

The Neurobiology of Addiction and Recovery

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New Roads Treatment Center, Utah

Dawn Farm Education Series
Ypsilanti, Michigan
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The most evil disease imaginable

...

- Wouldn't look like a "disease" at all
- Genetic, but with variable penetrance (genotype \neq phenotype)
- Repulsive symptoms easily confused with "willful badness"
- Self-deception as a clinical feature
- Poor prognosis if untreated, but some will get better (inexplicably)
- Chronic and relapsing (not acute, nor cured)
- Culturally & politically divisive (would tap into society's deepest prejudices, stigma, superstitions and attack its core values)
- Would only submit to "weird" solutions: peer support, patient accountability, personal evaluation, and spiritual

***Is Addiction Really a
“Disease?”***

**“Choice” vs.
“Disease”**

“Choice” vs. “Disease”

- Free Will exists
 - Responsibility
 - Can stop
 - Punishment and Coercion DO work
 - BEHAVIORS
- No Free Will
 - No Responsibility
 - Can't stop
 - Punishment and Coercion DON'T work
 - SYMPTOMS

Long-Term Course of Opioid Addiction

Yih-Ing Hser, Ph.D.

UCLA Integrated Substance Abuse Programs

Addiction Seminar (Psychiatry 434)



Supported by the National Institute on Drug Abuse
(P30 DA016383)

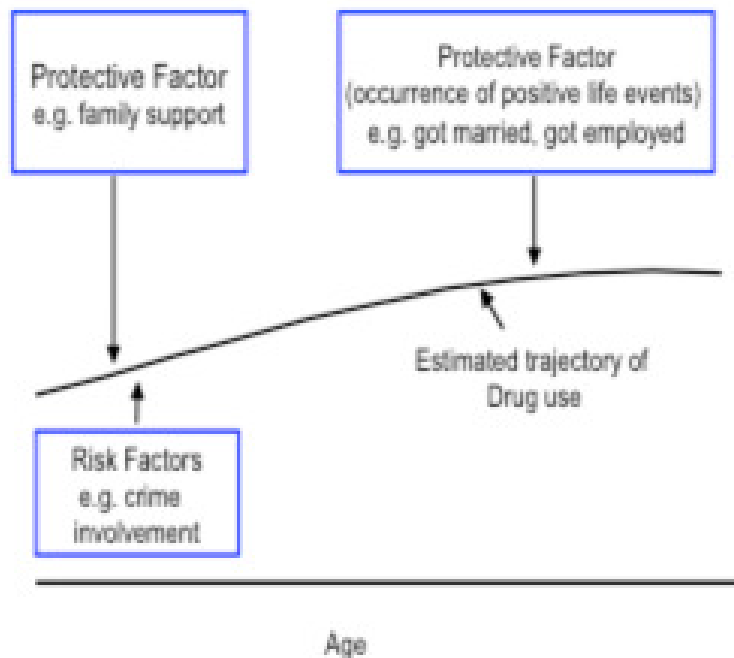


Life Course Perspective on Drug use

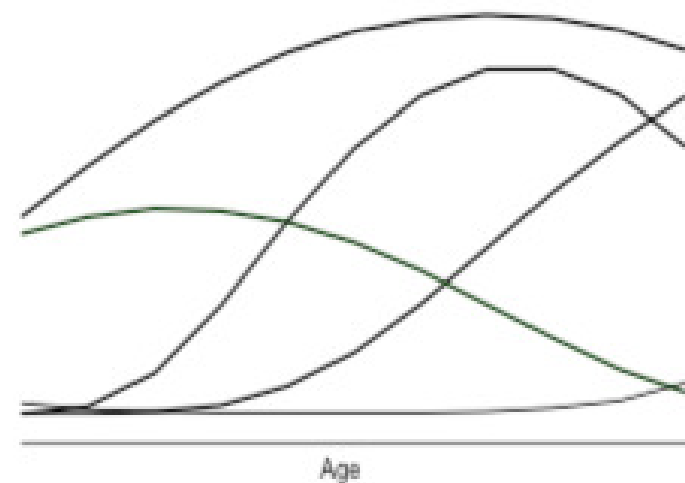
1. Life course theory recognizes the importance of time, timing, and temporal processes in the study of human behavior and experience over the life span, characterized by trajectories, transitions, and turning points
2. Persistence of drug use resembles chronic diseases: high relapse rates, non-compliance, require long-term care/management
3. Critical life events often lead to or explain changes
4. Social capital, situated choice are additional key concepts

Longitudinal Approach to Study Drug Use over Time

Life-course Drug Use Career



Trajectories of drug use are heterogeneous among individuals and can be classified as several distinctive trajectory groups



A 33-year Follow-up of Heroin-Dependent Sample

- A cohort of 581 male heroin addicts admitted to the California Civil Addict Program (CAP) in 1962-64 has been followed-up and interviewed over more than 30 years
- The CAP was the only major publicly-funded drug treatment program available in California in the 1960s
- The CAP provided a combination of inpatient and outpatient drug treatment to narcotics-dependent criminal offenders committed under court order

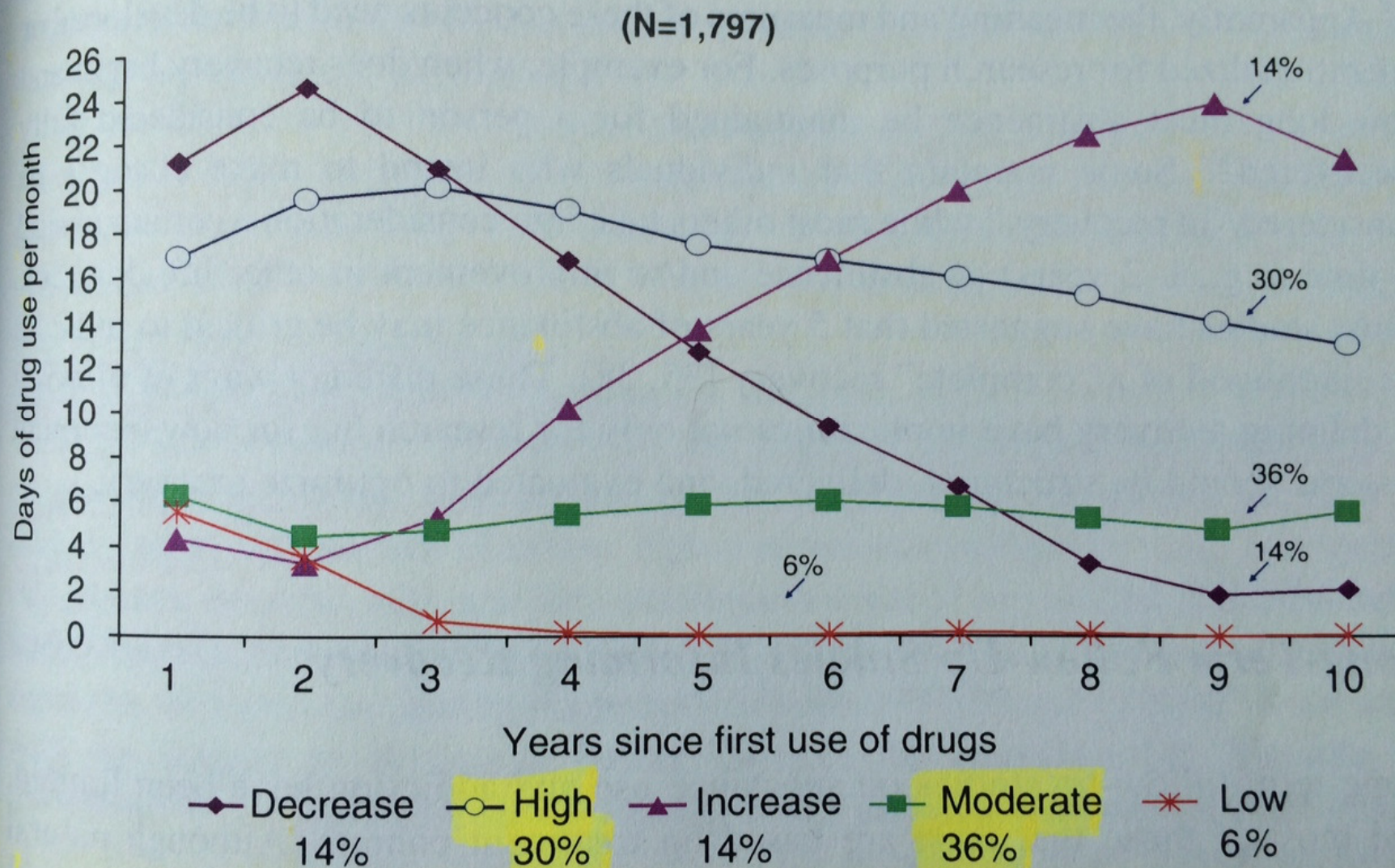


Fig. 2.4 Five distinctive drug use trajectories (N = 1,797)

