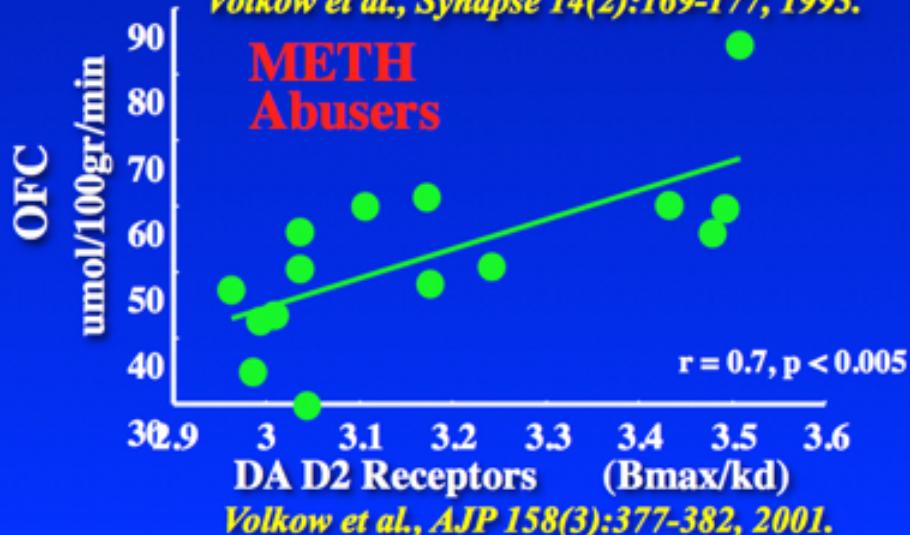


DA D2 Receptor Availability

# *Correlations Between D2 Receptors in Striatum and Brain Glucose Metabolism*



Volkow et al., *Synapse* 14(2):169-177, 1993.



Volkow et al., *AJP* 158(3):377-382, 2001.

# Periodic Table of the Intoxicants

1 ns*																									
Al ethanol																									
Mj THC	Cb cannabinol	Ha hashish	Sp cannibicyclo																						
Pc phencycl.	K ketamine	No nitrous	Dx DXM	Sa salvinorin																					
Ly pregabalin	Sm carisoprodol	Am zolpidem	So zaleplon	Lu eszopiclone	Ch chl. hydrate	G GHB	Q methaqual.	Pb phenobarb.	Sb secobarbital	Fb butalbital	Ep ephedrine	Mo modafinil	Ff phentermine	Ri methylphen.	Kh cathinone	Ba MDPV	X MDMA	A amphetam.	Me methamph.						
Bu buprenorph.	Na nalbuphine	St butorphanol	Ul tramadol	Kr mitragynine	Tw pentazocine	Dv propoxyph.	O opium	Co codeine	Vi hydrocod.	Ox oxycodone	Cz chlordiaz.	Oz oxazepam	Tz temazepam	Lz lorazepam	Rz flunitraz.	Dz diazepam	Hz triazolam	Kz clonazepam	Xz alprazolam						
Or org solvents	Pe petrol gases	Ae aerosols	An amyl nitrite	De diethyl ether	Cl chloroform	Ih inhal. anes.	Po propofol																		
88 ns food/sugar	89 ns* sex	90 ns relationships	91 ns codepend.	92 ns* gambling	93 ns cults	94 ns performance	95 ns shopping	96 ns* rage	97 ns* media																

Kevin T. McCauley, MD

88 ns food/sugar	89 ns* sex	90 ns relationships	91 ns codepend.	92 ns* gambling	93 ns cults	94 ns performance	95 ns shopping	96 ns* rage	97 ns* media
F	Sx	Ri	Cd	Gm	Cu	Pf	Sh	Rg	Mi

# **Strategies to deal with the DOPAMINE (REWARD) component of addiction**

- Daily “dopamine load” assessment
- Take out the Dopamine “spikes”
- Nicotine cessation
- Avoid cross-addiction
- Put normal Dopamine releases (normal, competing rewarding activities) back in
- Judiciously chosen medications



# “Rat Park” Study

Bruce K. Alexander

Alexander BK, Coambs, RB, Hadaway PF. The effect of housing and gender on morphine self-administration in rats.  
Psychopharmacology(1978) 58, 175-179.



# “Rat Park” Study (Alexander)

- Morphine consumption by rats housed in isolation vs socially
- Isolated rats drank more morphine ( $n = 32$  rats)
- Both groups drank plenty of morphine, and 5 rats died of morphine overdoses (2 in the isolated group and 3 in the socially-housed group)
- Implication: morphine is more reinforcing in isolated environments and less so in enriched environments
- Study has some problems, and subsequent replication studies had mixed results
- Point taken: Housing matters
- But: how do you know “cross-addiction” didn’t occur?

# ASAM Definition: Relapse

- Persistent relapse / and risk thereof
- Even after periods of abstinence
- Triggered by:
  1. Re-exposure to drug itself (DA release in NAc)  
**drug-induced reinstatement**
  - 2.
  - 3.

# Dopamine begins reward but quickly fades to support cues

- DRUG-induced fast DA increases in the striatum (incl NAc) mediate their rewarding effects
- In addiction: DRUG-induced DA increases (as well as subjective rewarding effects) are markedly blunted (pharmacologic effects fade)
- In addiction: but CUE-induced DA increases in the striatum are still significant and are associated with self-reports of craving (conditioned responses strengthened)
- In addiction: lower levels of striatal DAD2Rs

# ASAM Definition: Relapse

- Persistent relapse / and risk thereof
- Even after periods of abstinence
- Triggered by:
  1. Re-exposure to drug itself (DA release in NAc)  
**drug-induced reinstatement**
  2. Exposure to drug cues (GLU release in Amygdala/Hipp)  
**cue-induced reinstatement**
  - 3.

# Addiction is a disorder of ...

5.

4.

3. MEMORY (habits, cues)

glutamate

2. REWARD (incentive salience)

synaptic remodeling

1. GENES (vulnerability)

dopamine

dopamine receptors

polymorphisms

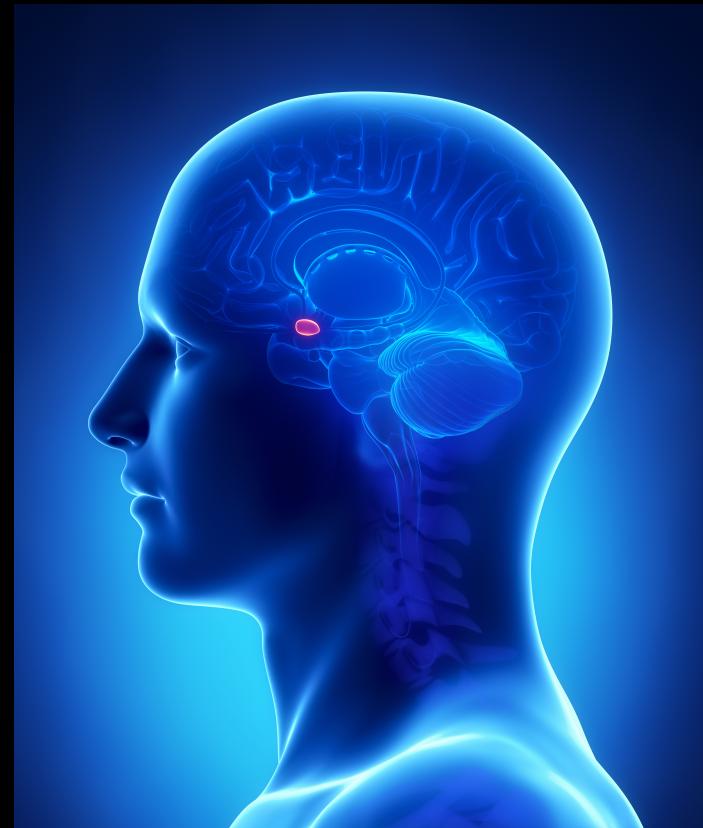
epigenetic changes

# The Memory System

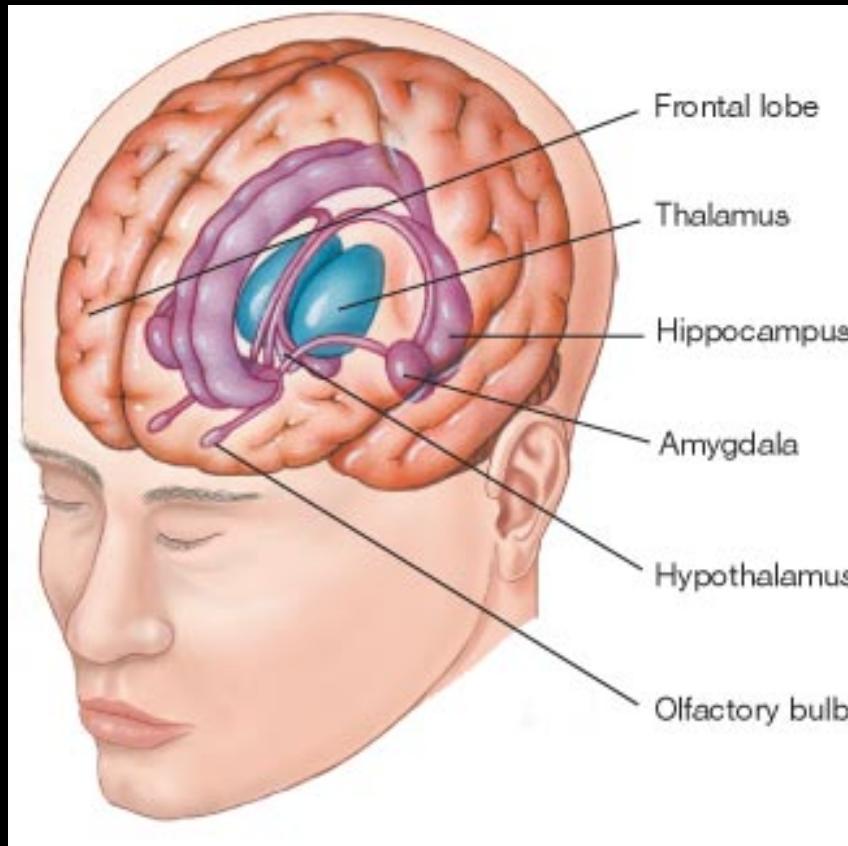
Hippocampus



Amygdala



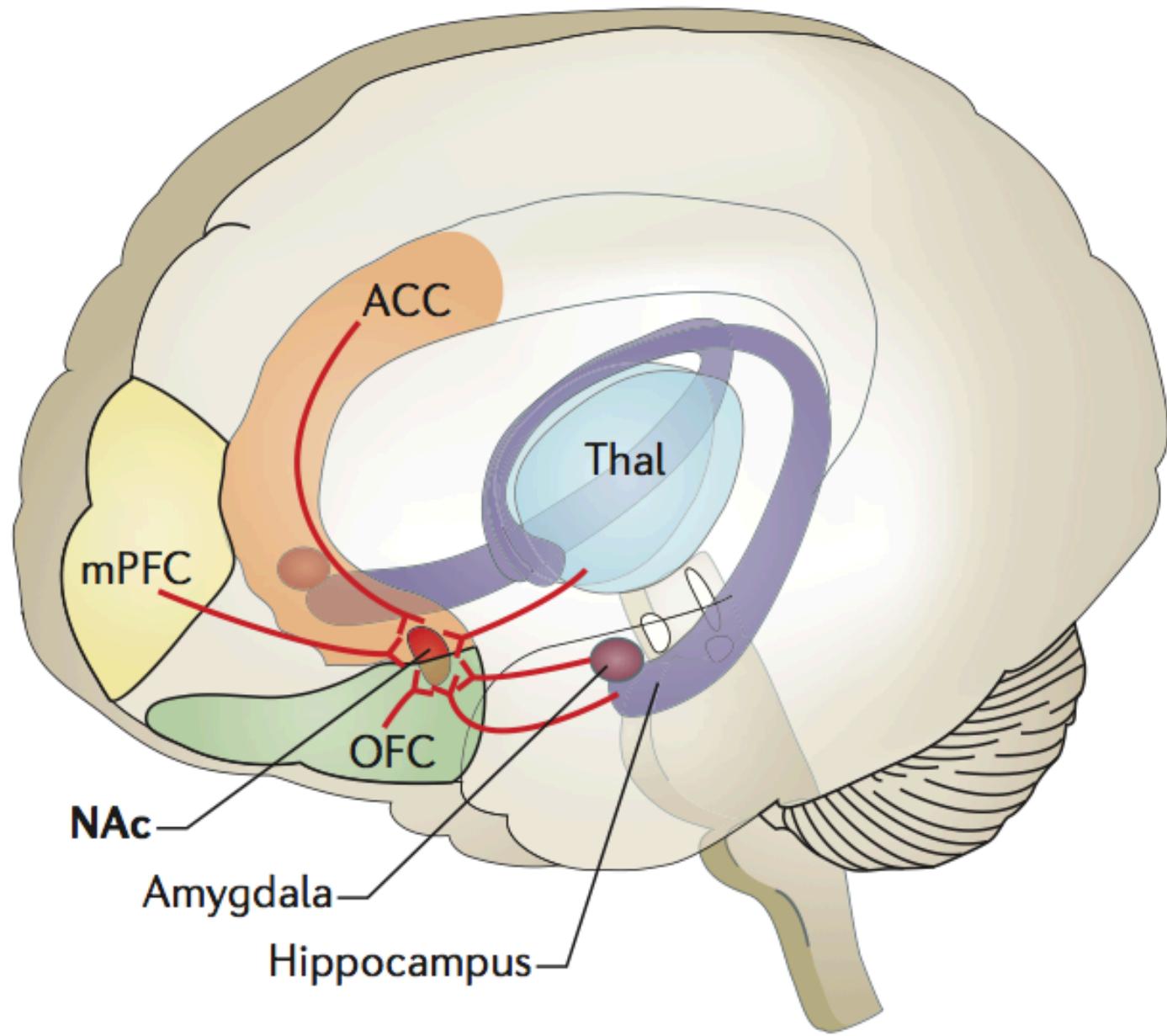
# Amygdala



- Key role in conditioned responding, especially fear
- Drives an impulsive, non-reflective response selection (decision-making)
- Active during craving

