Rhode Island Governor's Council on Behavioral Health

Prevention Advisory Committee

RI PREVCON 2019

Neurobiology of Prevention

CCRI Knight Campus

January 10, 2019

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Past President, RI Society of Addiction Medicine

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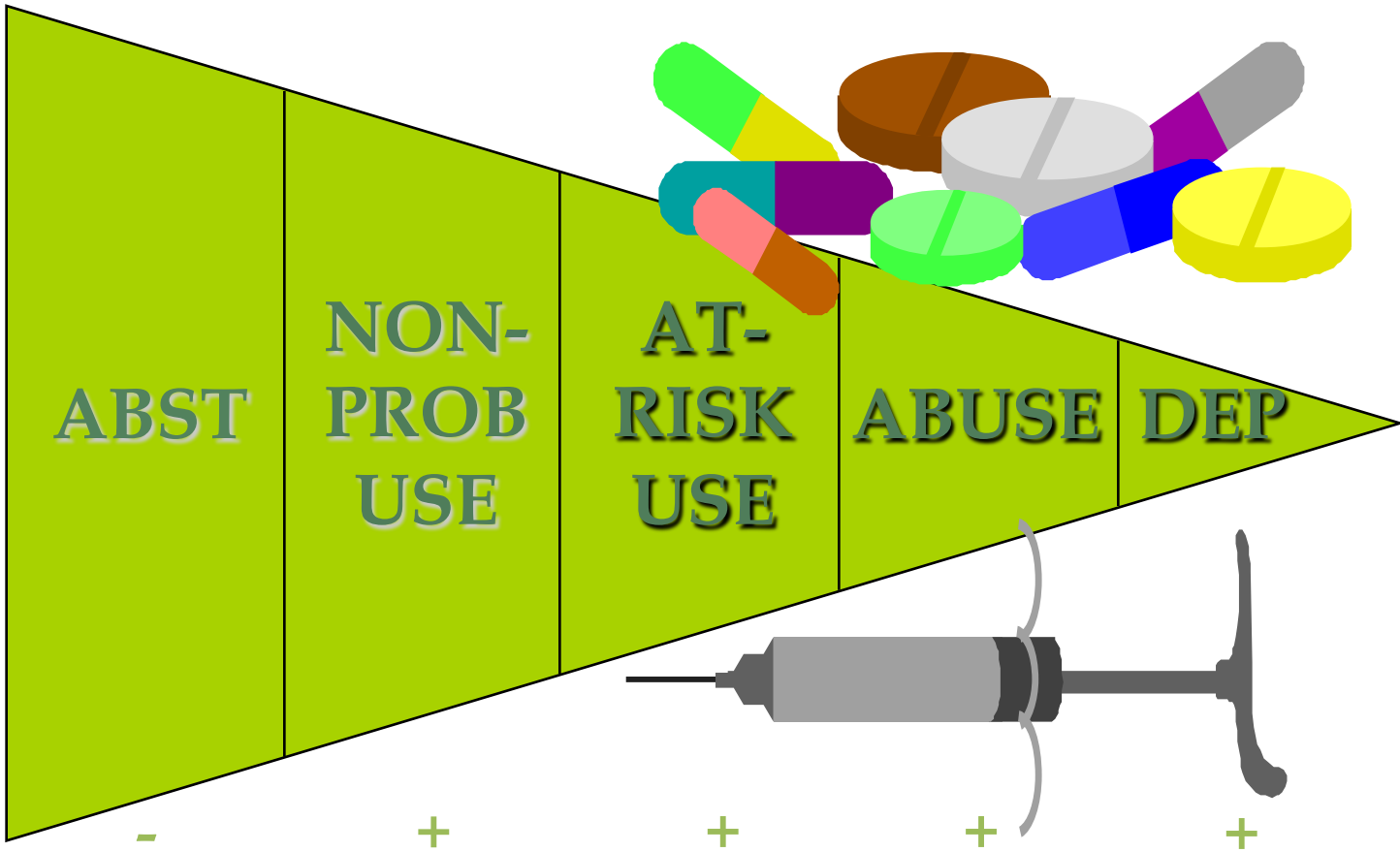
Leavell's Levels of Prevention