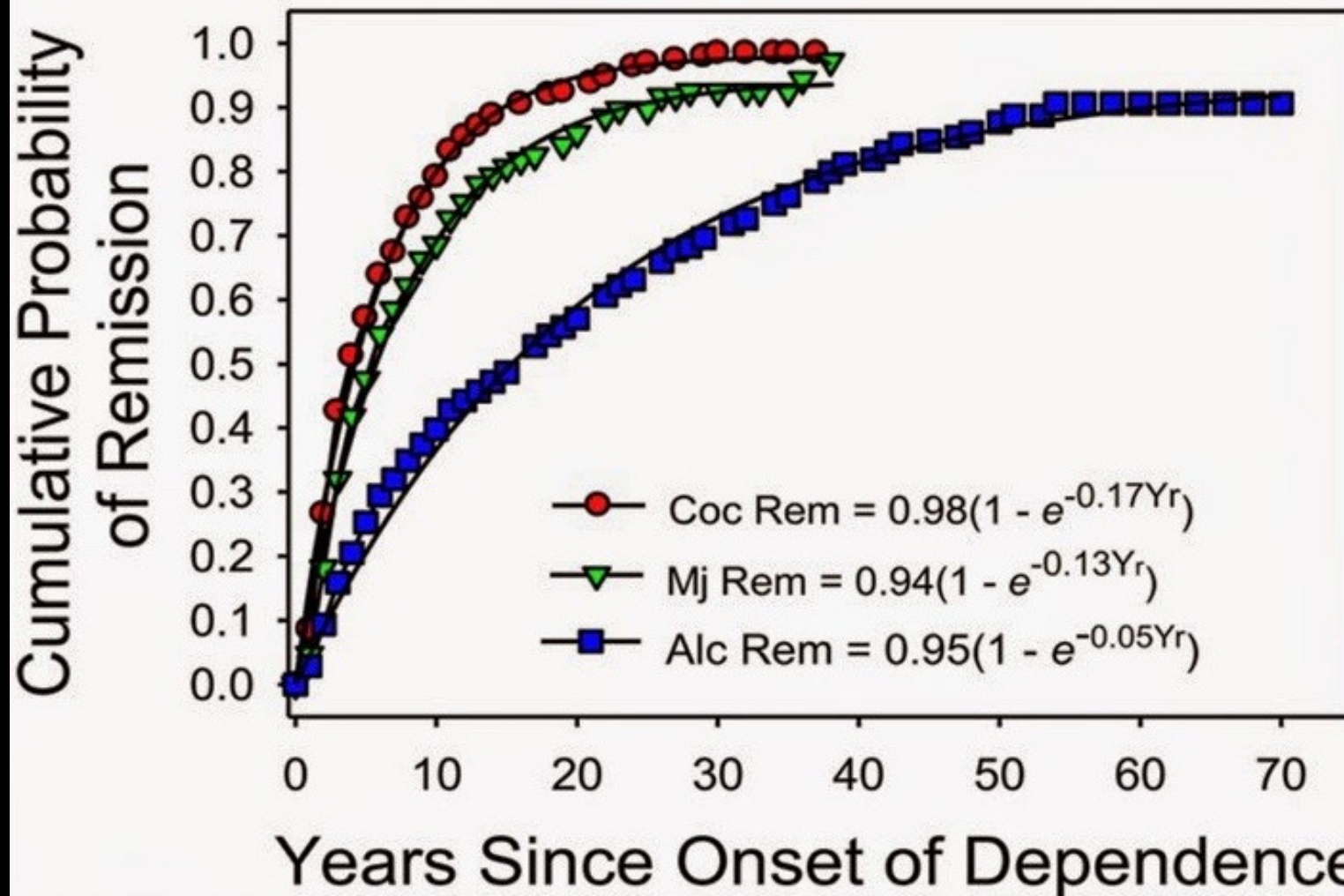
different groups, year

Gene Heyman, PhD



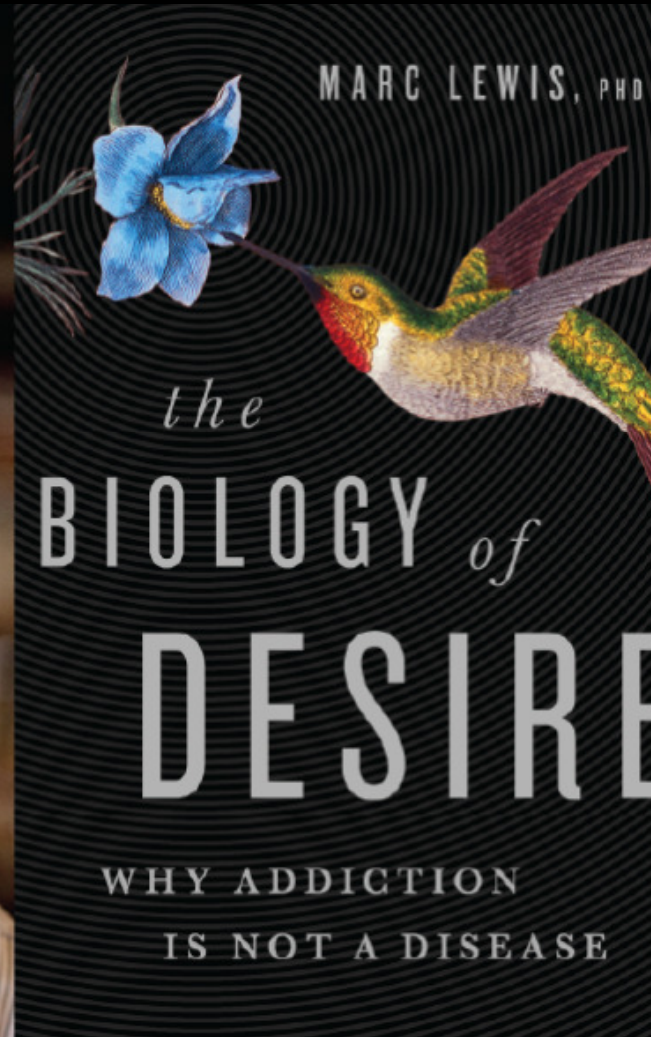
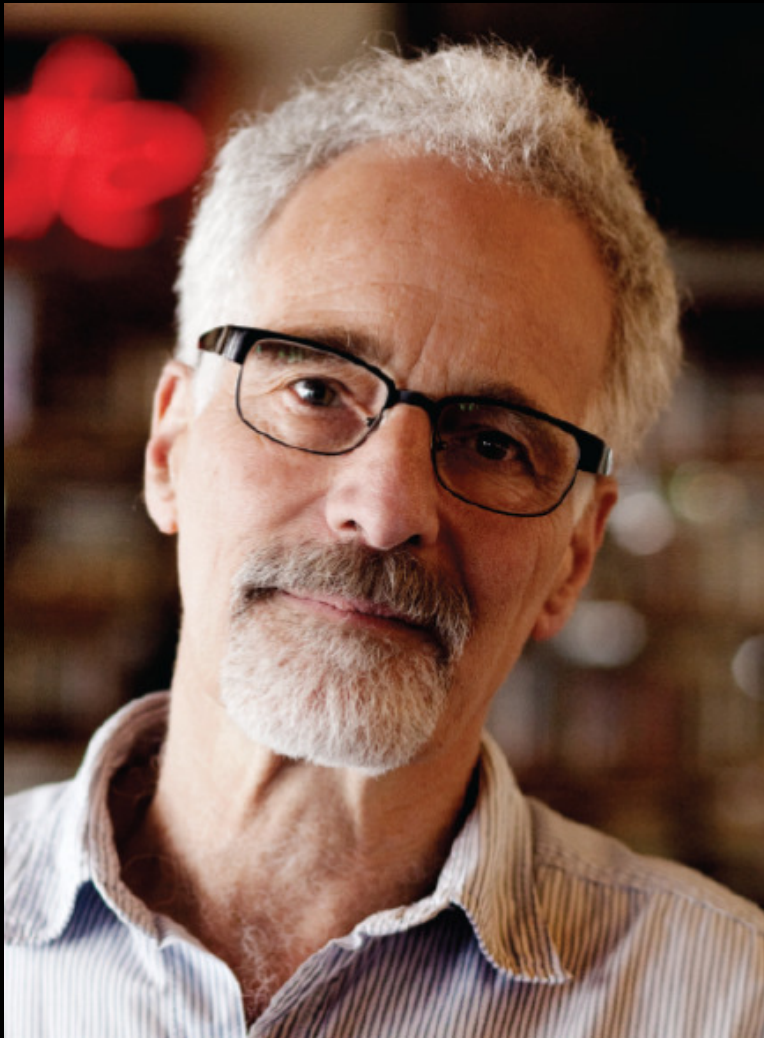
- Addiction is not a chronic disease
- Most addicts do stop on their own, without treatment, and do not display relapse chronicity
- Remission (“maturing out”) is the rule, not the exception
- Addicts do not need lifelong treatment
- Remission rates lower for legal drugs than illegal drugs

Likelihood of Remitting as a Function of Time Since Onset of Dependence



Lopez-Quintero C, et al. Probability and predictors of remission from lifetime nicotine, alcohol, cannabis, or cocaine dependence: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Addiction*. 2001(March); 106(3): 657-669.

Marc Lewis, PhD



Marc Lewis, PhD:

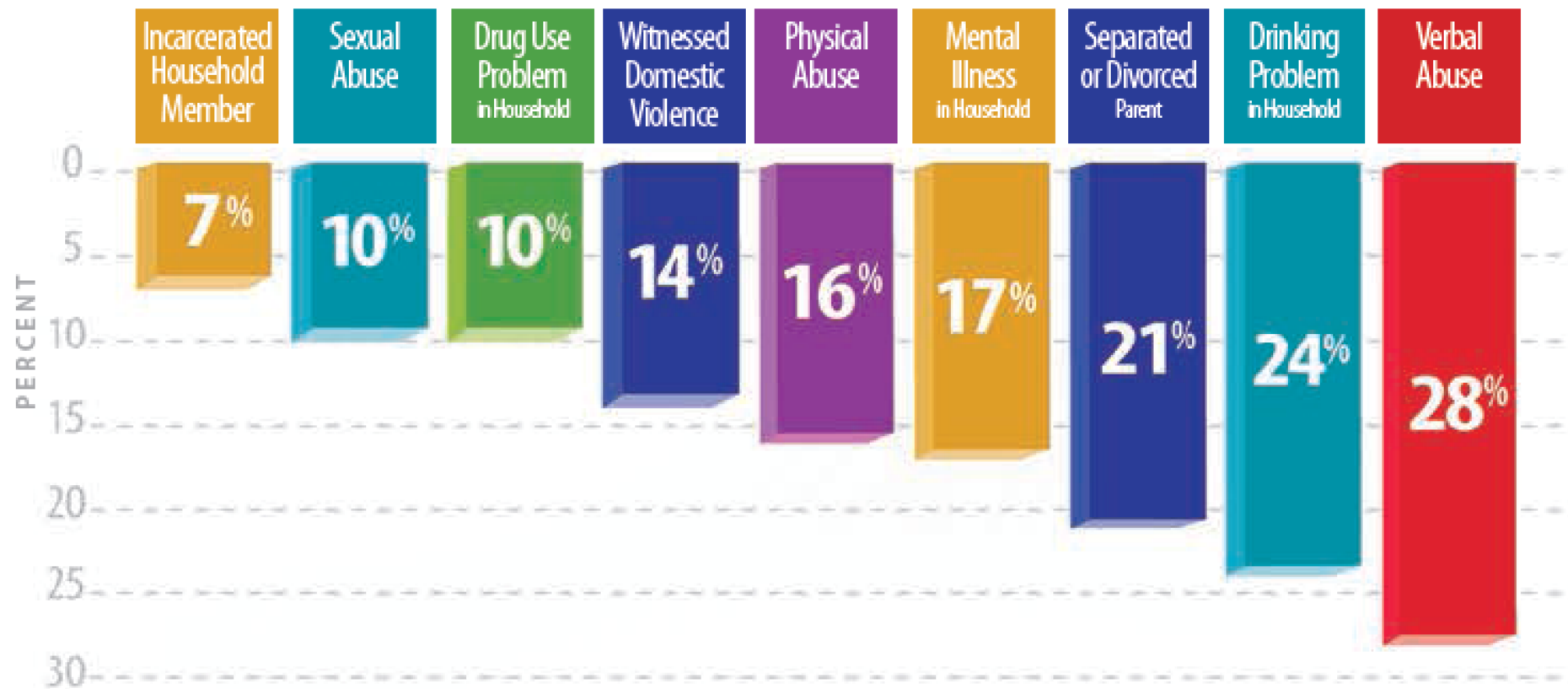
Addiction as a Developmental Stage

- Brain changes *per se* do not indicate pathology
- Plasticity (learning) is a normal function of the brain and 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)