# Addiction Neurochemical #2: Glutamate

- The most abundant neurochemical in the brain
- Critical in memory formation & consolidation
- All drugs of abuse and many addicting behaviors effect Glutamate which preserves drug memories and creates drug cues
- And ... glutamate is the neurochemical of “motivation” (it initiates drug seeking)



# The hypofrontal/craving brain state represents and imbalance between 2 brain drives

## Amygdalar-Cortical Circuit

- “**GO!**”
- Impulsive
- Non-reflective
- Poorly conceived
- Socially inappropriate

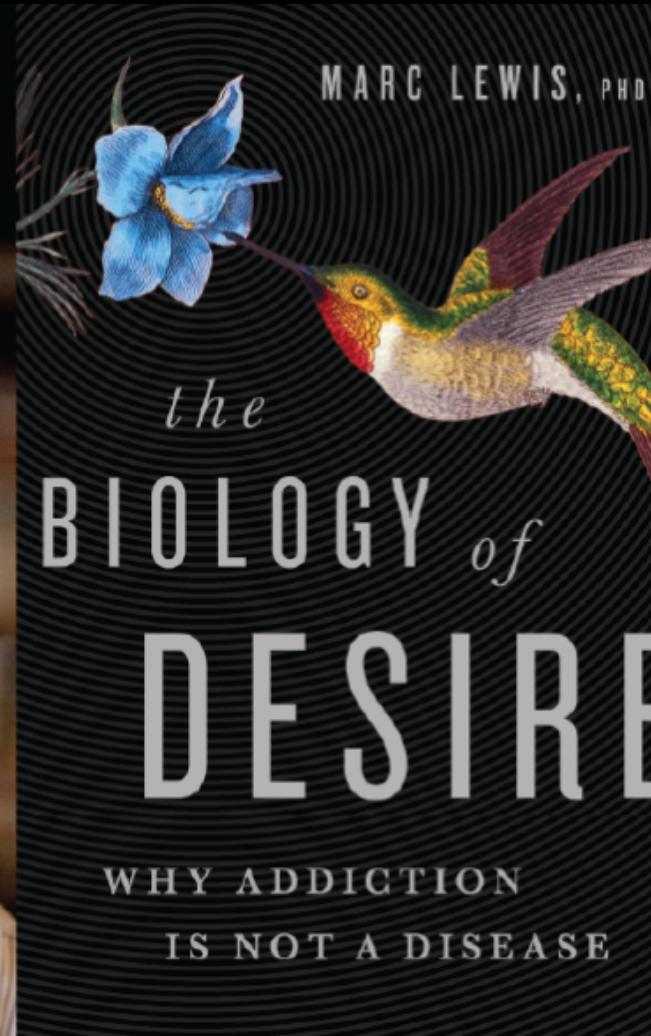
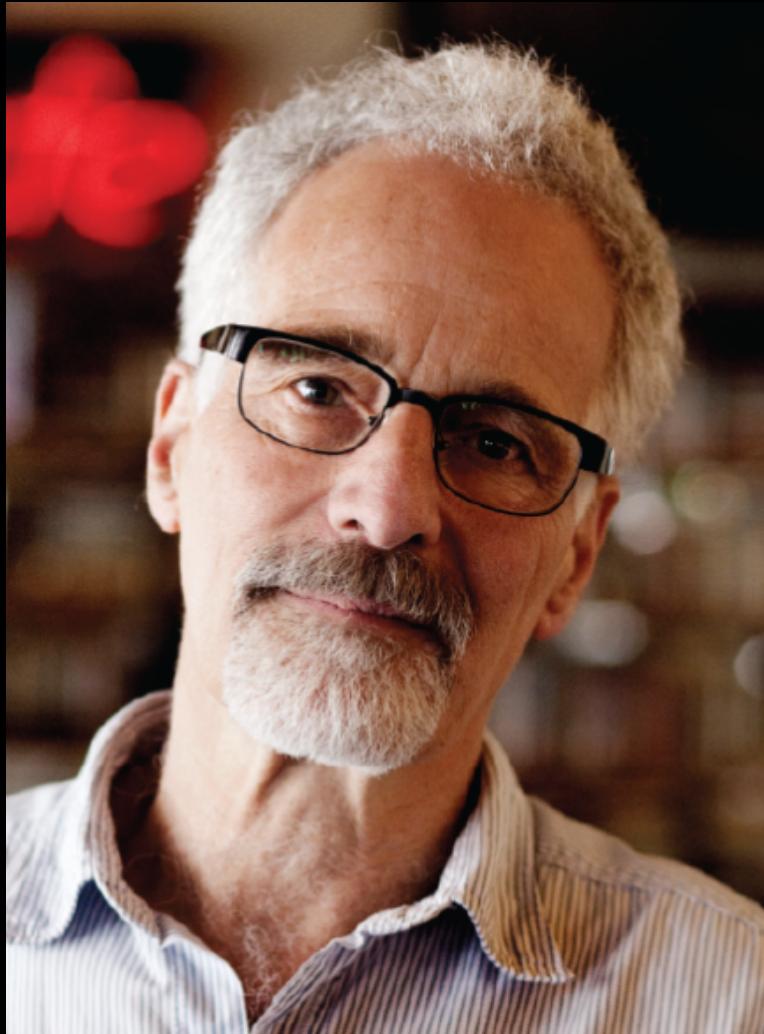
## Cortico-Striatal Circuit

- “**DON’T GO!**”
- Organized, Attentive
- Sensitive to consequences
- Well-planned
- Socially appropriate

**THERE’S TOO MUCH OF THIS**  
**(Behavioral Impulsivity)**

**THERE’S TOO LITTLE OF THIS**  
**(Failure of Behavioral Inhibition)**

# Marc Lewis, PhD



# Marc Lewis, PhD: Addiction as a Developmental Stage

- Brain changes *per se* do not indicate pathology
- Plasticity and synaptic pruning (learning) are normal functions of the brain
- Addiction is a particularly deep form of learning
- Motivated repetition remodels the brain causing intense desire for drugs (craving), strong cues to repeat, over-valuation of drug, narrowing of focus,
- The very thing that got a person into addiction (plasticity) can get them out (development past addiction into recovery)
- Getting to “core issues” is important

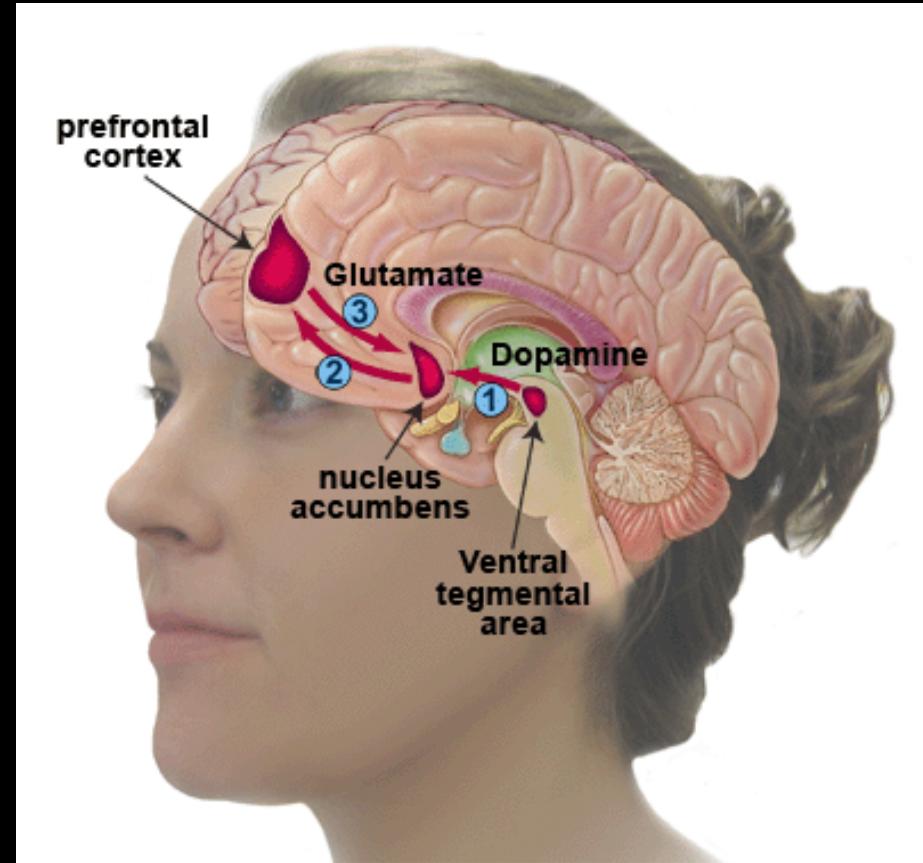
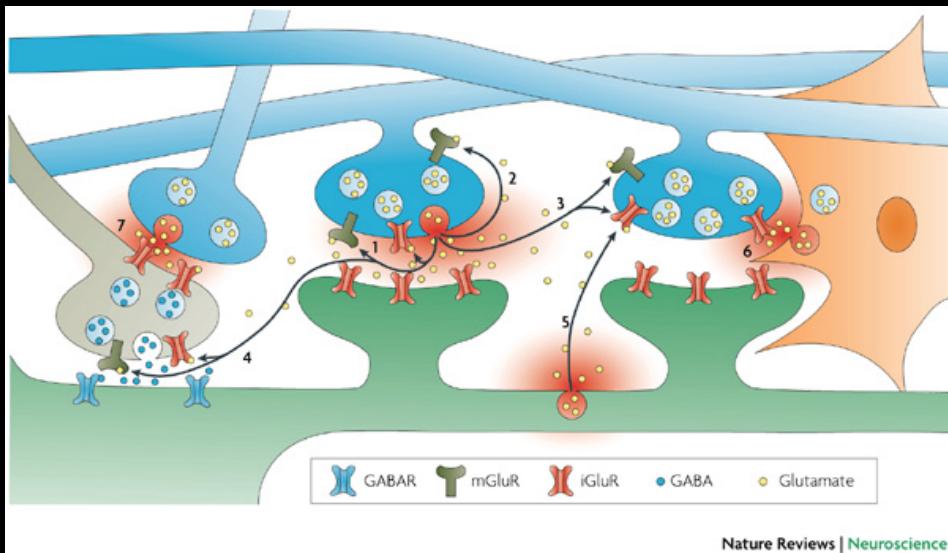
# Glutamate “spillover”

- Enduring vulnerability to relapse due to recruitment of “corticofugal” GLU projections to striatum
- Excess GLU “spills” out of the synapse to bind to extra-synaptic GLU receptors
- Changes in synaptic plasticity leads to pathologic learning and memory
- Result: impairment of inhibition of drug seeking

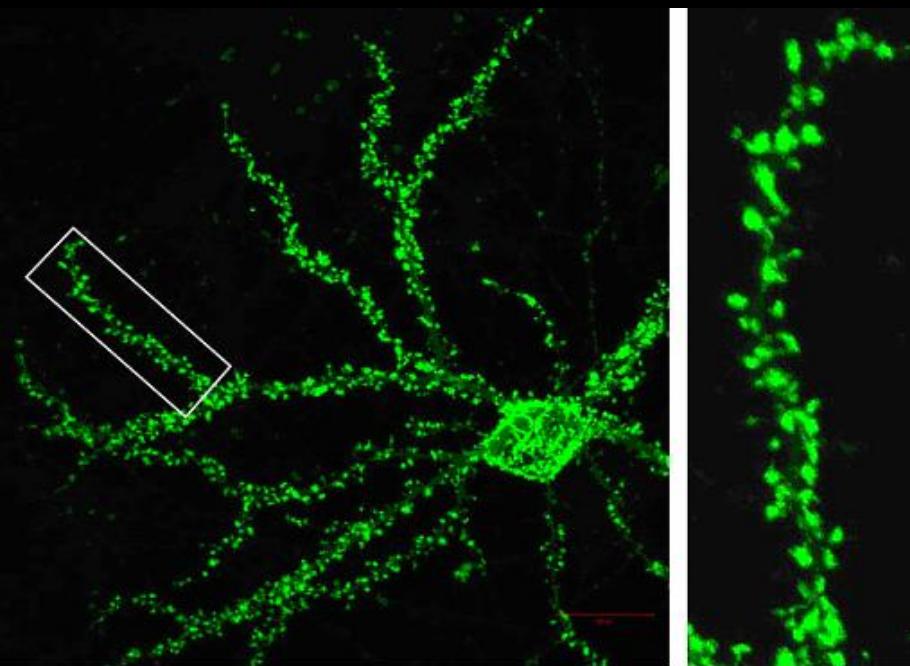


Peter W. Kalivas, PhD  
Department of Neurosciences  
Medical University of South Carolina

# GLU synaptic plasticity



# Transcription Factor: $\Delta$ FosB



- Mediates the structural plasticity induced in the NAc by cocaine
- Changes in number, shape and size of dendritic spines of NAc DAD1R-expressing MSNs
- Larger changes in spine density with self-admin over experimenter-admin of cocaine
- Also induced by chronic consumption of natural rewards (sucrose, high fat foods, sex, wheel running)
- “ $\Delta$ FosB is both necessary and sufficient for many of the changes in the brain after chronic drug exposure”

# **Strategies to deal with the GLUTAMATE (MEMORY) component of addiction**

- Prepare for triggers
- Avoid triggers as much as it is possible to do so (avoiding old places, playmates, etc)
- Self-talk in moments of craving (CBTx)
- Peers, behavioral barriers, frequent monitoring
- Medications

# ASAM Definition: Relapse

- Persistent relapse / and risk thereof
- Even after periods of abstinence
- Triggered by:
  1. Re-exposure to drug itself (DA release in NAc)  
**drug-induced reinstatement**
  2. Exposure to drug cues (GLU release in Amygdala/Hipp)  
**cue-induced reinstatement**
  3. Exposure to Envir Stress (CRF release in Amygdala)  
**stress-induced reinstatement**

# Addiction is a disorder of ...

5.