Stage of disease	Level of prevention	Type of response
Pre-disease	Primary Prevention	Health promotion and Specific protection
Latent Disease	Secondary prevention	Pre-symptomatic Diagnosis and treatment
Symptomatic Disease	Tertiary prevention	•Disability limitation for early symptomatic disease •Rehabilitation for late Symptomatic disease

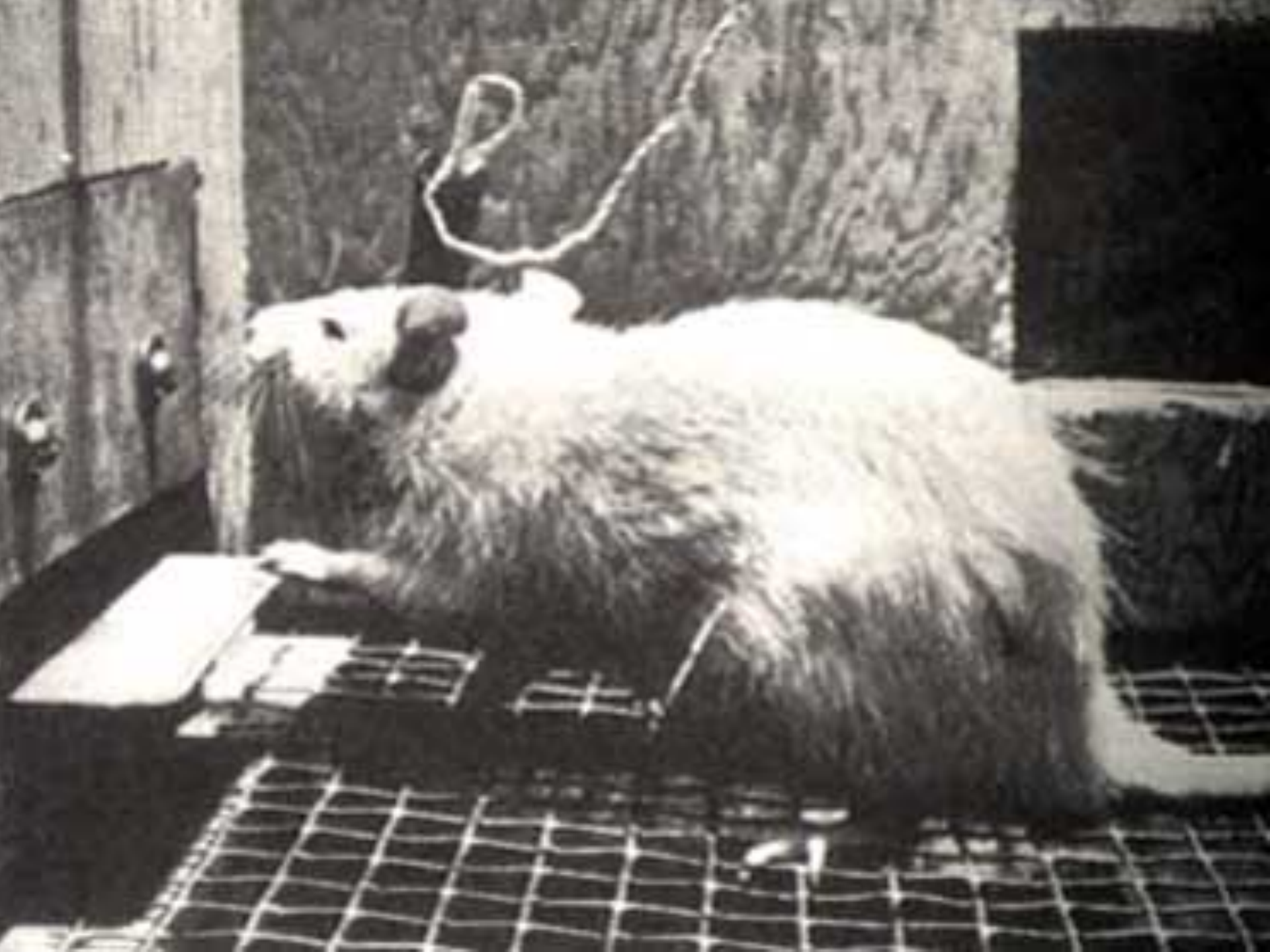


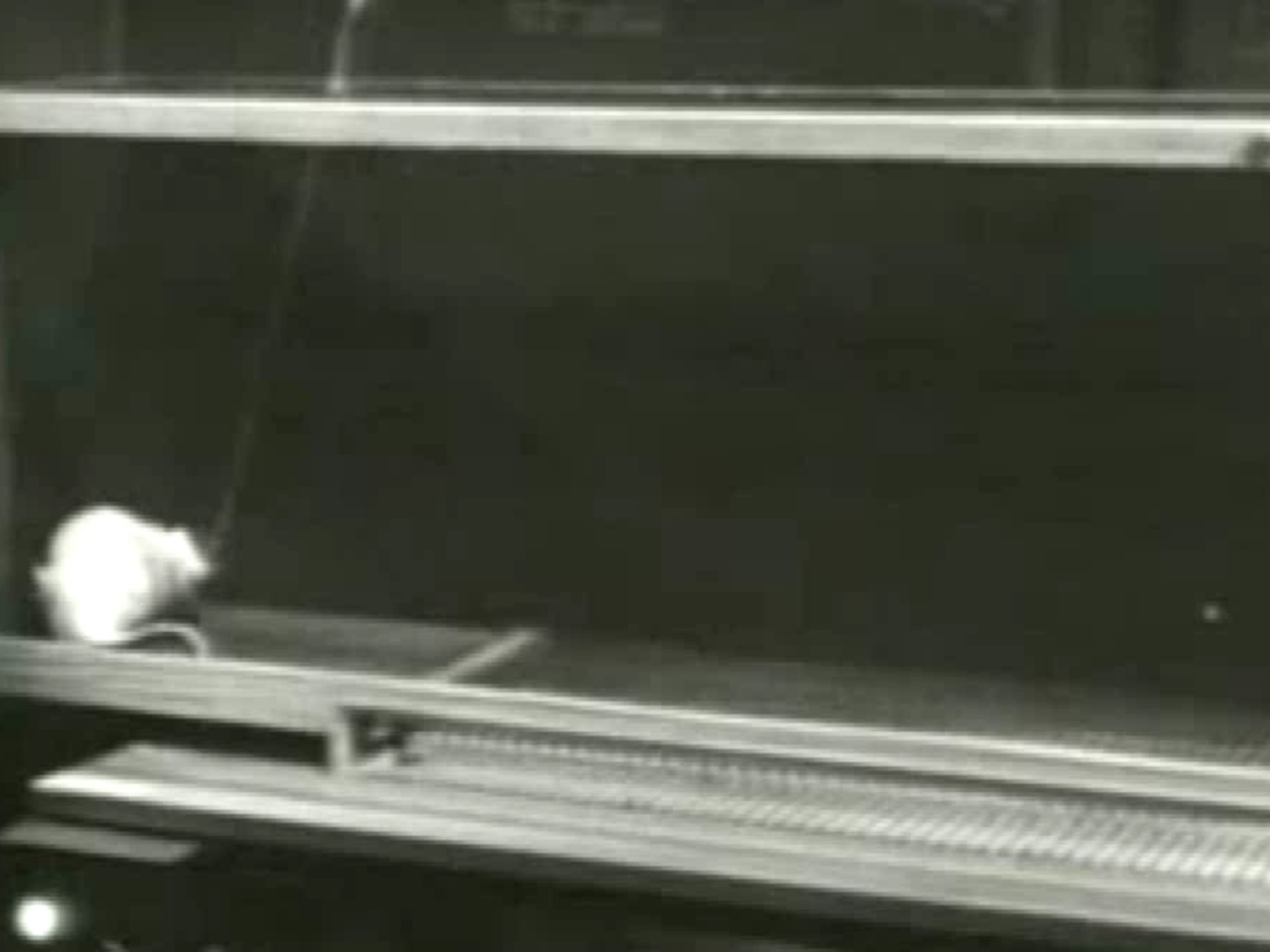
Use	-	+	+	+	+
Consequences	-	-	-/+	+	++
Repetition	-	-	-	+	+
Loss of control, preoccupation, compulsivity, physical dependence					+