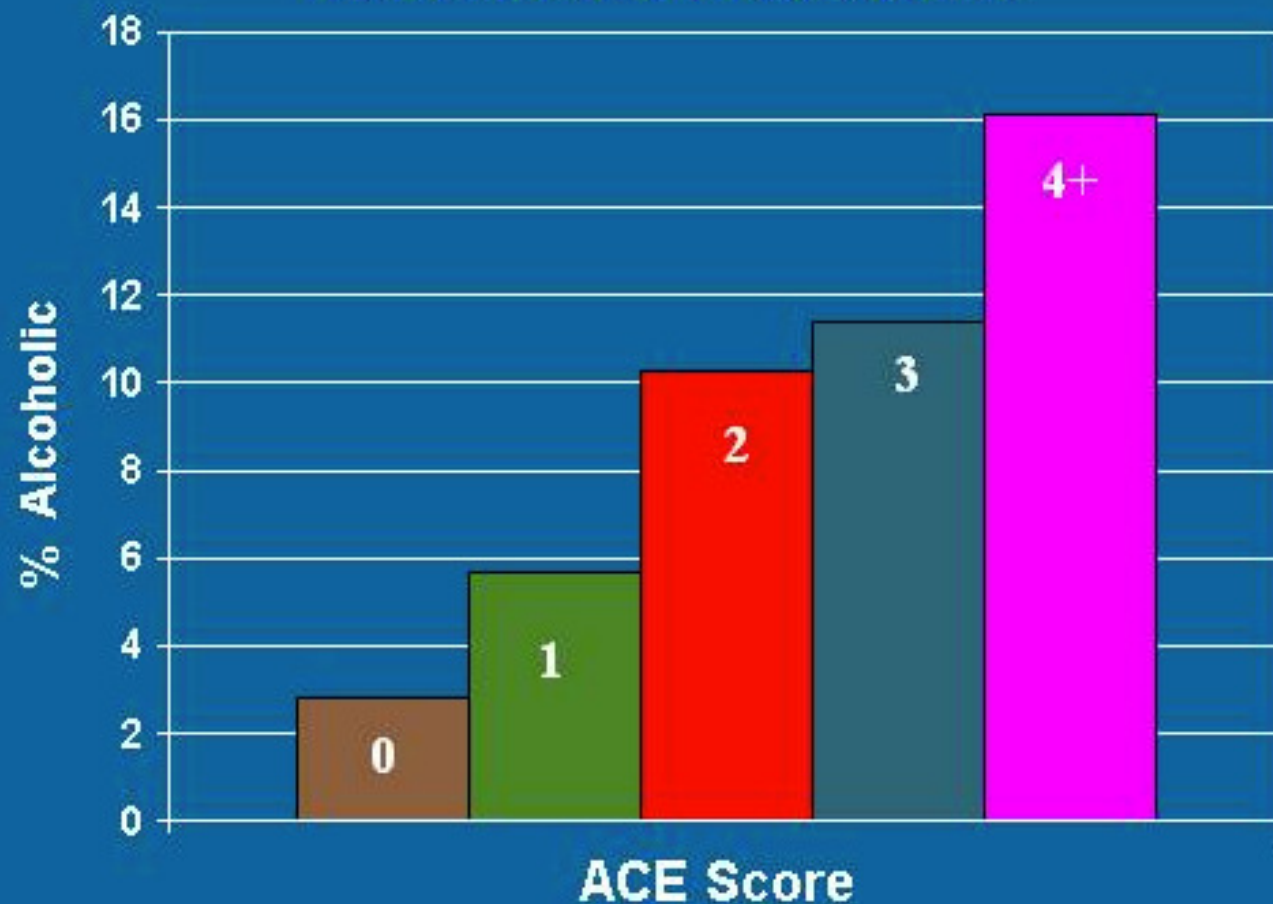
Getting to “core issues” is important

PREVALENCE OF INDIVIDUAL ACES

MINNESOTA 2011



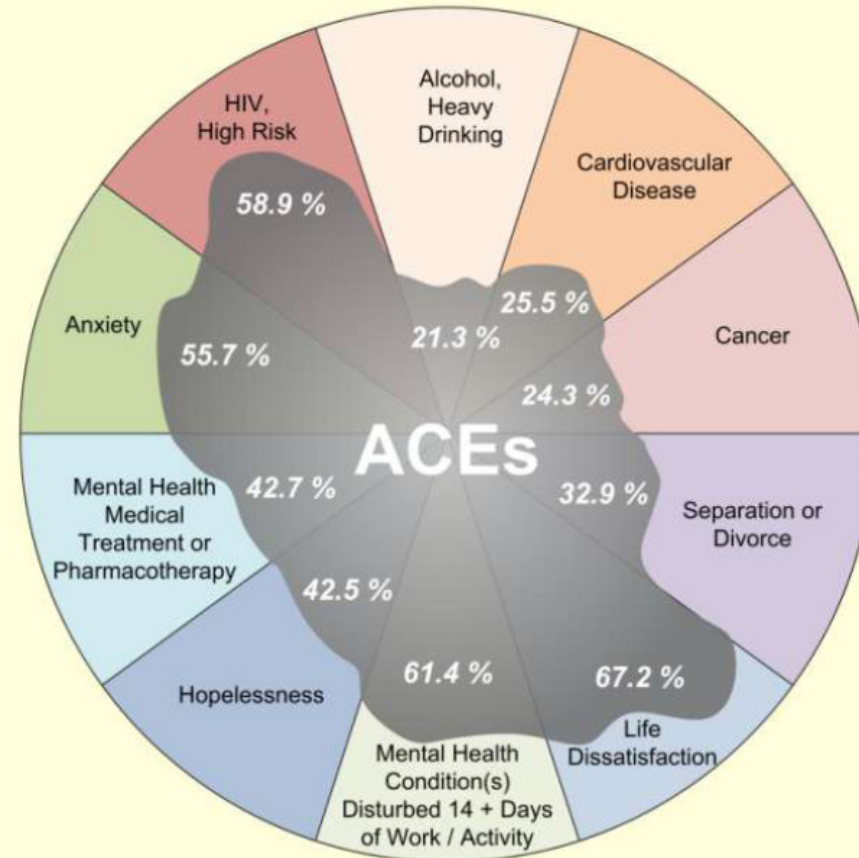
Childhood Experiences vs. Adult Alcoholism



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
mechs.)

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)
- 4. ... STRESS (anti-reward system)
- 3. ... MEMORY (learning)
- 2. ... REWARD (hedonic system)
- 1. ... GENES (vulnerability)

Five Theories of Addiction

5. Pathology of Motivation and Choice
(Kalivas & Volkow)
4. Stress and Allostasis
(Koob & LeMoal)
3. Pathology of Learning & Memory
(Hyman, Everitt & Robbins)
2. Incentive-sensitization of Reward
(Robinson & Berridge)
1. Genetic Vulnerability
(Schuckit et al)

What goes into a “choice?”

- Valuation
- Risk Taking
- Novelty-seeking
- Impulsivity
- Empathy/Narcissism
- Memory/Stress/Trauma
- Social Status

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

Addiction is a disorder of ...

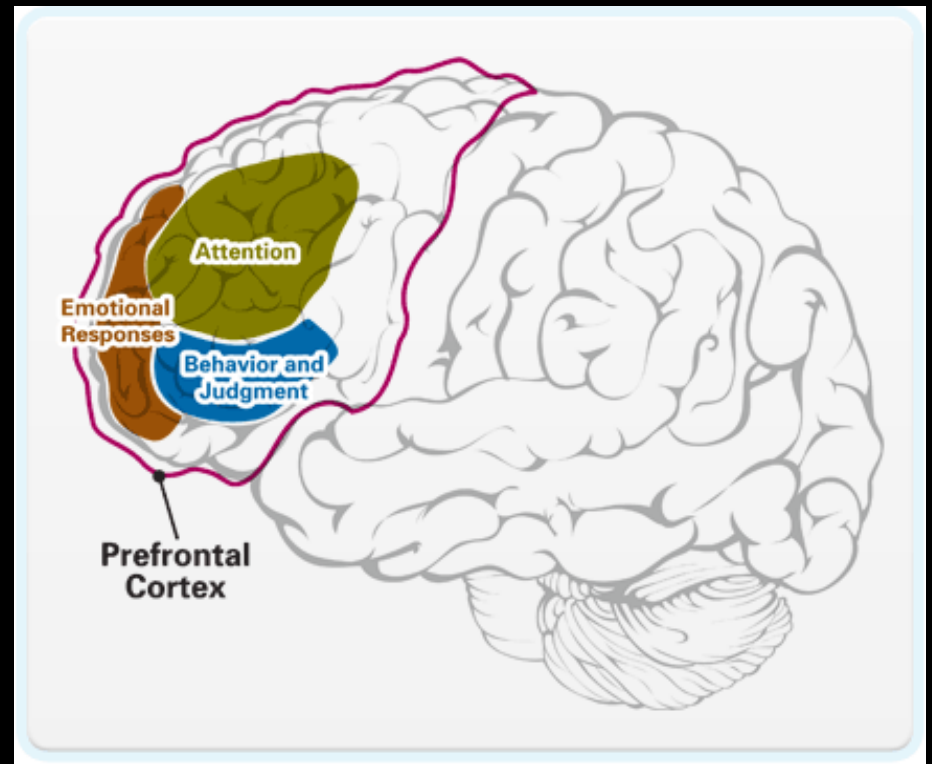
- 5. ... CHOICE (motivation)
- 4. ... STRESS (anti-reward system)
- 3. ... MEMORY (learning)
- 2. ... REWARD (hedonic system)
- 1. ... GENES (vulnerability)

Individual characteristics that predict high vulnerability to drug-seeking behavior

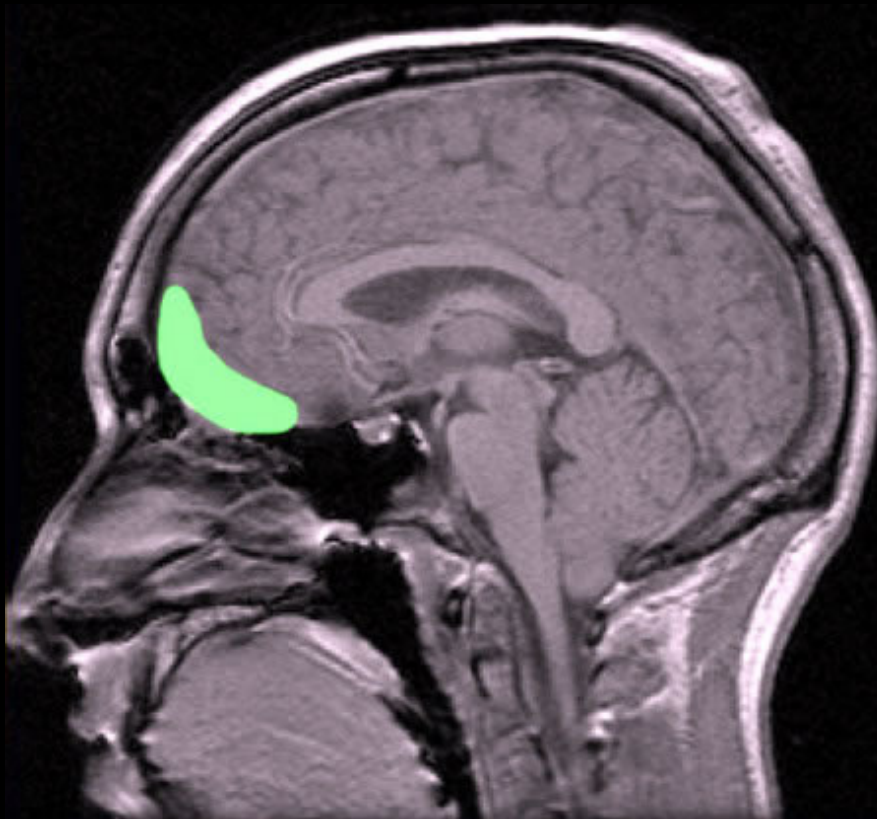
- High stress reactivity
- High novelty-induced locomotor activity
- High novelty-seeking
- High trait impulsivity