4. STRESS (anti-reward system)

HPA axis

3. MEMORY (habits, cues)

glutamate

synaptic remodeling

2. REWARD (incentive salience)

dopamine

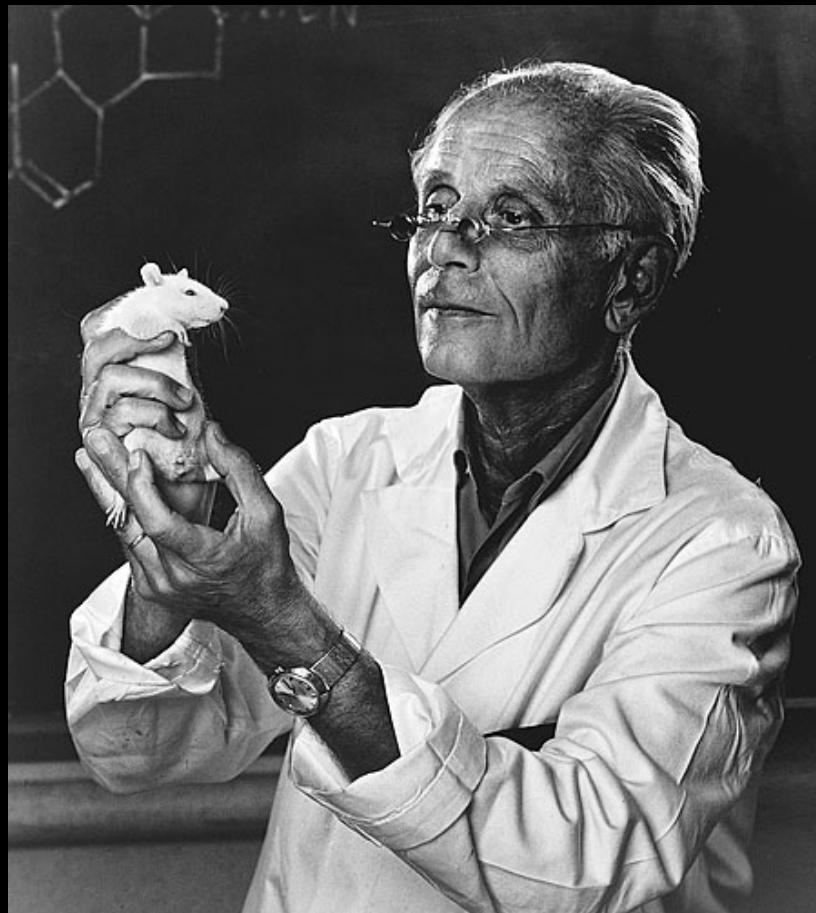
dopamine receptors

1. GENES (vulnerability)

polymorphisms

epigenetic changes

# What counts as “Stress?”

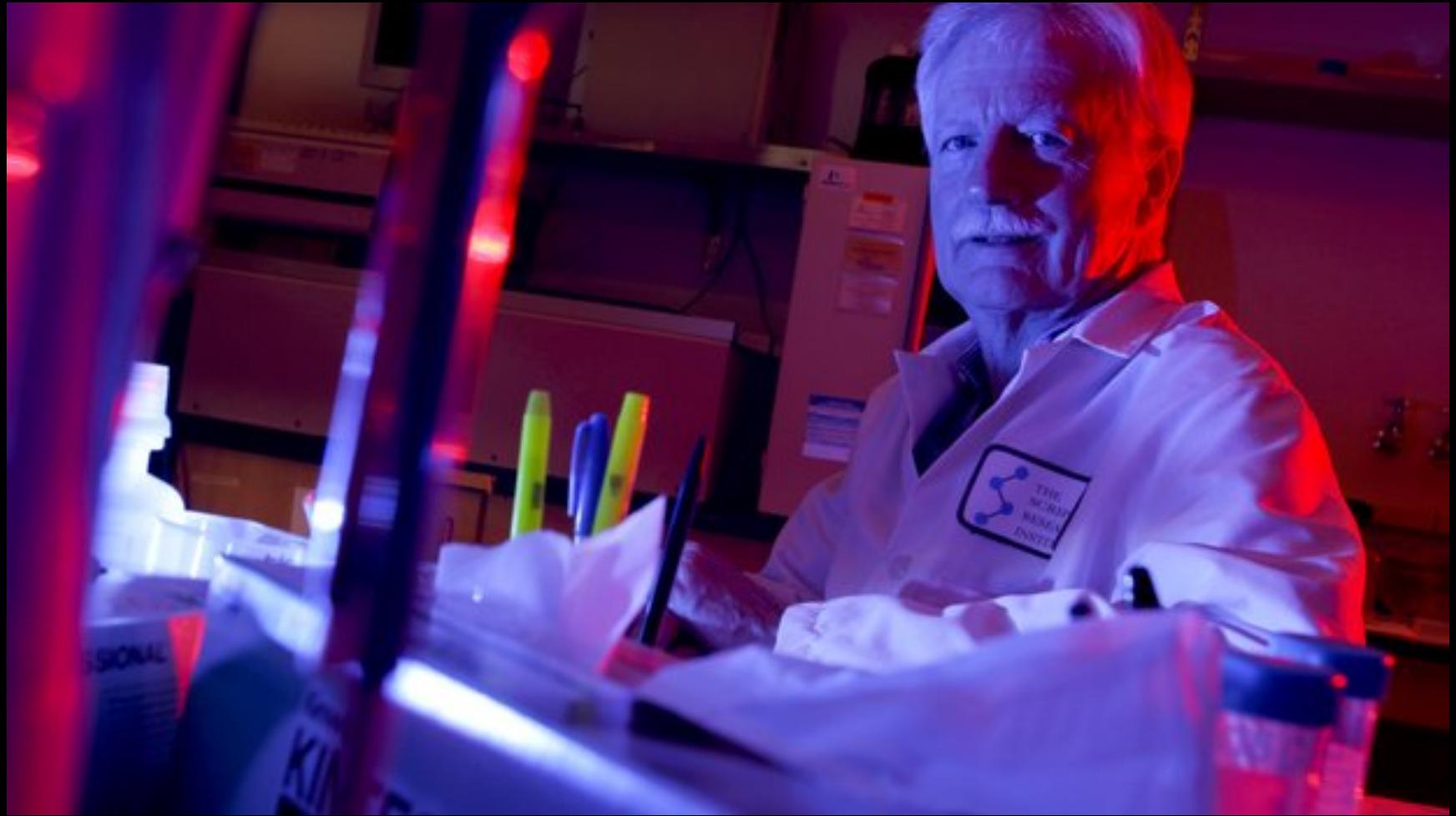


Janos "Hans" Selye, PhD (1907-1982)

- Any unpredictable or uncontrollable event that exceeds the regulatory capacity of the organism, and that threatens or could threaten an organism's physical or psychosocial integrity
- Eustress: healthy, “good” stress; perceived as a positive challenge, feelings of control/mastery, associated with meaning, hope and well-being; positive effect on healing and immunity
- Dystress: “bad” stress; sustained arousal that goes unresolved; failing performance; increasing anxiety; cumulatively taxing; hysteresis

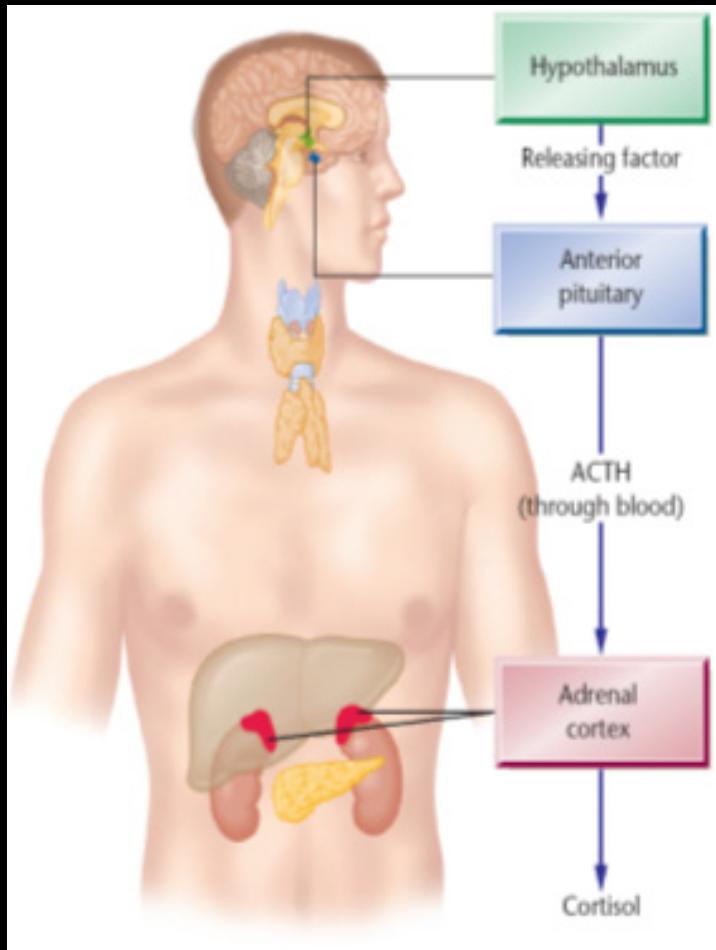
# **Childhood Trauma & Chronic Repeated Stress affect all 5 stages of SUD illness course**

- 1. INITIATION: first time substance use & initial experimentation**
- 2. REGULAR USE: shift from experimental to regular use**
- 3. ABUSE/DEPENDENCE: escalation from regular substance use to abuse/dependence**
- 4. MOTIVATION TO QUIT: behavioral & emotional control**
- 5. RELAPSE: craving, negative affect**