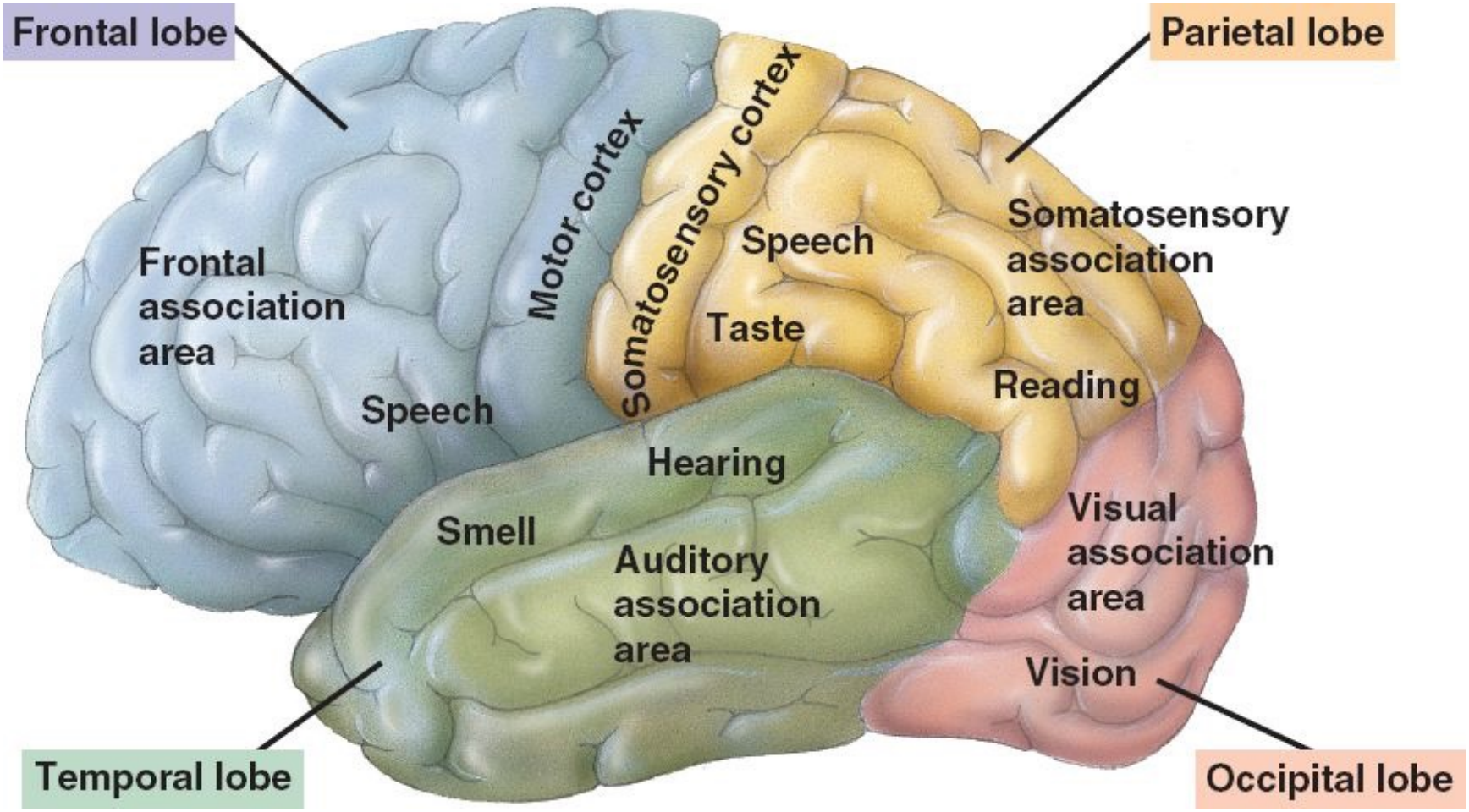
AA Sayings: Pathophysiology

- I'm a normal person, minus two drinks
- One drink is too many and a thousand is not enough
- Insanity is defined as doing the same thing over and over again, expecting different results
- Alcoholics heal from the outside in, but feel from the inside out
- Alcoholism is the only disease that tells you, you don't have it
- Death, insanity or recovery