Stanford Marshmallow Experiment

- Mischel, Shoda & Rodriguez, 1989
- Children offered a choice between
 1. One small immediate reward
 - OR
 2. Two small delayed rewards
- Children that could delay gratification had better life outcomes (higher SAT scores, higher educational attainment, lower BMI)

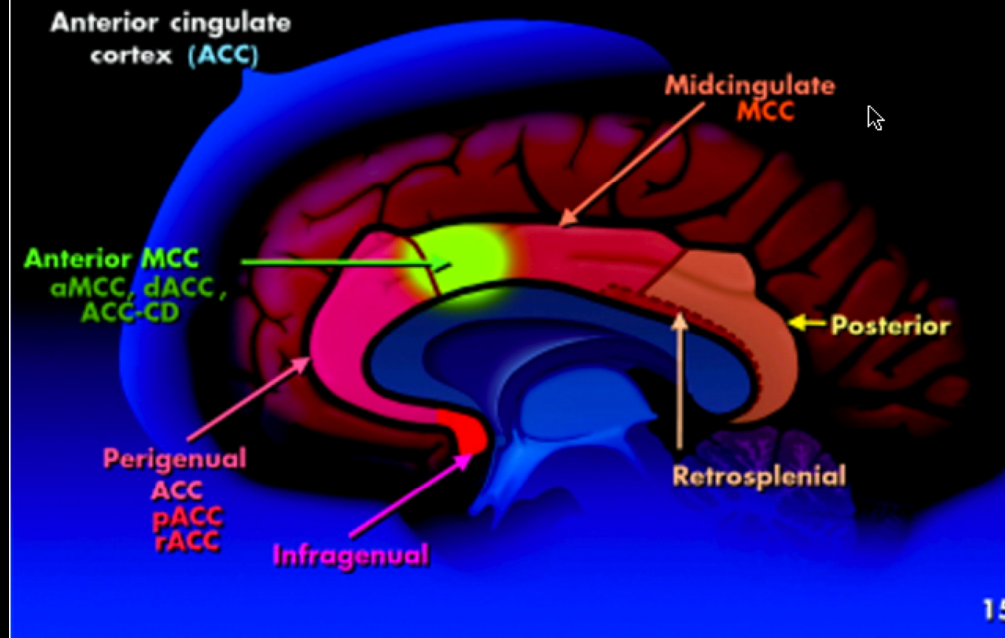


Orbitofrontal Cortex (OFC)



- 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

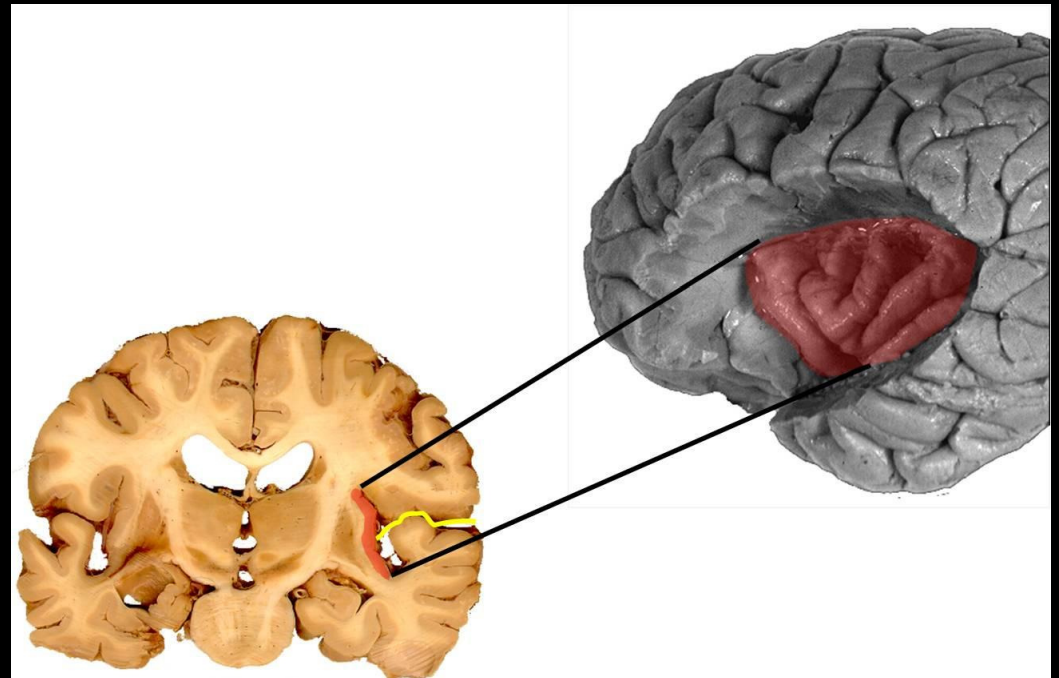
Anterior Cingulate Cortex (ACC)



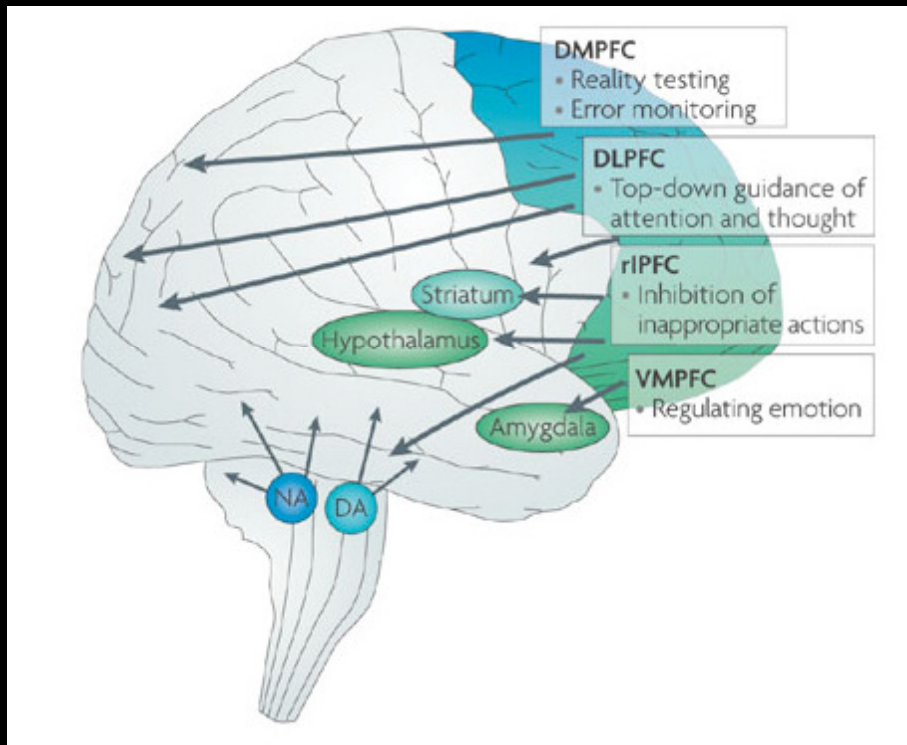
- Works with OFC: decision-making based on reward values
- But also generates new actions based on past rewards/punishments
- Appreciation and valuation of social cues
- MRI: active in tasks

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



Prefrontal Cortex (PFC)



- **EXECUTIVE DECISION-MAKING**
 - Motivation for goal-directed activity
 - Planning and problem-solving
 - Attention to tasks
 - Inhibition of impulsive responses
 - Weighing consequences of future actions
 - Flexibility of responses (rule shifting)
 - Reflective decision-making
- Gives us the capacity to use past experience and knowledge to make sense of our current behavior*

Addiction is a disorder of ...

5.

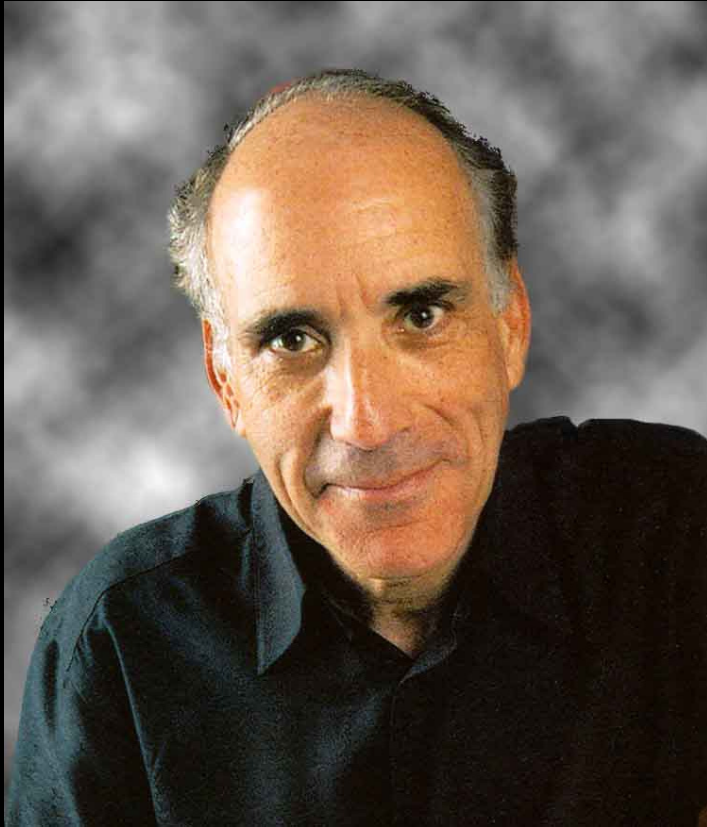
4.

3.

2.