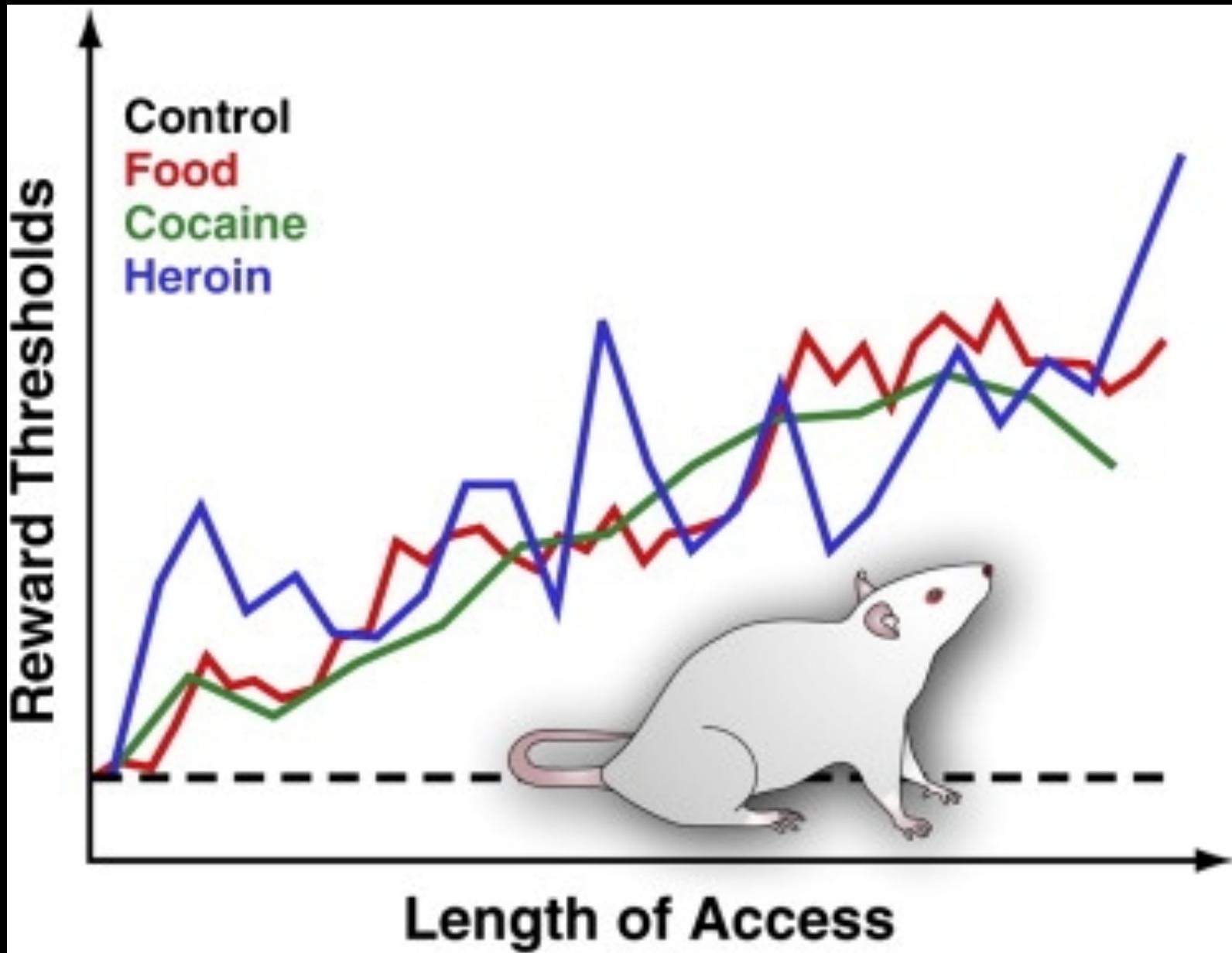


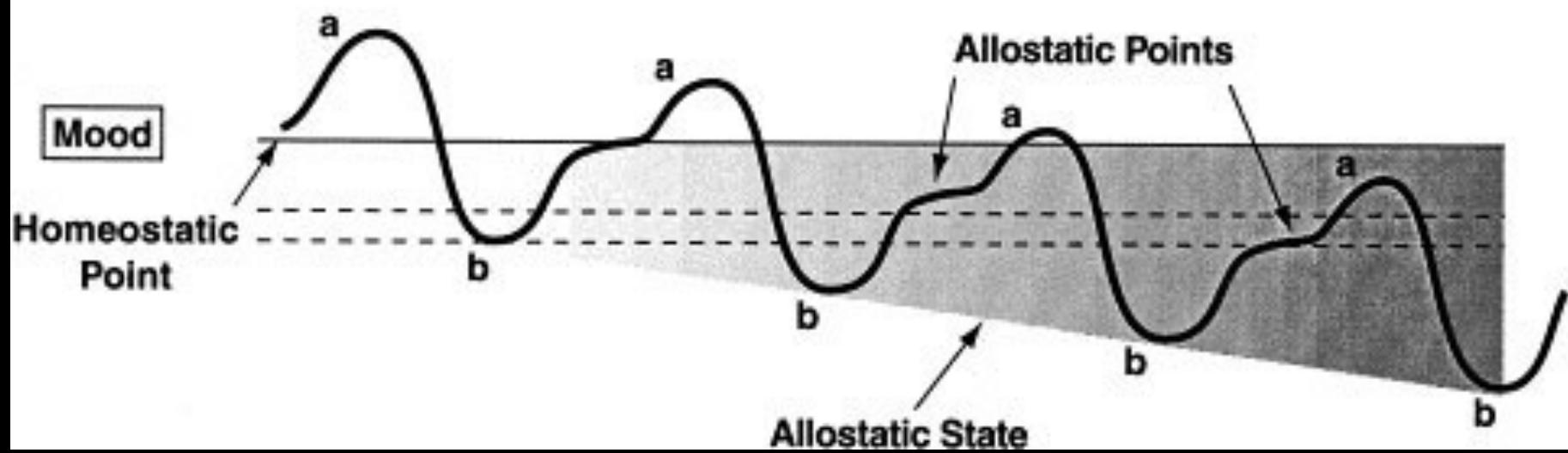
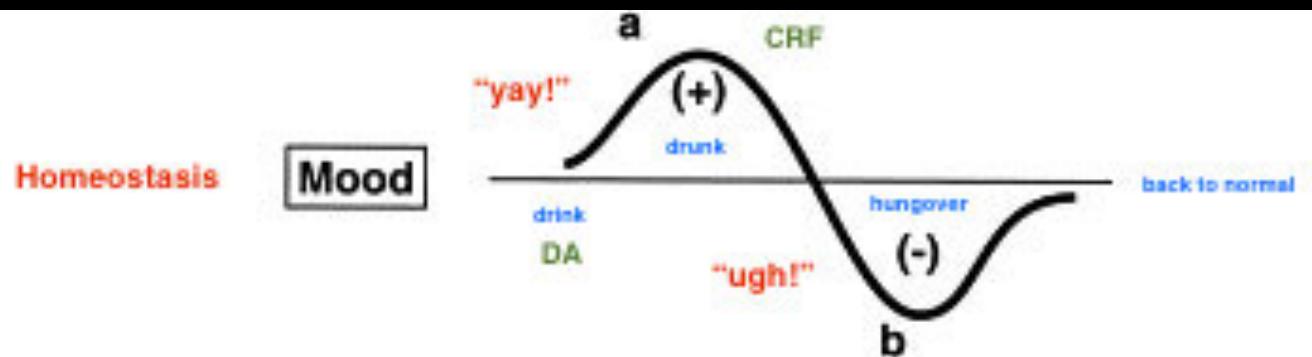
**George Koob, PhD**  
**Chair, Neurobiology of Addictive Disorders**  
**Scripps Neurosciences Institute**

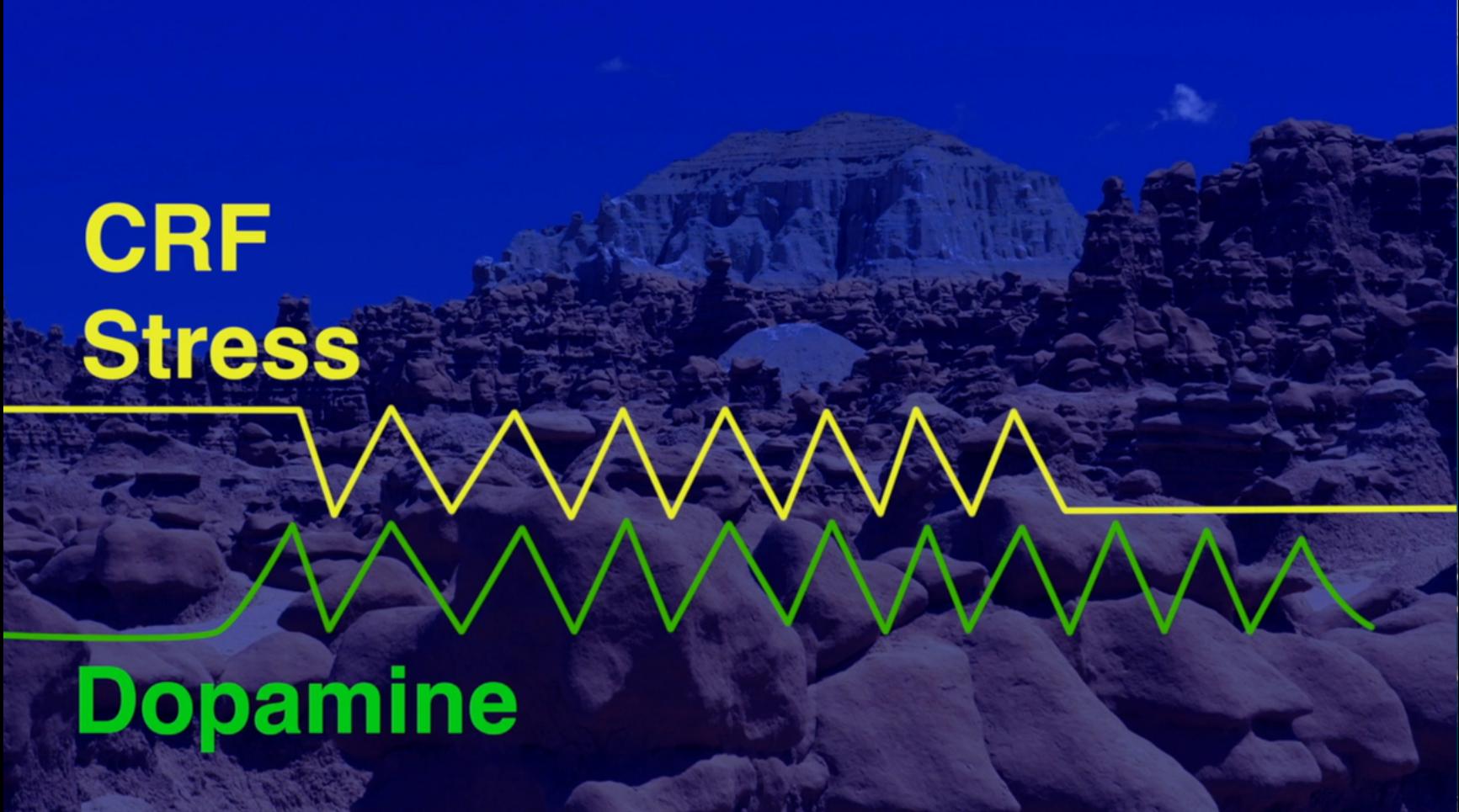
# *Hypothalamic-Pituitary-Adrenal (HPA) Axis*



- Hypothalamus releases **Corticotropin-Releasing Factor (CRF)**
- CRF goes to Pituitary Gland to release **ACTH (and  $\beta$ -endorphin)**
- Cortisol goes to Adrenal Glands to release **Glucocorticoids and Cortisol**
- Glucocorticoids and Cortisol mobilize the stress system
- Glucocorticoids feed-back to Hypothalamus to slow the release of CRF







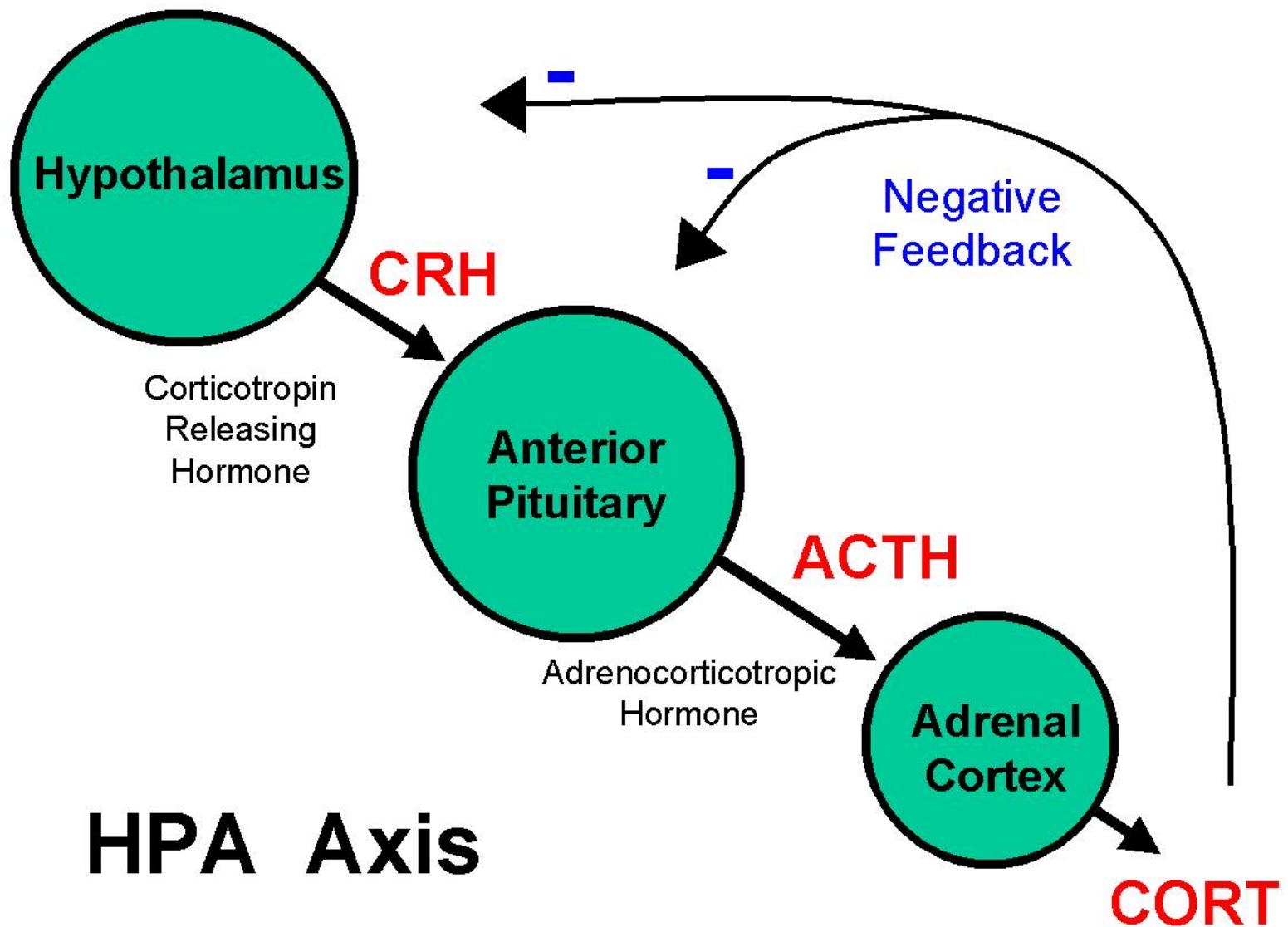
**CRF  
Stress**

**Dopamine**



# Hedonic Allostasis Theory (Koob & LeMoal)

- With continued drug use and withdrawal, the “anti-reward” system is recruited to counter-balance excess Dopamine (with the stress hormone CRF)
- Brain is unable to maintain normal “homeostasis”
- So the brain reverts to “allostasis” - change of the hedonic “set point” under stress in a desperate attempt to maintain stability
- Current Rx/Tx focus: CRF1-antagonists as anti-craving drugs