1. ... GENES (vulnerability)

Genetic Vulnerability vs Resilience



Mark Schuckit, MD
U.C. San Diego

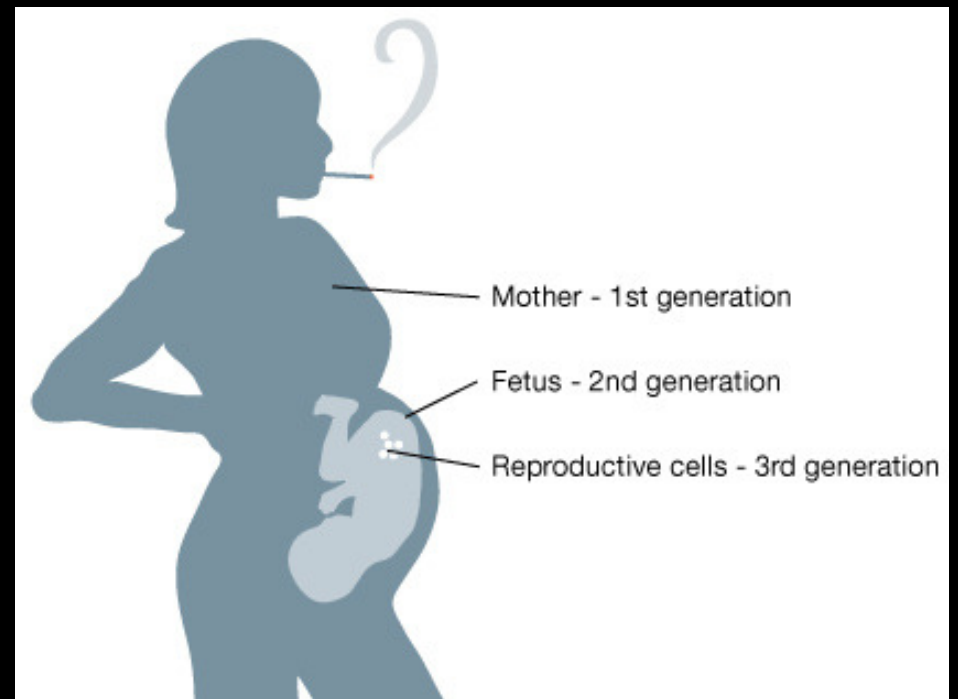
- Genetic difference determine “low responders” vs. “high responders” to the effects of **alcohol** (low responders are more likely to become alcoholics)
- There are genetic differences in how people respond to **methylphenidate (Ritalin)** injections (some like it, some don't care) implying different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

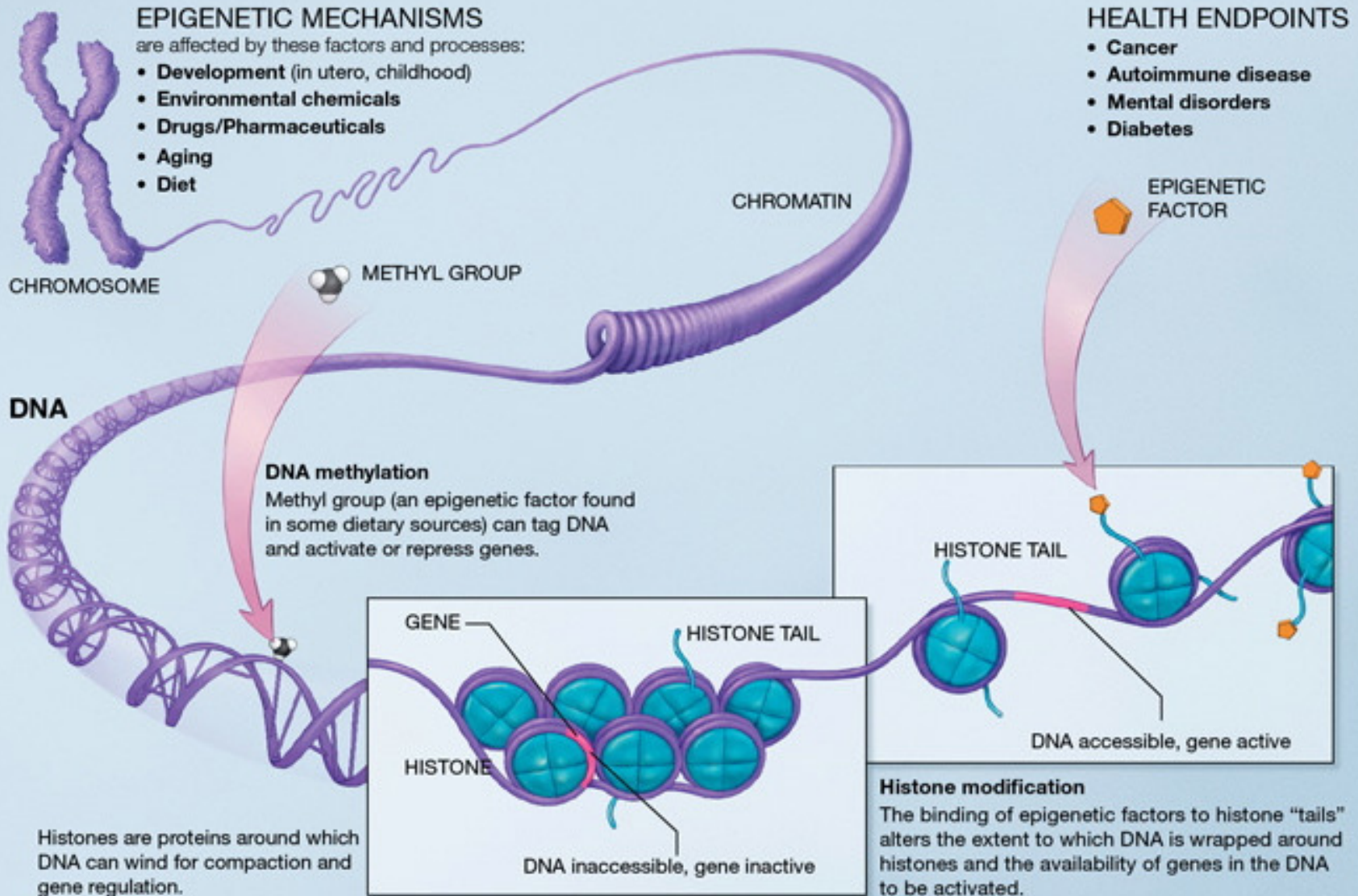
Epigenetics

- 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





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 (hedonic system)

1. ... GENES (vulnerability)

Addiction Neurochemical #1: Dopamine

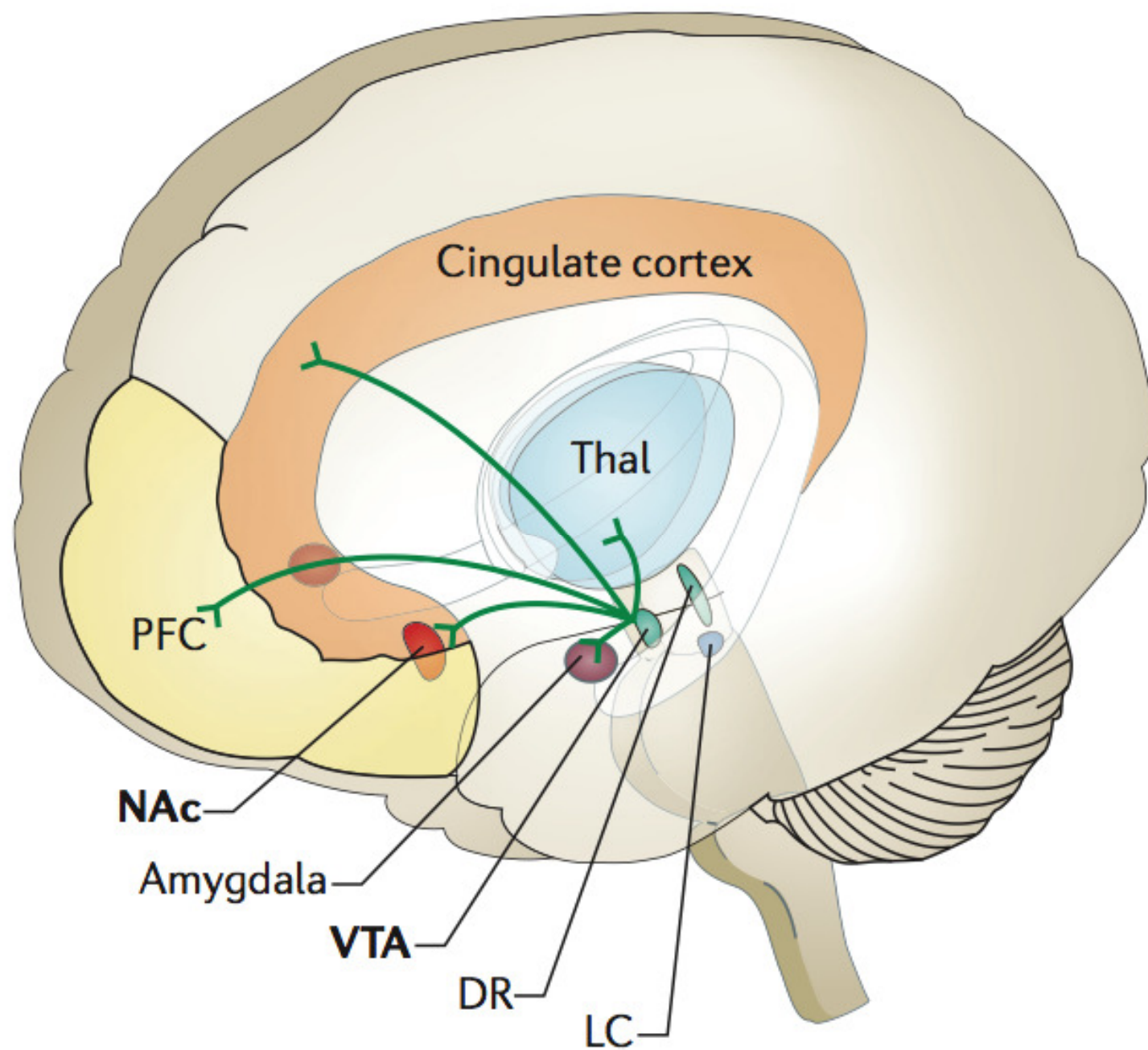
- All drugs of abuse and potential compulsive behaviors release Dopamine
- Dopamine is the first chemical in the cascade of chemicals that generate a rewarding experience
- DA is the chemical of salience (survival importance)
- DA is more about “wanting” than “liking”
- DA is more about expectation than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

Incentive-Sensitization (Robinson & Berridge)

- Distinguished between a “liking” and a “wanting” role for Dopamine (it’s more about “wanting”)
- Created *hyper-dopaminergic* Dopamine Transporter “knock-down” mice (mice with increased synaptic Dopamine)
- Observed increased intake of reinforcing substances in these mice and greater thwarting of obstacles to get them (i.e. more “wanting”)
- But did not observe greater “liking” of these substances by these mice

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



Computational Neuroscience



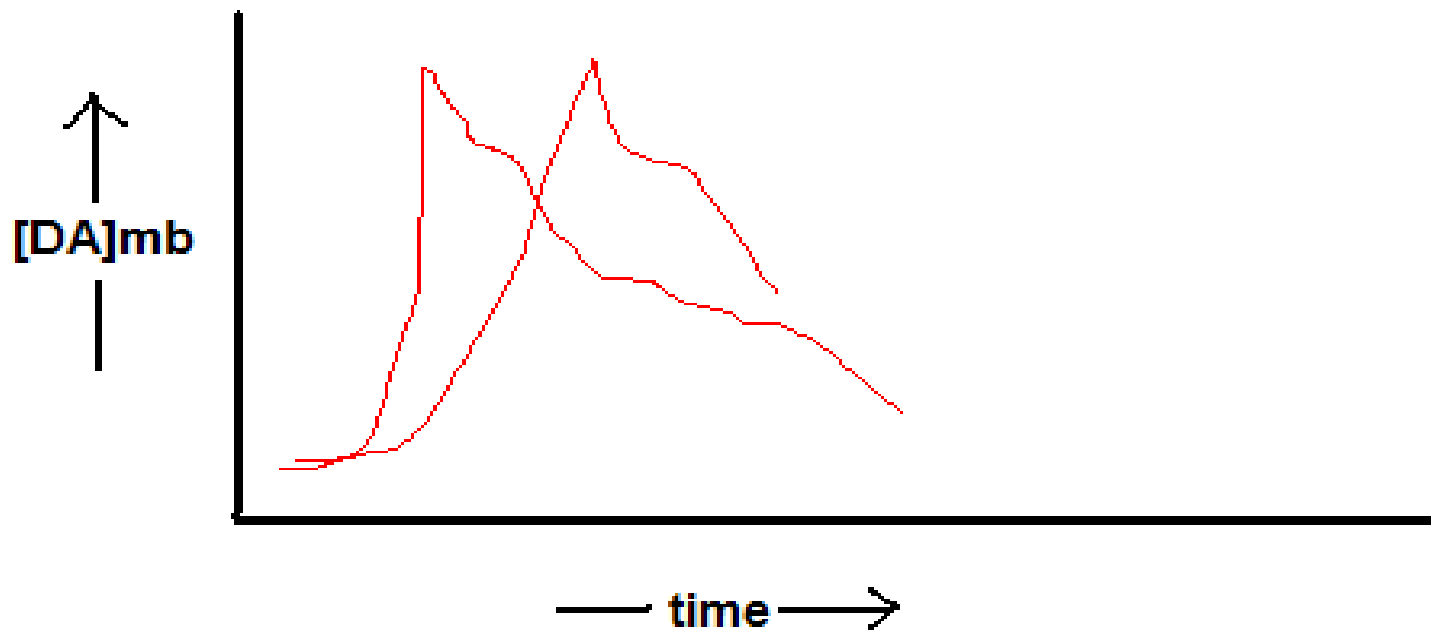
A. David Redish, PhD
University of Minnesota

- Computational models of human decision-making and addiction
- How do agents process information to make a decision?

Dopamine-Releasing Chemicals

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

Drugs cause Dopamine Surges in the midbrain reward system

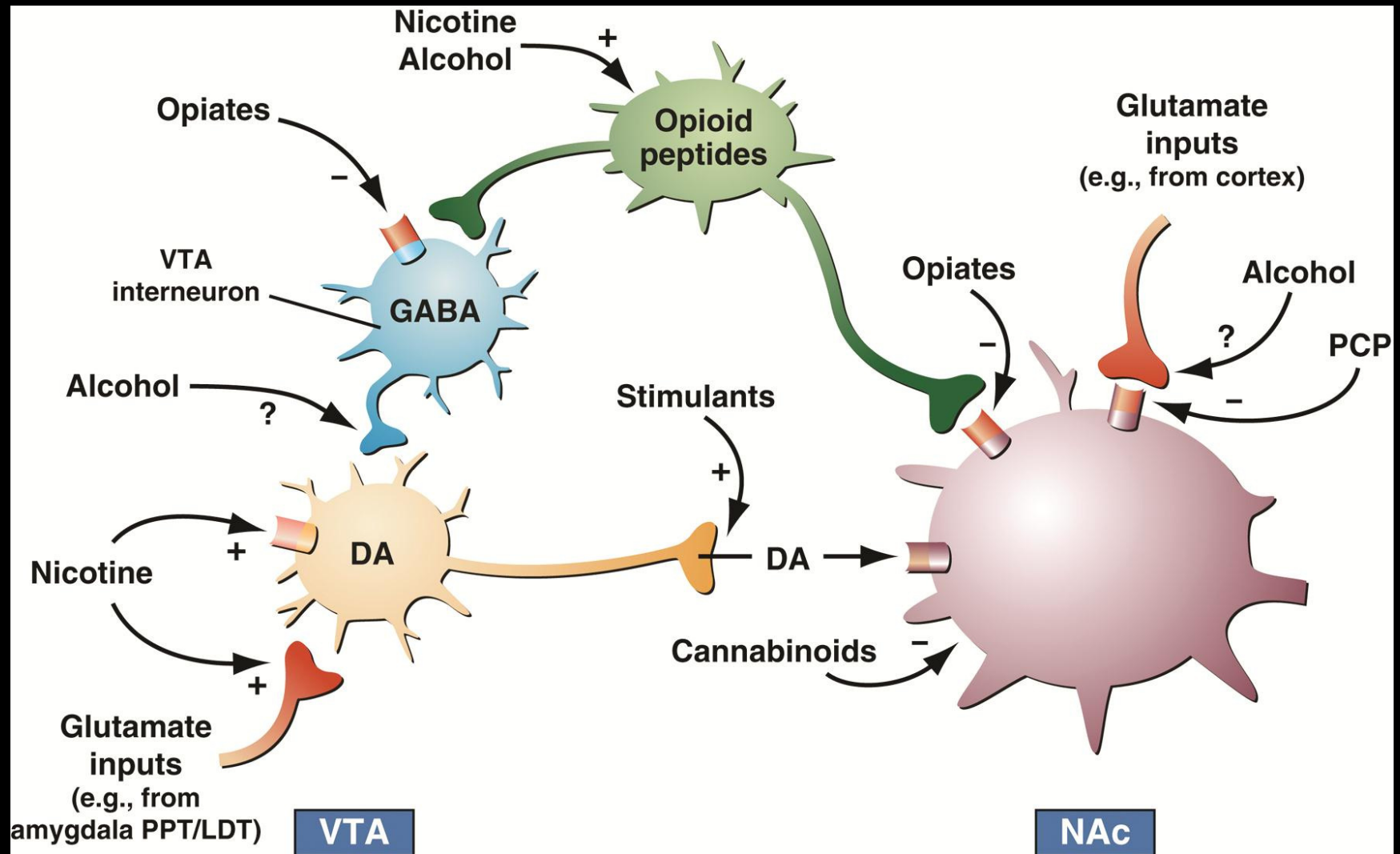


Dopamine-Releasing Behaviors

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

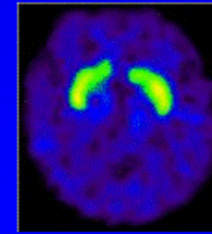
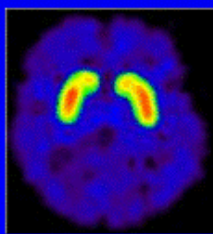
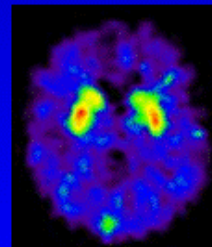
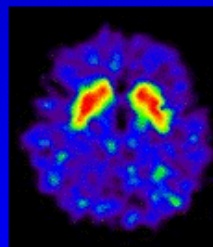
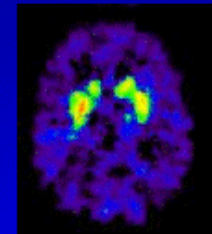
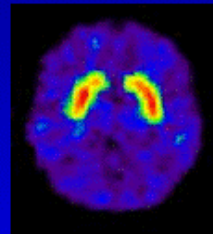
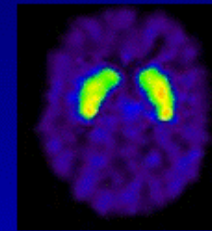
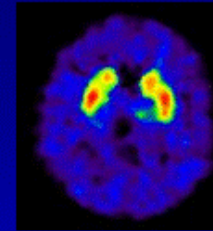
The Full Spectrum of Addiction

- Alcohol & Sedative/Hypnotics
- Opiates/Opioids
- Cocaine
- Amphetamines
- Entactogens (MDMA)
- Entheogens/Hallucinogens
- Dissociants (PCP, Ketamine)
- Cannabinoids
- Inhalants
- Nicotine
- Caffeine
- Anabolic-Androgenic
- Food (Bulimia & Binge Eating)
- Sex
- Relationships
- Other People
(“Codependency,” Control)
- Gambling
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- Performance
(“Work-aholism”)
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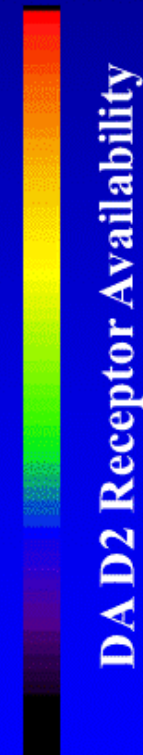
Functionally...

Dopamine D2 Receptors are Decreased by Addiction



Control

Addicted



Periodic Table of the Intoxicants

																1 ns ⁺ Al ethanol																		2 CII C cocaine															
																3 ns Cf caffeine		4 otc ⁺ N nicotine																															
5 Cl Cb cannabinol		6 Cl Mj THC		7 Cl Ha hashish		8 Cl Sp cannibicyclo																		9 ns Ab thujone		10 Cl Ib ibogaine		11 Cl Ms mescaline		12 Cl Ps psilocybin		13 Cl 2c DOC		14 Cl Dp DPT		15 Cl Dt DMT		16 Cl L LSD											
17 ns No nitrous ox.		18 otc Dx DXM		19 Cl/ns Sa salvinorin		20 ClII K ketamine		21 Cl Pc phencycl.																		22 otc ⁺ Ep ephedrine		23 CIV Mo modafinil		24 CIV Ff phentermine		25 ClII Ri methylphen.		26 Cl Kh cathinone		27 Cl Ba MDPV		28 Cl X MDMA		29 Cl/II A amphetam.		30 Cl/II Me methamph.							
31 CV Ly pregabalin		32 CIV Sm carisoprodol		33 CIV Am zolpidem		34 CIV So zaleplon		35 CIV Lu eszopiclone		36 CIV Ch chl. hydrate		37 Cl/III G GHB		38 Cl Q methaqual.		39 CIV Pb phenobarb.		40 ClII Sb secobarbital		41 ClIII Fb butalbital		42 CIV Cz chlordiaz.		43 CIV Oz oxazepam		44 CIV Tz temazepam		45 CIV Lz lorazepam		46 na Rz flunitraz.		47 CIV Dz diazepam		48 CIV Hz triazolam		49 CIV Kz clonazepam		50 CIV Xz alprazolam											
51 ClIII ⁺ Bu buprenorph.		52 ns Na nalbuphine		53 CIV St butorphanol		54 CIV/ns Ul tramadol		55 ns Kr mitragynine		56 CIV Tw pentazocine		57 na Dv propoxyph.		58 ClII O opium		59 ClIII Co codeine		60 ClIII Vi hydrocod.		61 ClII Ox oxycodone		62 ClII Dm meperidine		63 ClII M morphine		64 Cl H heroin		65 Cl Ko desomorph.		66 ClII Di hydromorph.		67 ClII Op oxymorph.		68 ClII ⁺ Md methadone		69 ClII Fe fentanyl		70 ClII(v) Ca carfentanil											
71 ns An amyl nitrite		72 ns/Rx Po propofol		73 ns/Rx Ih inhal. anes.		74 ns Cl chloroform		75 ns De diethyl ether		76 ns Pe petrol gases		77 ns Ae aerosols		78 ns Or org solvents																		79 ClIII Ts testosterone		80 ClIII Bs boldenone		81 ClIII Ds methandro.		82 ClIII Ns nandrolone		83 ClIII Ss stanozolol		84 ClIII Os oxymethol.		85 ClIII As oxandrolone		86 ClIII(v) Fs trenbolone		87 ClIII Hs fluoxymest.	