***CHRONIC, SEVERE STRESS = ↑CRF***

***and ↑ CRF = ↓DAD2 receptors***

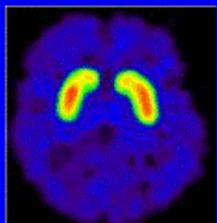
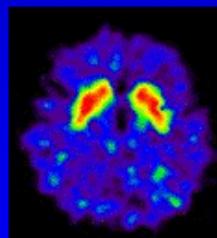
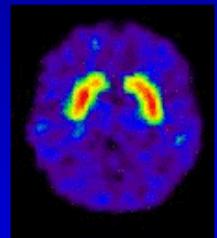
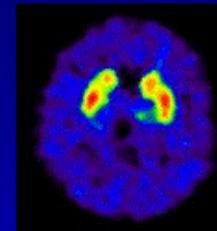
***and ↓DAD2 receptors = Anhedonia***

**Anhedonia: Pleasure “deafness”**

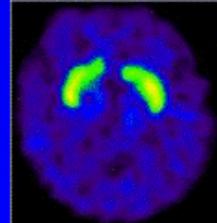
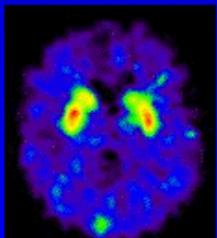
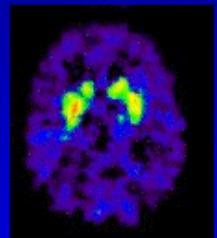
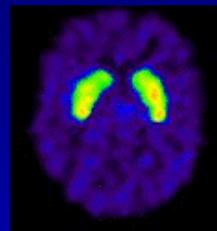
***(the patient is no longer able to derive normal pleasure from those things that have been pleasurable in the past)***

*Functionally...*

## Dopamine D2 Receptors are Decreased by Addiction



Control

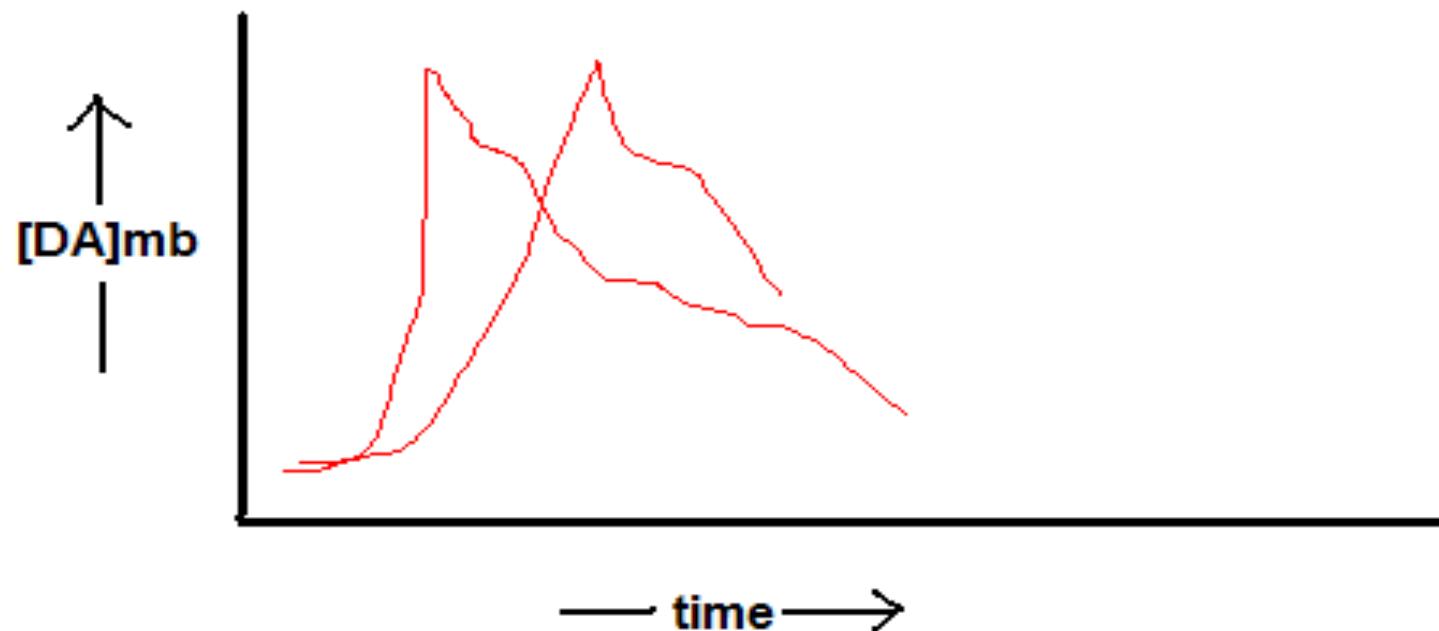


Addicted



DA D2 Receptor Availability

# *Drugs cause Dopamine Surges in the midbrain reward system*

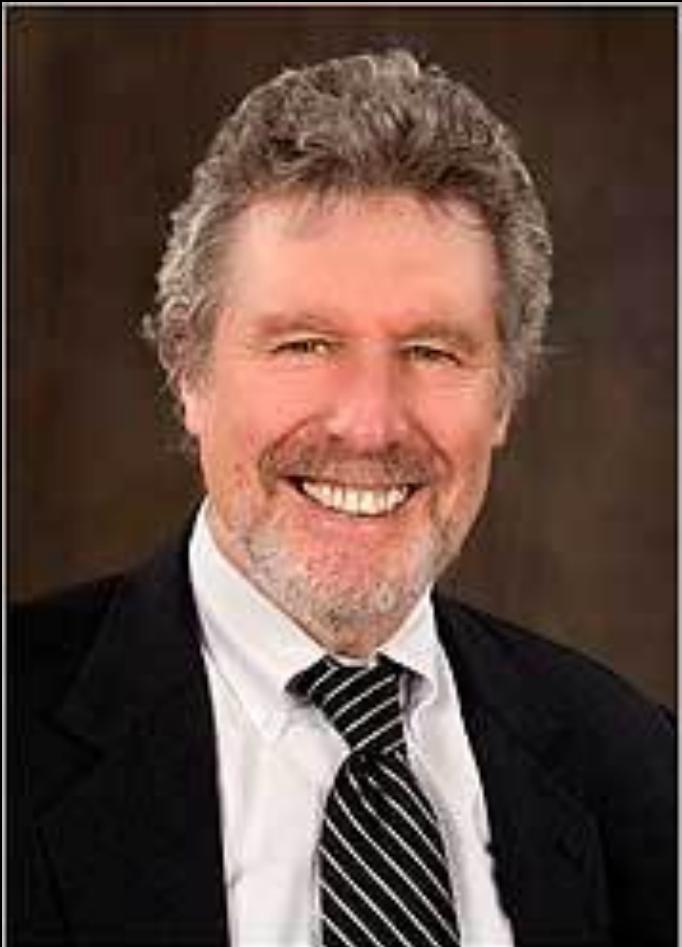


# Vietnam Vets Study (Robins, 1975)



- High prevalence of heroin use in US soldiers in Vietnam
- On returning to the US, they did not continue heroin use
- Drug use was situational
- Argument against addiction being a disease

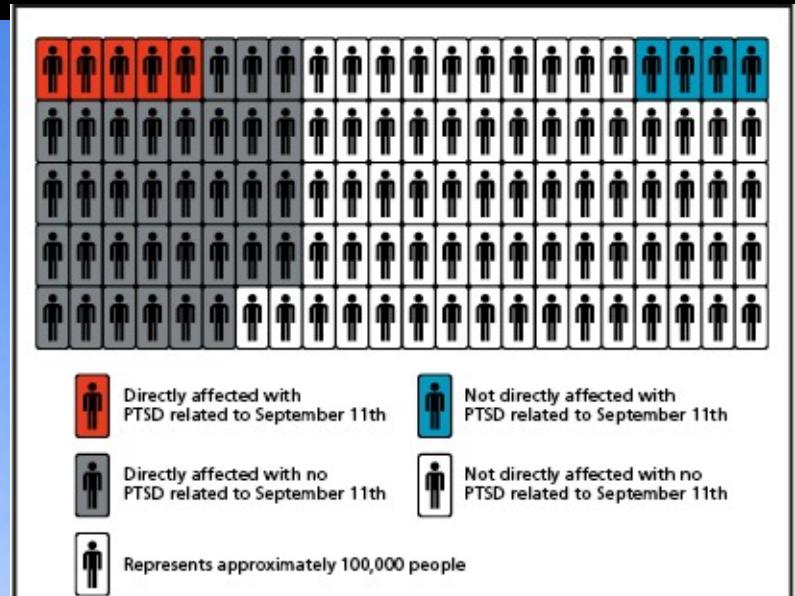
# Gene Heyman, PhD



- **Addiction is not a chronic disease**
- **Most addicts do stop on their own, without treatment, and do not display relapse chronicity**
- **Remission (“maturing out”) is the rule, not the exception**
- **Addicts do not need lifelong treatment**
- **Remission rates lower for legal drugs than illegal drugs**

# Sandro Galea, MD

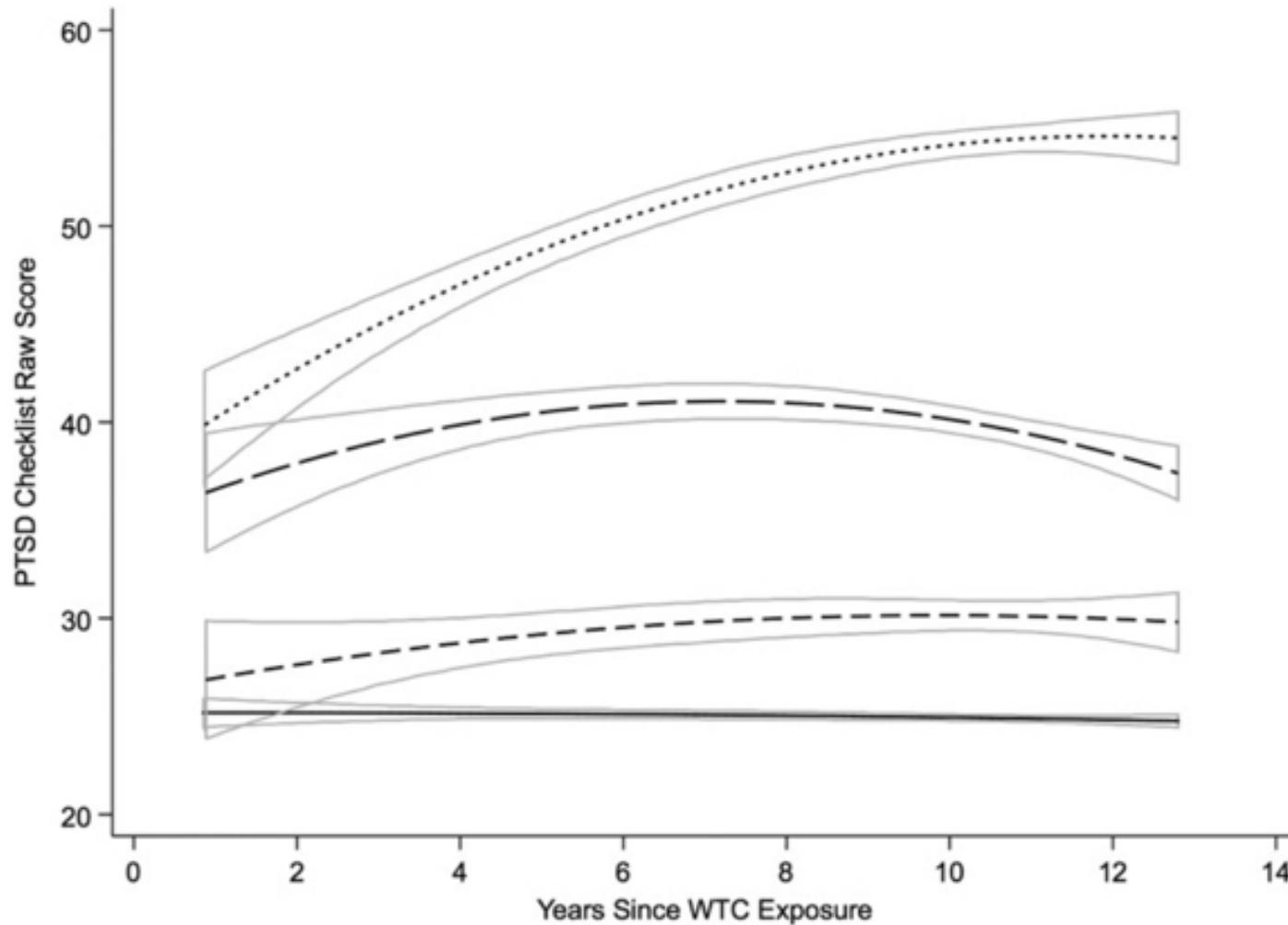
What if we deal only with individuals at risk?



**FIGURE 5.** Schematic representation of the number of people in the New York City metropolitan area who were directly affected by the September 11, 2001, attacks, those who were not, and the number of cases of PTSD in each group in the first 6 months after September 11th.