Kevin T. McCauley, MD

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



“Rat Park” Study

Bruce K. Alexander

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



ASAM Definition: Relapse

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

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

ASAM Definition: Relapse

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- Even after periods of abstinence
- Triggered by:
 1. Brief 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

(learning)

2. ... REWARD

(hedonic system)

1. ... GENES

(vulnerability)

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)

Glutamate “spillover”

- Enduring vulnerability to relapse due to recruitment of “cortico-fugal” 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



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

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

Amygdalar-Cortical Circuit

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

THERE'S TOO MUCH OF
THIS

(Behavioral Impulsivity)

Cortico-Striatal Circuit

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

THERE'S TOO LITTLE OF
THIS

(Failure of Behavioral
Inhibition)

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)

3. ... MEMORY (learning)

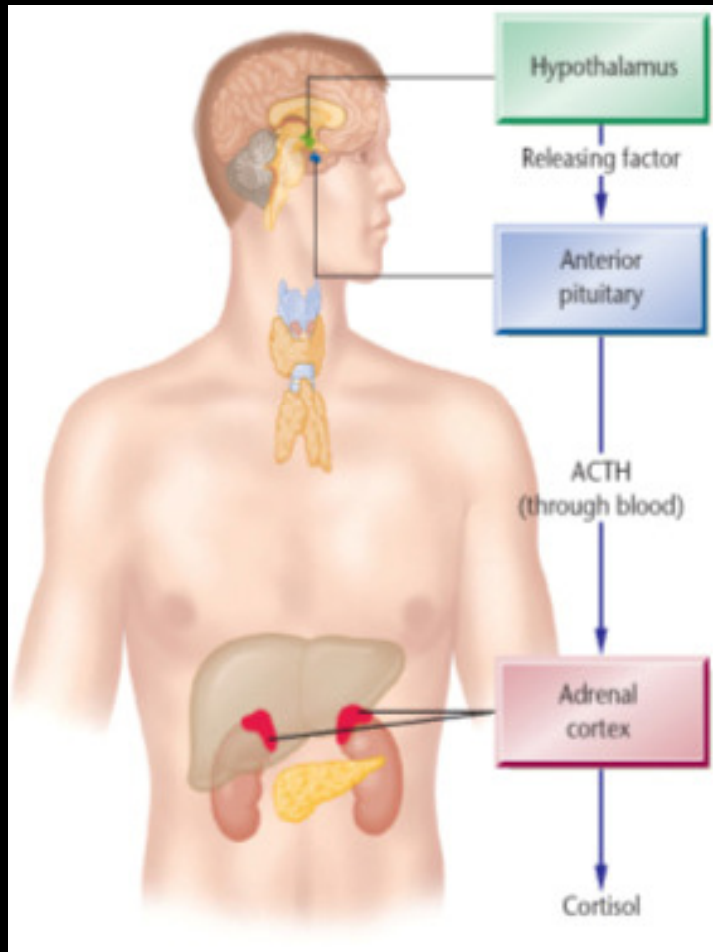
2. ... REWARD (hedonic system)

1. ... GENES (vulnerability)

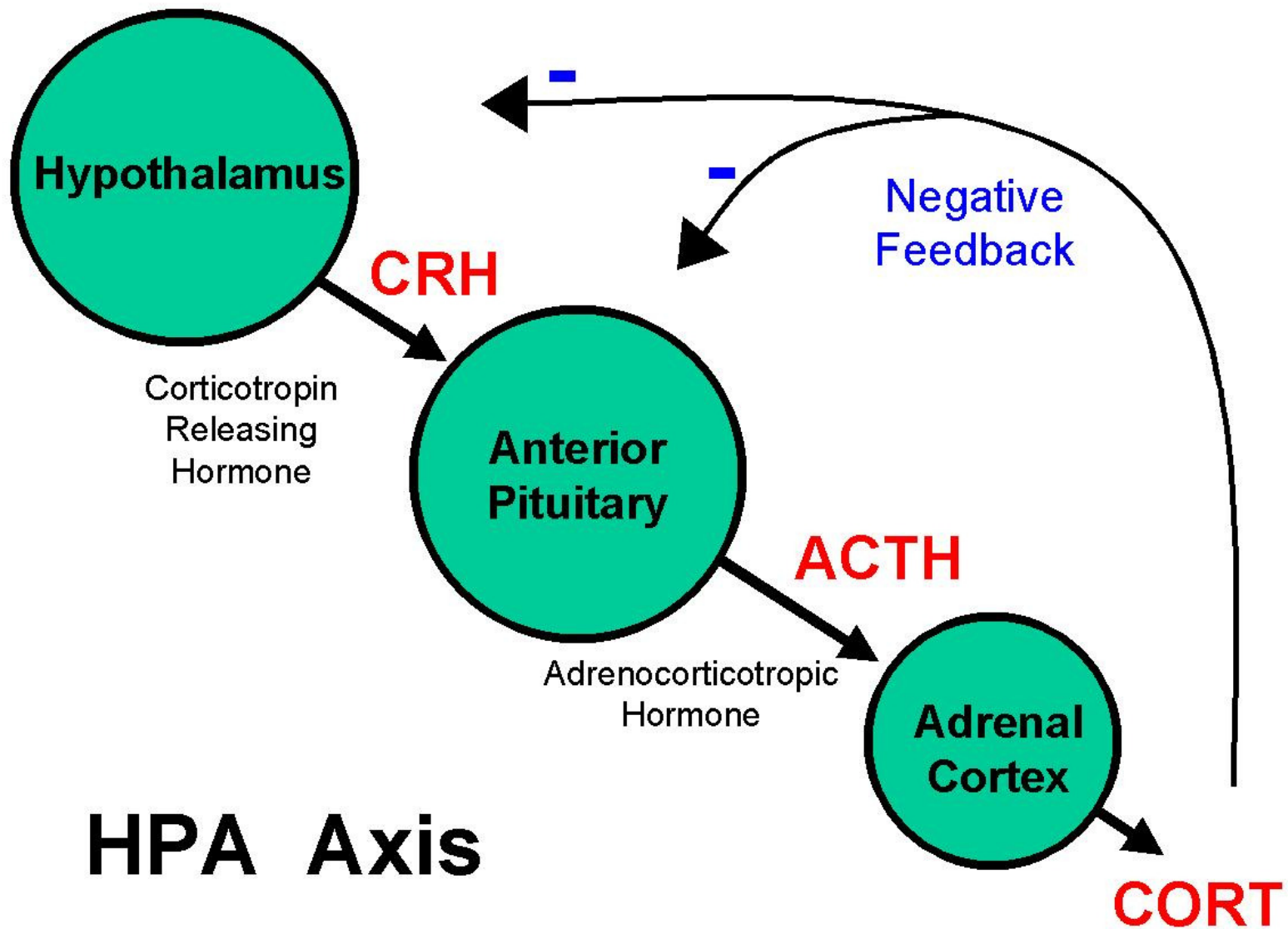
Hedonic Allostasis Theory (Koob & LeMoal)

- 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

Hypothalamic-Pituitary-Adrenal (HPA) Axis



- Hypothalamus releases
Corticotropin-Releasing Factor (CRF)
- CRF goes to Pituitary Gland to release
ACTH (and β -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



CHRONIC, SEVERE STRESS = \uparrow CRF

and \uparrow CRF = \downarrow DAD2 receptors

and \downarrow 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)*

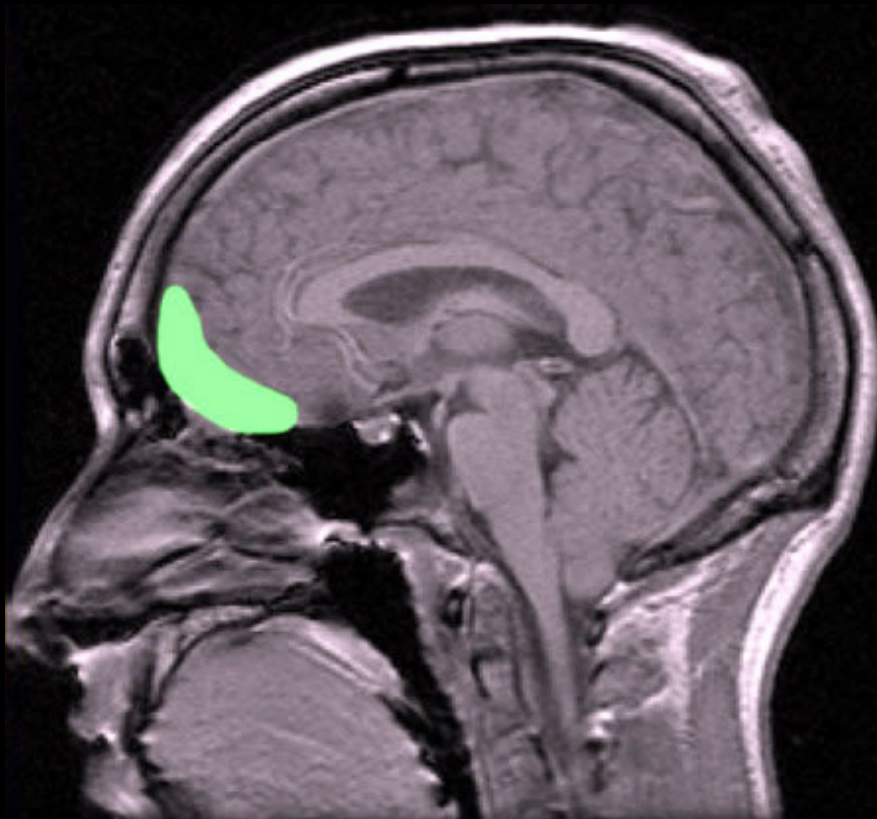
Strategies to deal with the STRESS component of addiction

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

Addiction is a disorder of ...

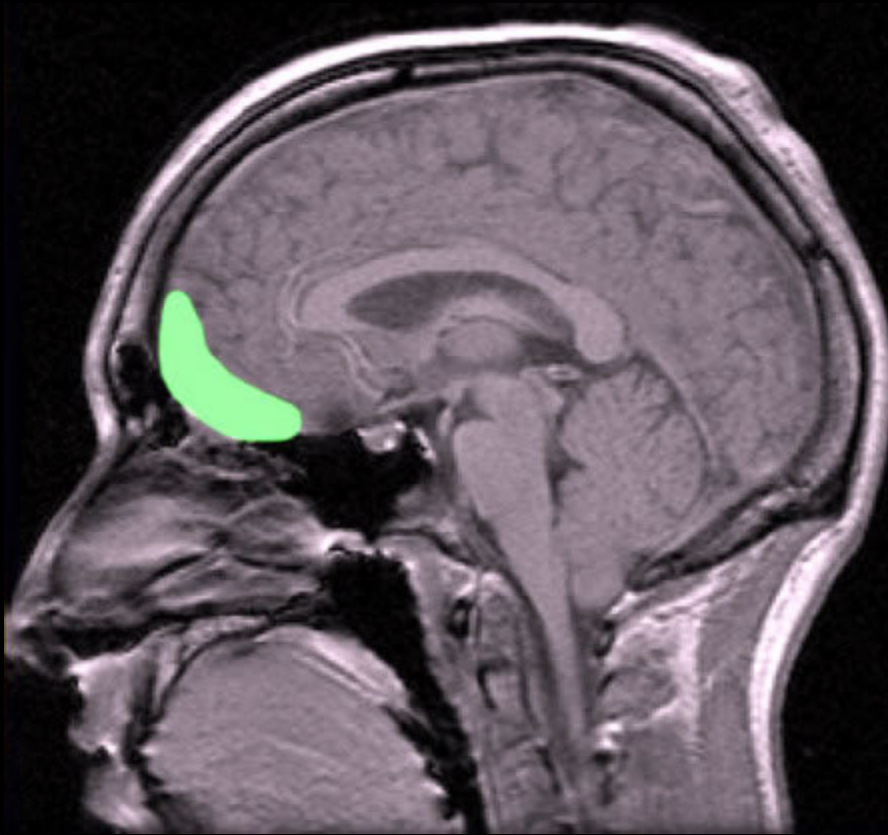
- 5. ... CHOICE (motivation)
- 4. ... STRESS (anti-reward system)
- 3. ... MEMORY (learning)
- 2. ... REWARD (hedonic system)
- 1. ... GENES (vulnerability)