PTSD=posttraumatic stress disorder.

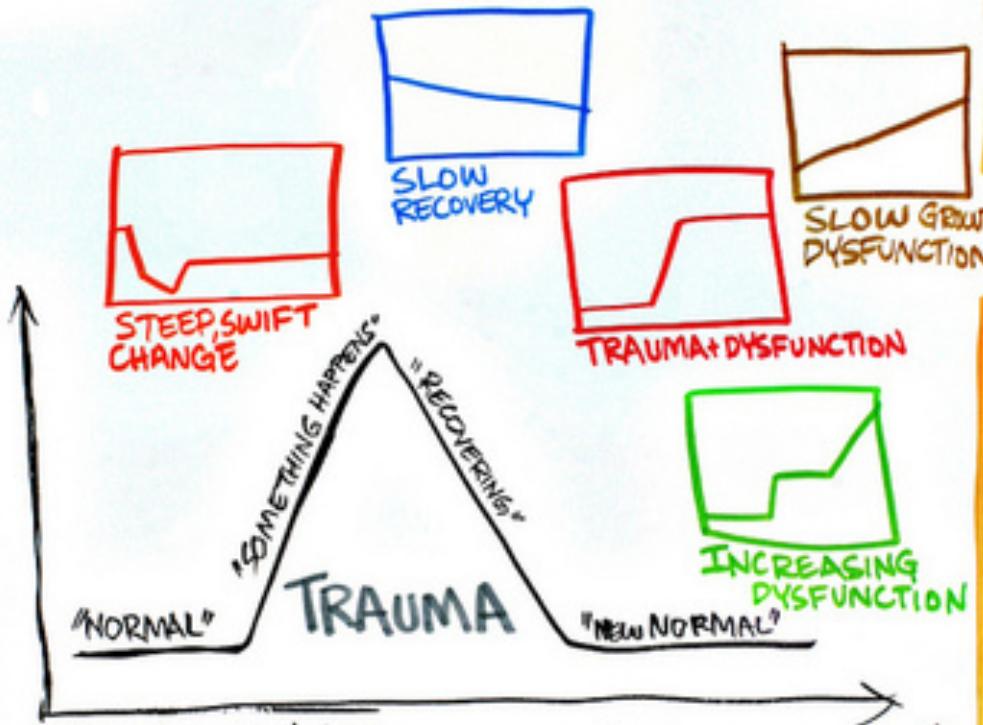
Galea S, Resnick H. *CNS Spectr.* Vol 10, No 2. 2005.



**Fig. 2.** Predicted trajectories derived from longitudinal models of PTSD Checklist data for responders with no history of World Trade Center (WTC) post-traumatic stress disorder (PTSD) (—), and partial (---), remitted (- - -) and active WTC-PTSD (· · ·). The boxes outlined in solid gray represent 95% confidence intervals.

TOWARD  
RESILIENCE

SANDRO  
GALEO



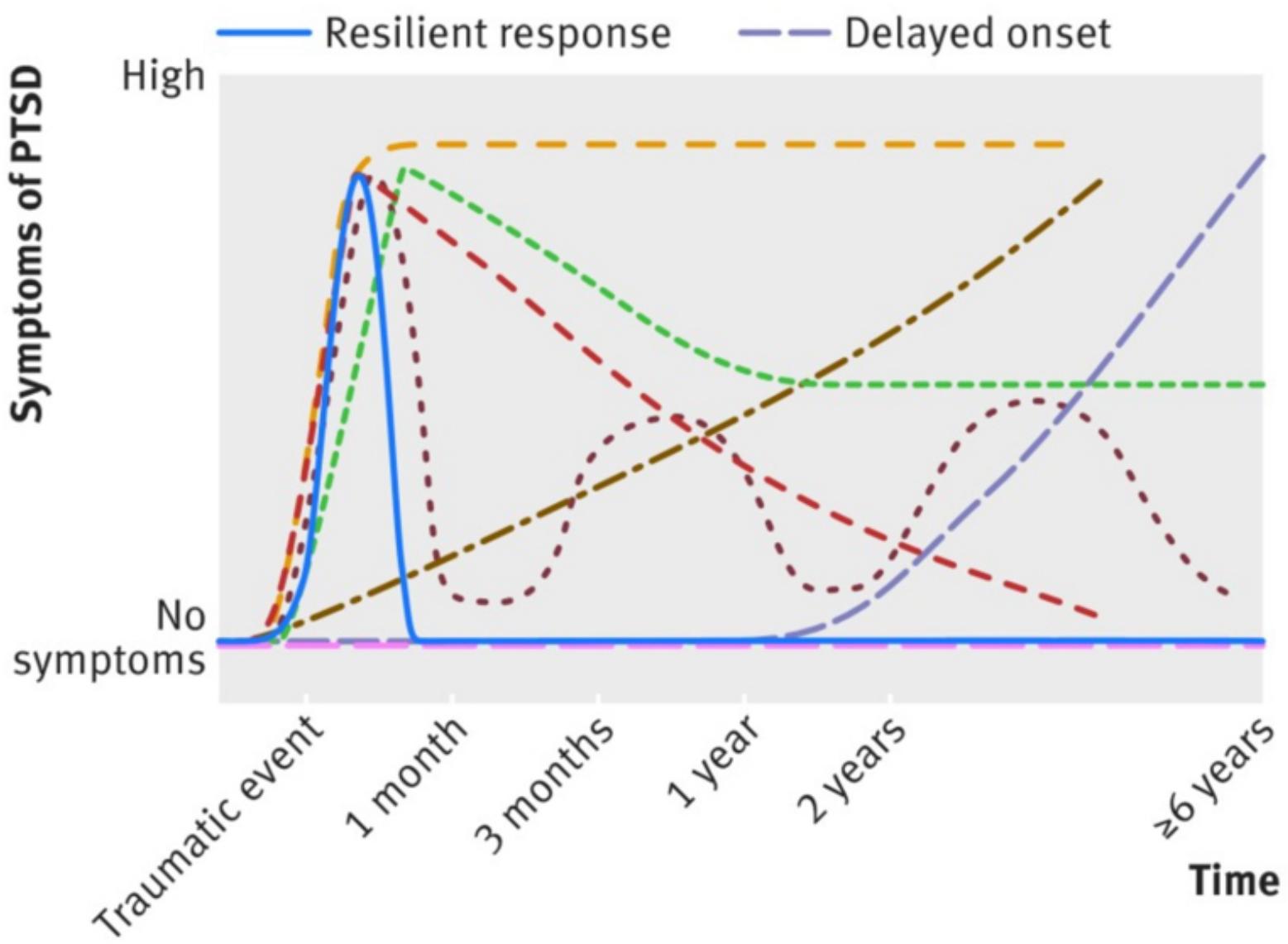
90%  
PEOPLE  
EXPERIENCE  
TRAUMA  
in their  
LIVES

SHIFT  
the CURVE!



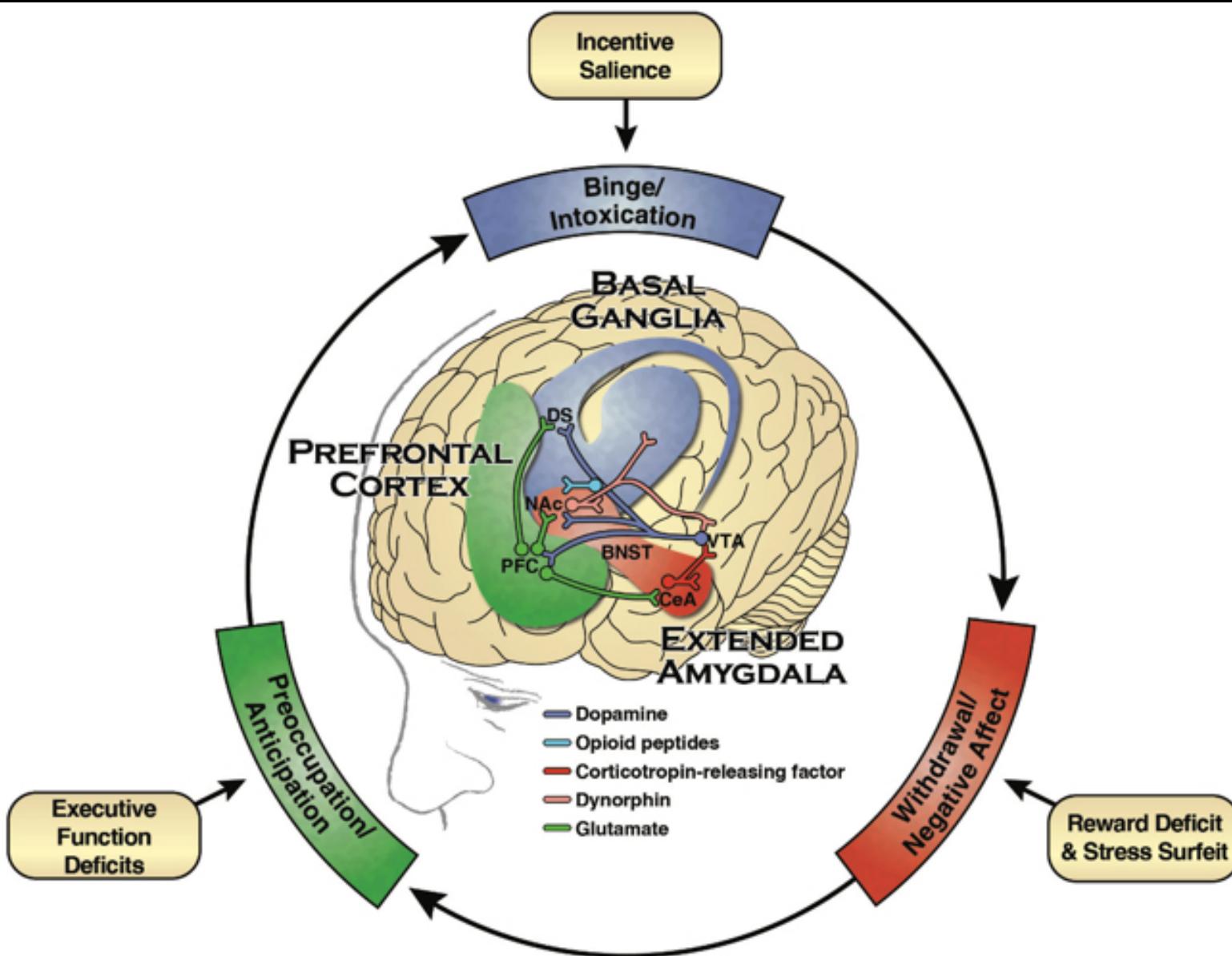
Pop!Tech  
2012

PETER  
DURAND



# **Strategies to deal with the STRESS component of addiction**

- **Safe housing**
- **Recognize unconscious aspects of relapse**
- **Ritualistic, daily (hourly) stress management activities**
- **Supportive peers**
- **Medication (alpha- and beta-blockade)**
- **Minimize social dominance**



# Stage 1 – Binge/Intoxication

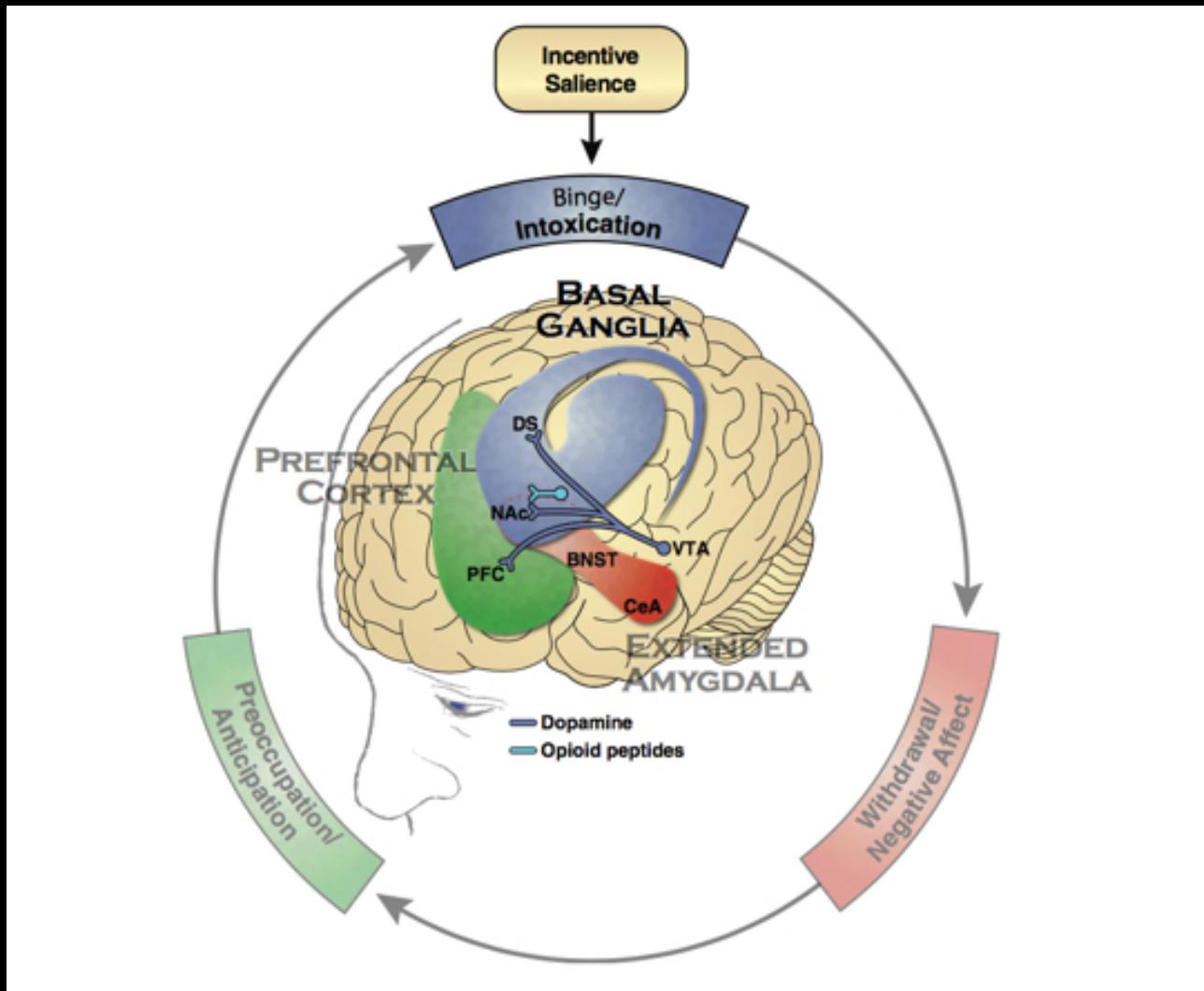
Brain areas: Basal ganglia (VTA, NAc, DS)

Primary chemical: Dopamine

Primary process: Incentive Salience

# Stage 1: Binge/Intoxication

consumption of intoxicating substance/experience of pleasurable effects



## **Stage 1 – Binge/Intoxication**

Brain areas: Basal ganglia (VTA, NAc, DS)

Primary chemical: Dopamine

Primary process: Incentive Salience

## **Stage 2 – Withdrawal/Negative Affect**

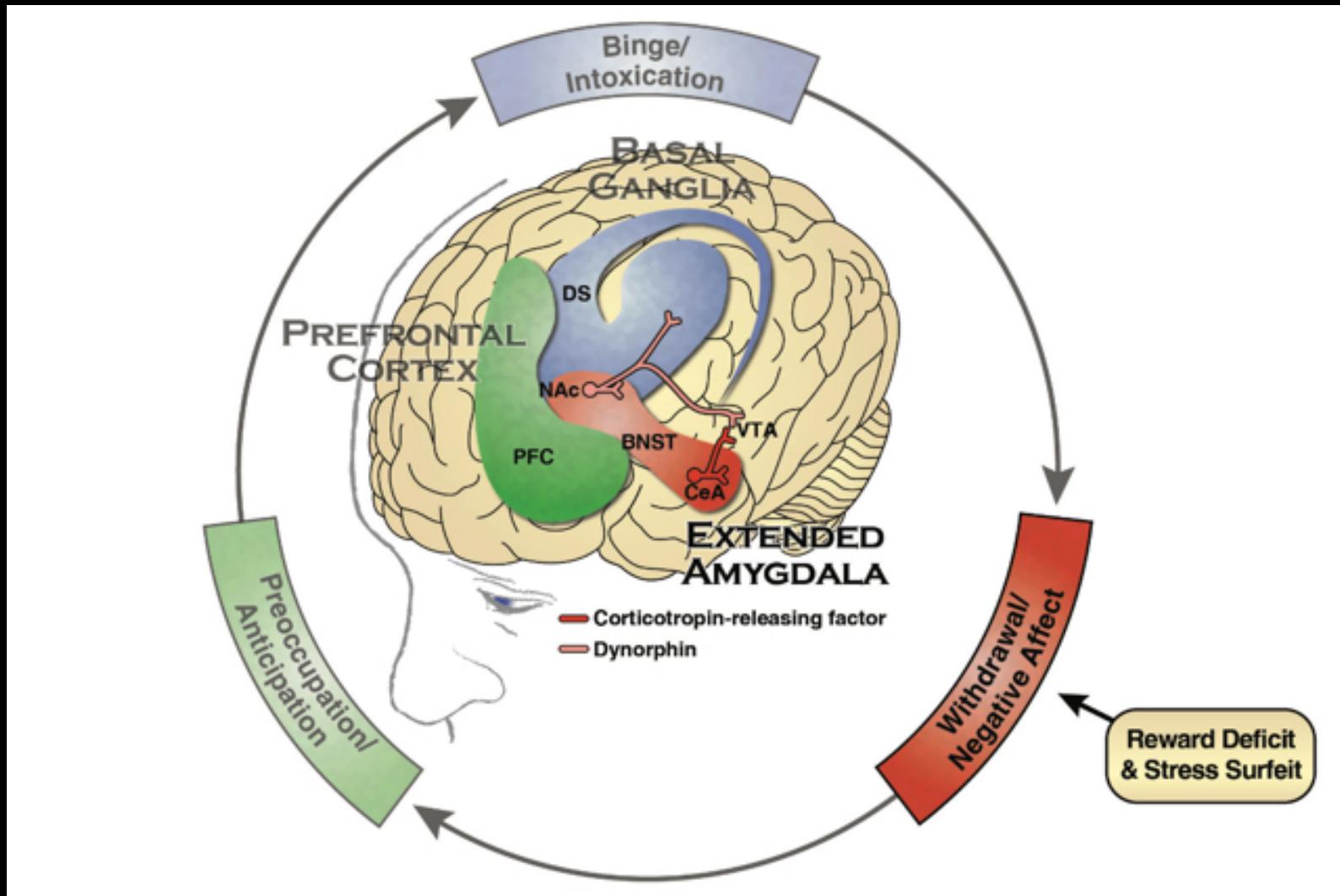
Brain areas: Extended Amygdala (BNST, CeA, Nas)

Primary chemicals: CRF, Dynorphin

Primary process: Reward deficit/Stress surfeit

# Stage 2: Withdrawal/Negative Affect

negative emotional state in absence of substance



## **Stage 1 – Binge/Intoxication**

Brain areas: Basal ganglia (VTA, NAc, DS)

Primary chemical: Dopamine

Primary process: Incentive Salience

## **Stage 2 – Withdrawal/Negative Affect**

Brain areas: Extended Amygdala (BNST, CeA, Nas)

Primary chemicals: CRF, Dynorphin

Primary process: Reward deficit/Stress surfeit

## **Stage 3 – Preoccupation/Intoxication**

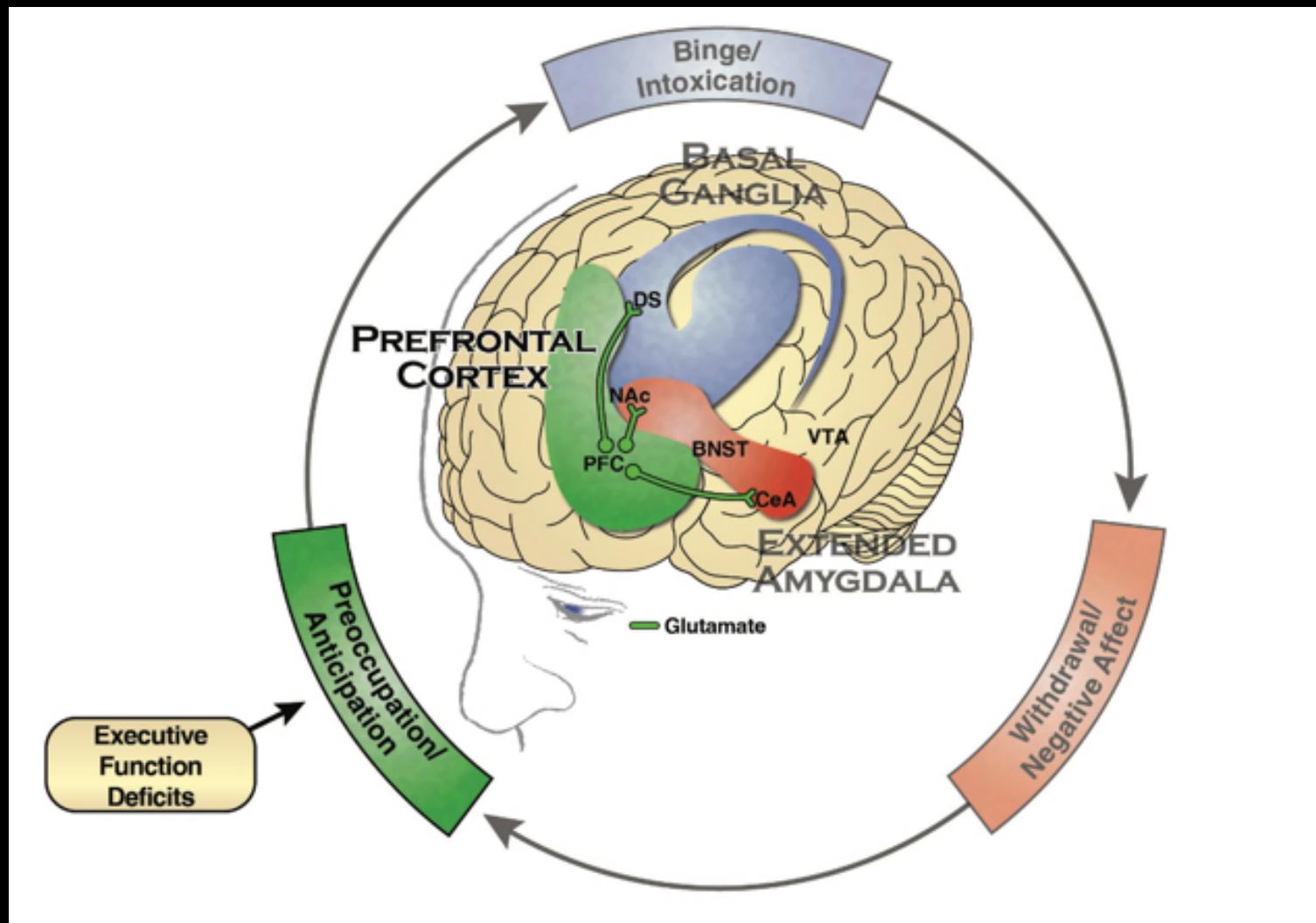
Brain areas: Prefrontal Cortex

Primary chemical: Glutamate

Primary process: Executive function deficits

# Stage 3: Preoccupation/Anticipation

drug seeking after a period of abstinence



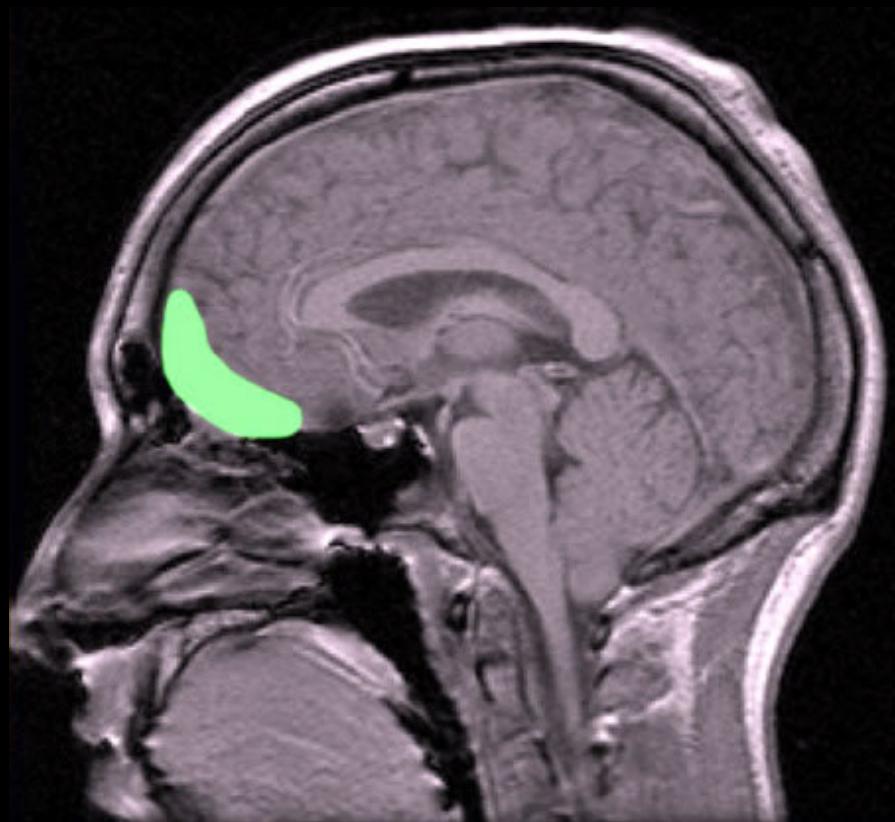
# *Craving / Drug Seeking*

- Not quite as conscious as deliberative acts
- More automatic - like driving a car home from work without really thinking about it
- “I was vaguely aware that what I was doing was not too smart”
- “There I was again with a drink in my hand thinking that this time things would be different”