Orbitofrontal Cortex (OFC)



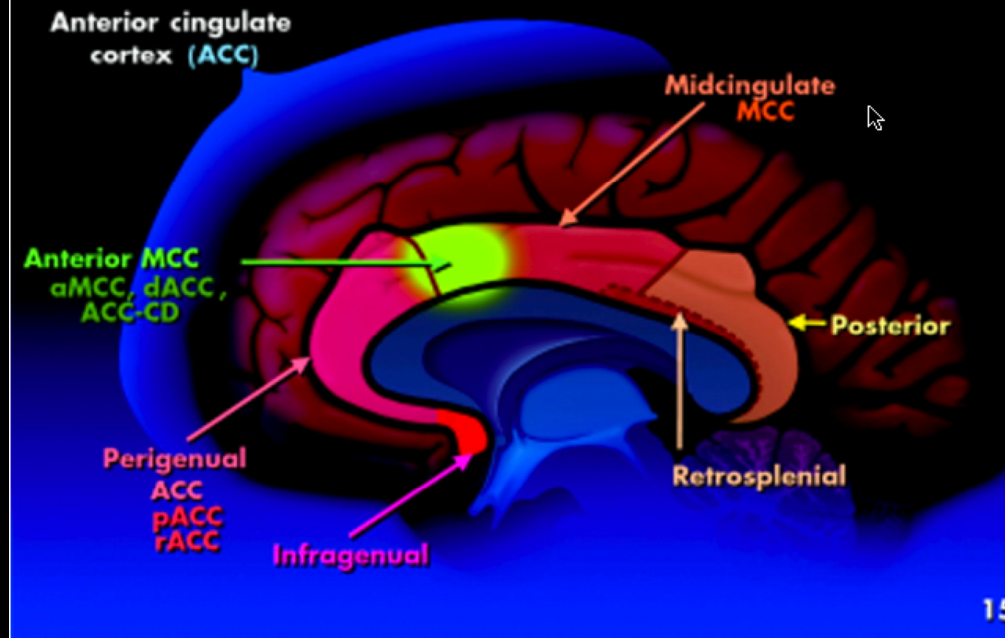
- Decision-making guided by rewards
- Integrates sensory and emotional information from lower limbic structures
- Flexible assignment of value to environmental stimuli to motivate or inhibit choices & actions
- Self-monitoring and social responding

damage to Orbitofrontal Cortex (OFC)



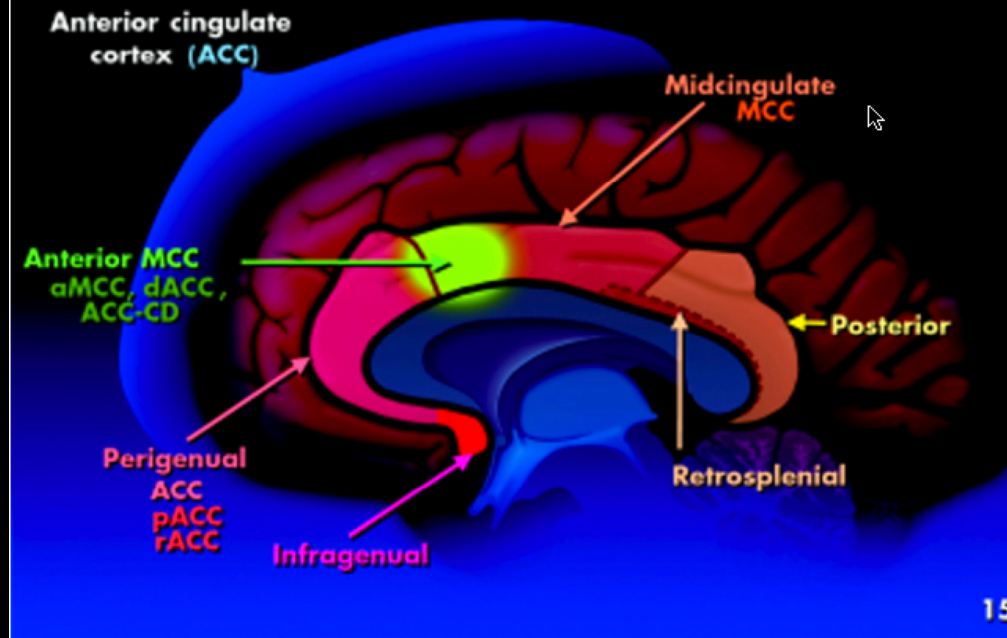
- Causes a loss of a crucial behavioral guidance system
- Responses are impulsive and inappropriate
- Deficits of self-regulation
- Inability to properly assign value to rewards (such as money vs. drugs)
- Tendency to choose small & immediate rewards over larger but

Anterior Cingulate Cortex (ACC)



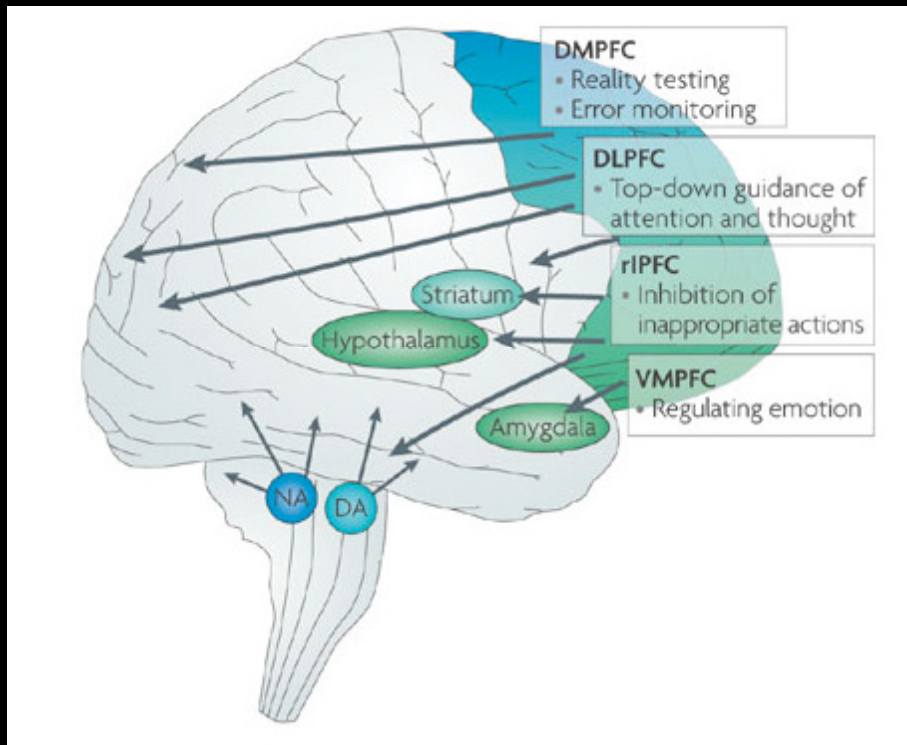
- Works with OFC: decision-making based on reward values
- But also generates new actions based on past rewards/punishments
- Appreciation and valuation of social cues
- MRI: active in tasks

damage to Anterior Cingulate Cortex (ACC)



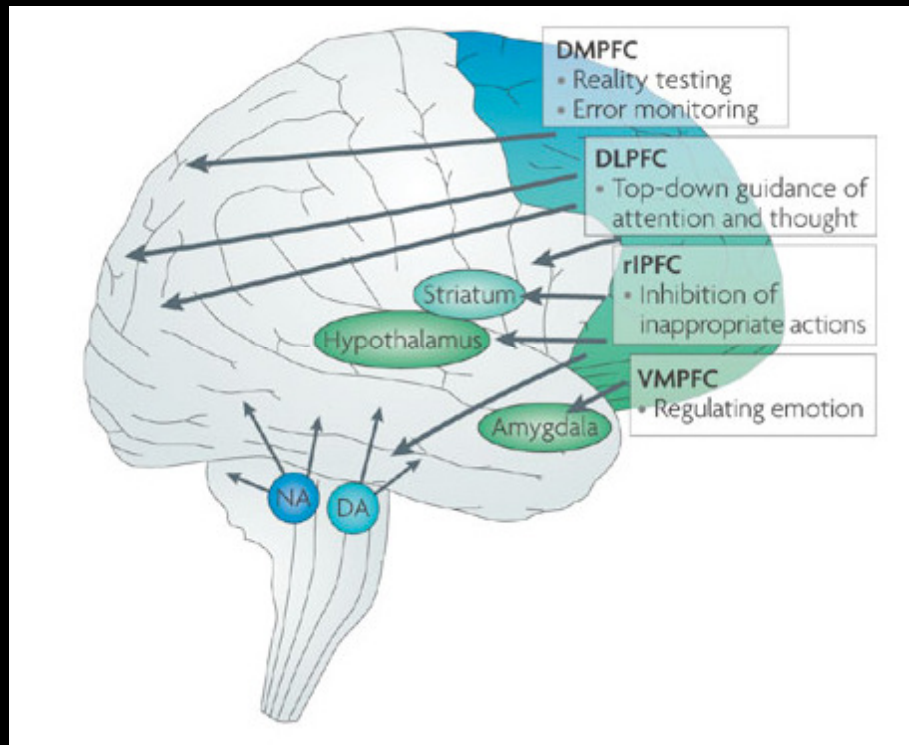
- Just as with OFC damage: causes a loss of a crucial behavioral guidance system
- Inflexibility/Inability to respond to errors in the past with regard to rewards/punishments
- Deficits in social responding due to decreased awareness of social cues

Prefrontal Cortex (PFC)



- **EXECUTIVE DECISION-MAKING**
 - Motivation for goal-directed activity
 - Planning and problem-solving
 - Attention to tasks
 - Inhibition of impulsive responses
 - Weighing consequences of future actions
 - Flexibility of responses (rule shifting)
 - Reflective decision-making
- Gives us the capacity to use past experience and knowledge to make sense of our current behavior*

damage to Prefrontal Cortex (PFC)



- **Failure of Executive Functioning**
- Premature, unduly risky, poorly conceived actions
- Emotional crises
- Emotions inappropriate to the situation
- Lack of emotional expression (alexithymia)
- Sensation seeking
- 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

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)

AA: using NON - Rational Concepts

- **TRIBE** (*“the fellowship of alcoholics”*)
- **MYTH** (*Bill ’s Story, etc.*)
- **RITUAL** (*“what it was like, what happened, and...”*)
- **FAITH** (*“Keep coming back, it works”*)
- **HOPE** (*The Promises*)
- **ACCEPTANCE** (*“...the answer to all my problems”*)

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