# Addiction is a disorder of ...

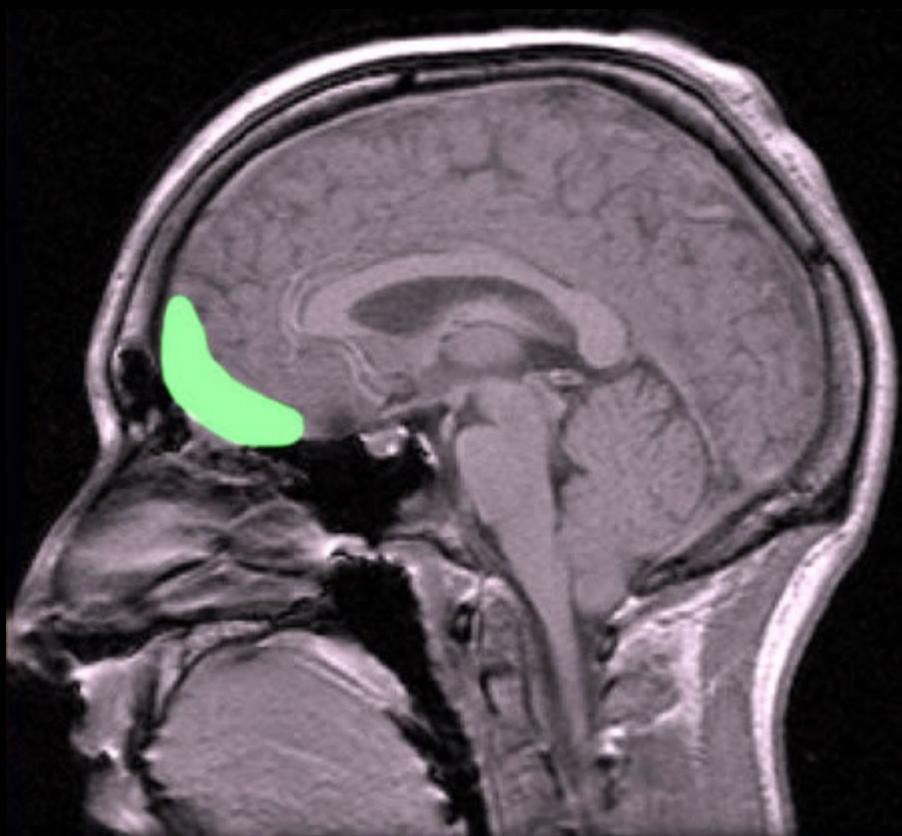
- |           |                       |                                     |
|-----------|-----------------------|-------------------------------------|
| 5. CHOICE | (motivation, insight) | OFC, ACC, PFC, IC                   |
| 4. STRESS | (anti-reward system)  | HPA axis                            |
| 3. MEMORY | (habits, cues)        | glutamate<br>synaptic remodeling    |
| 2. REWARD | (incentive salience)  | dopamine<br>dopamine receptors      |
| 1. GENES  | (vulnerability)       | polymorphisms<br>epigenetic changes |

# Orbitofrontal Cortex (OFC)



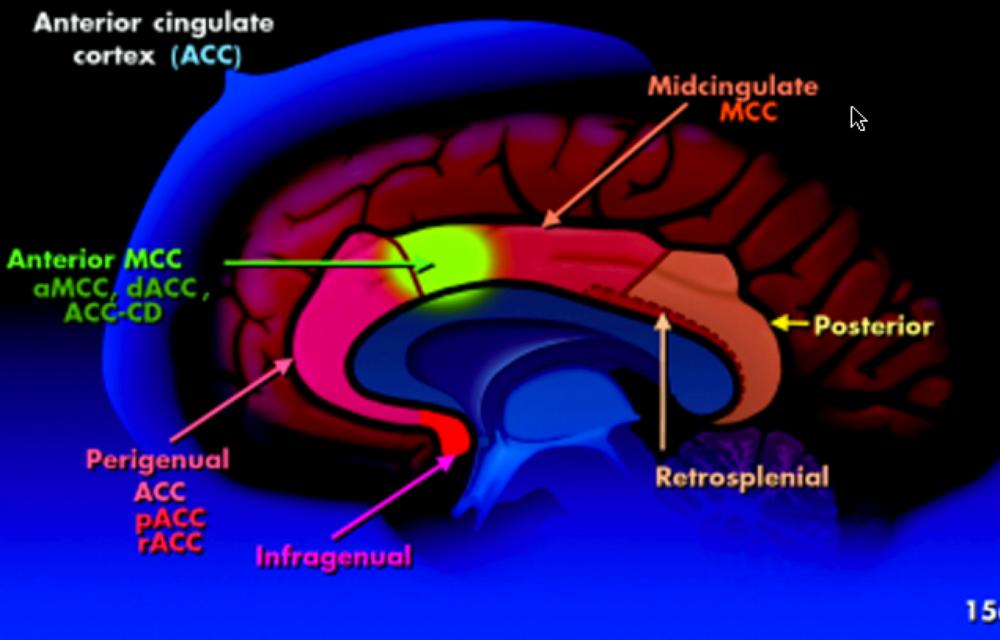
- Decision-making guided by rewards
- Integrates sensory and emotional information from lower limbic structures
- Flexible assignment of value to environmental stimuli to motivate or inhibit choices & actions
- Self-monitoring and social responding

# *damage to* Orbitofrontal Cortex (OFC)



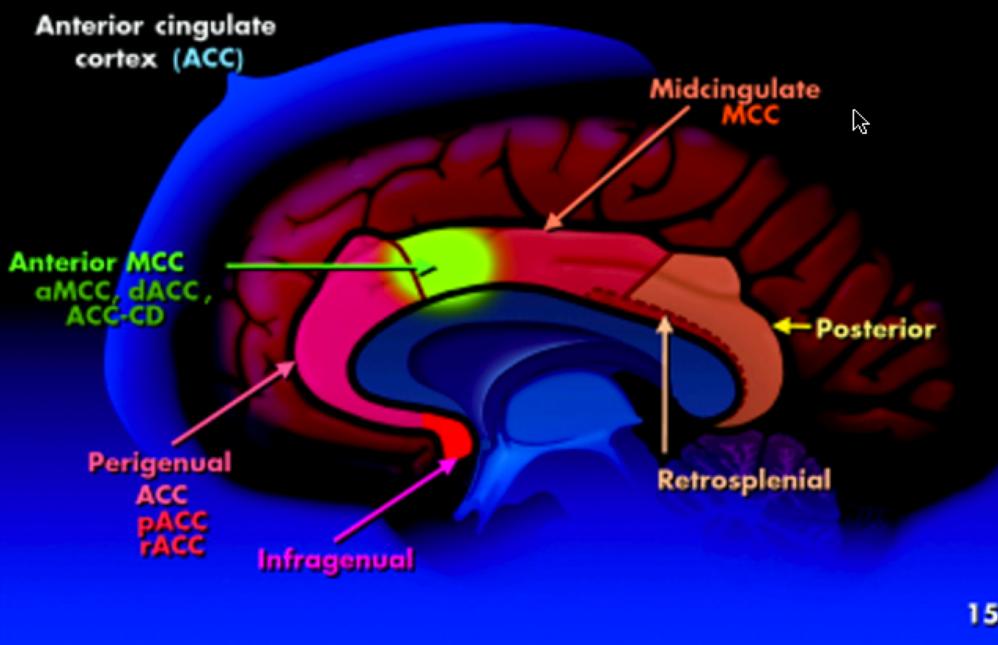
- Causes a loss of a crucial behavioral guidance system
- Responses are impulsive and inappropriate
- Deficits of self-regulation
- Inability to properly assign value to rewards (such as money vs. drugs)
- Tendency to choose small & immediate rewards over larger but delayed rewards

# Anterior Cingulate Cortex (ACC)



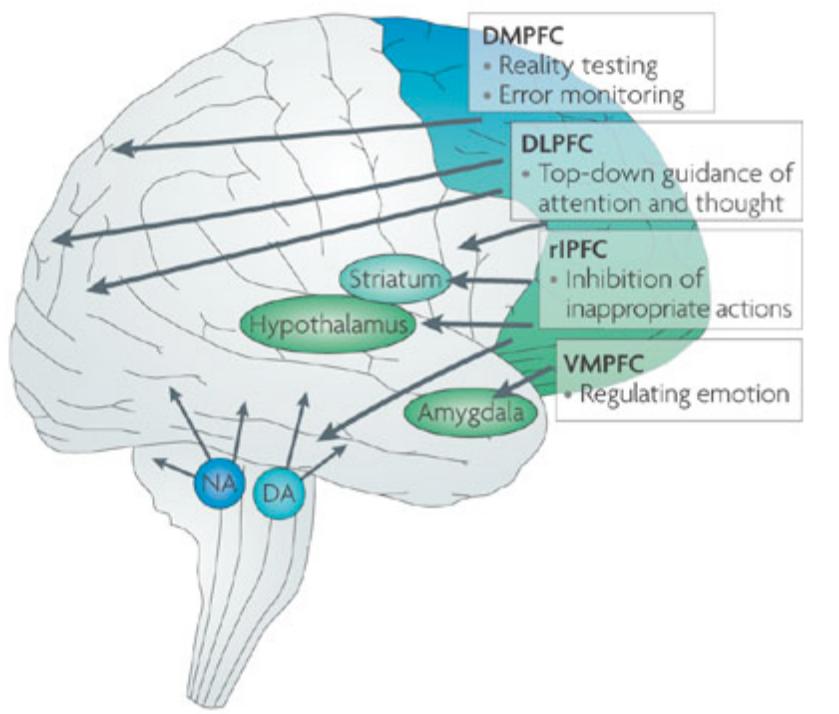
- Works with OFC: decision-making based on reward values
- But also generates new actions based on past rewards/punishments
- Appreciation and valuation of social cues
- MRI: active in tasks requiring empathy and trust

# *damage to Anterior Cingulate Cortex (ACC)*



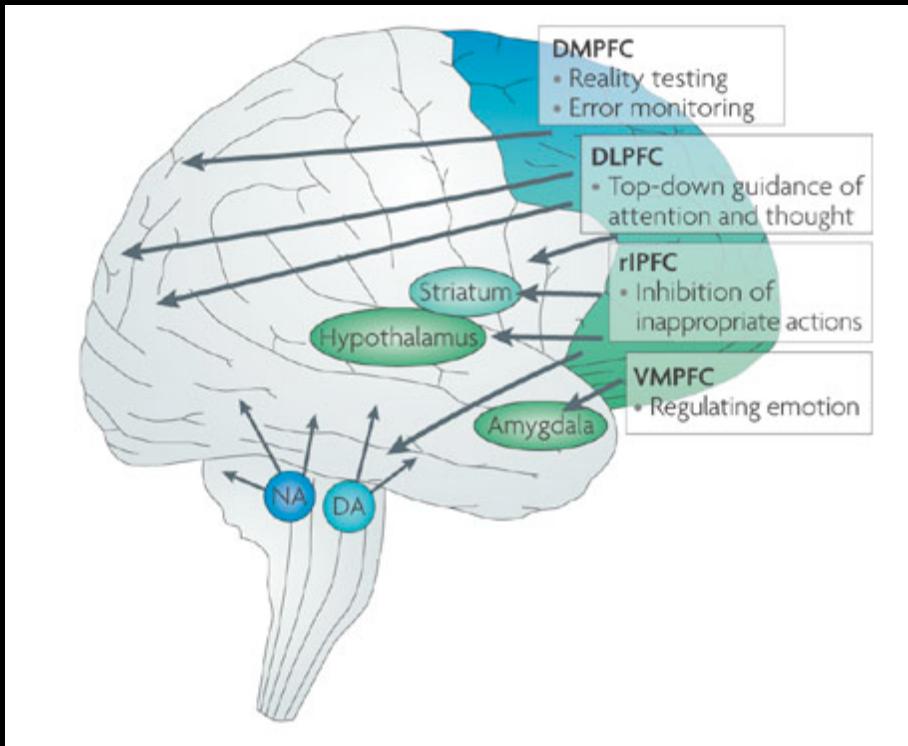
- Just as with OFC damage: causes a loss of a crucial behavioral guidance system
- Inflexibility/Inability to respond to errors in the past with regard to rewards/punishments
- Deficits in social responding due to decreased awareness of social cues

# Prefrontal Cortex (PFC)



- Behavioral regulation
- Reflective decision-making
- Inhibition of socially inappropriate actions
- Emotional and sensory integration
- Planning complex behaviors
- Personality expression

# *damage to* Prefrontal Cortex (PFC)



- **FAILURE OF EXECUTIVE FUNCTIONING**
- **Premature, unduly risky, poorly conceived actions**
- **Rapid, impulsive responses without reflection or premeditation**
- **Urgency**
- **Sensation seeking**
- **Expressed emotions inappropriate to the situation**
- **Deficits in attention**
- **Lack of perseverance**
- **Insensitivity to consequences**

# **Strategies to deal with the FRONTAL CORTEX (CHOICE) component of addiction**

- Medical/craving/psychiatric stabilization
- Abstinence
- Peer support (small, single-gender, long-term)
- Agency-building exercises
- Service work, working with newcomers
- Purposeful, meaningful goals
- Subject > Object

# ASAM Addiction Definition (Aug 2011)

A stress-induced (HPA axis),  
genetically-mediated (polymorphisms, epigenetic mech.)  
primary, chronic and relapsing brain disease  
of reward (nucleus accumbens),  
memory (hippocampus & amygdala),  
motivation and related circuitry (ACC, basal forebrain)  
that alters motivational hierarchies such that addictive  
behaviors supplant healthy, self-care behaviors

# *Addiction is a disorder of ...*

- 6. ... MEANING**      (spirituality?)
- 5. ... CHOICE**        (motivation)
- 4. ... STRESS**        (anti-reward system)
- 3. ... MEMORY**       (learning)
- 2. ... REWARD**       (hedonic system)
- 1. ... GENES**        (vulnerability)

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**The Meadows of Wickenburg**

**[www.protectingsobriety.com](http://www.protectingsobriety.com)**

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