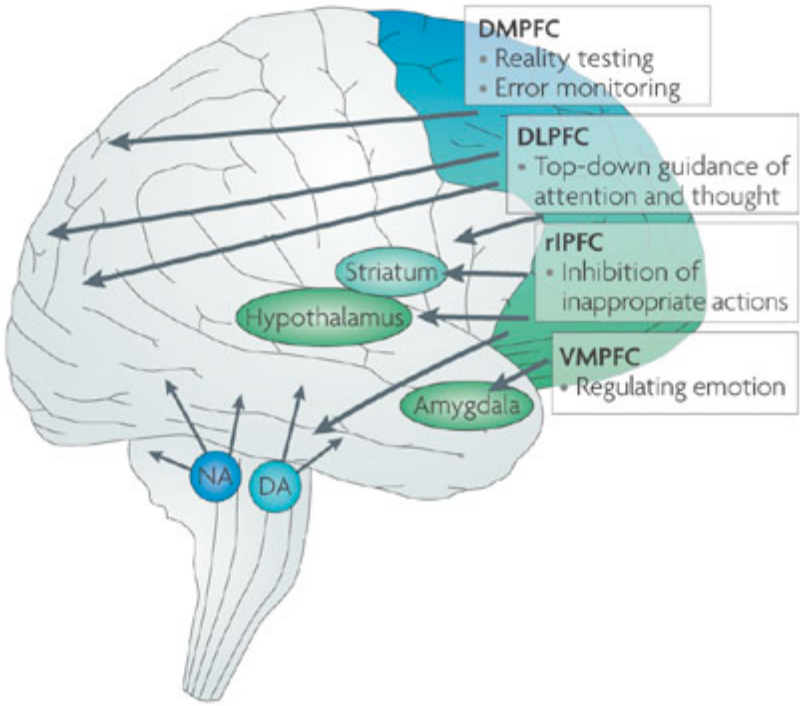
The Reward Pathway and Addiction






Frontal lobe
Parietal lobe
Motor cortex
Somatosensory cortex
Frontal association area
Speech
Speech
Taste
Somatosensory association area
Reading
Hearing
Smell
Auditory association area
Visual association area
Vision
Temporal lobe
Occipital lobe

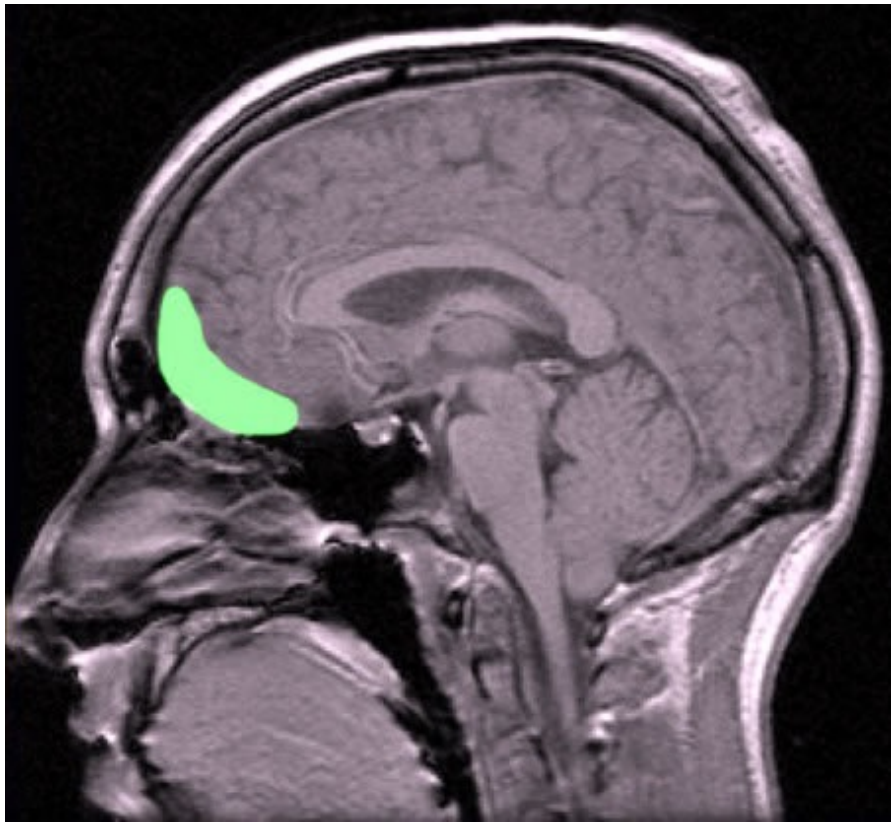
Prefrontal Cortex (PFC)



- 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

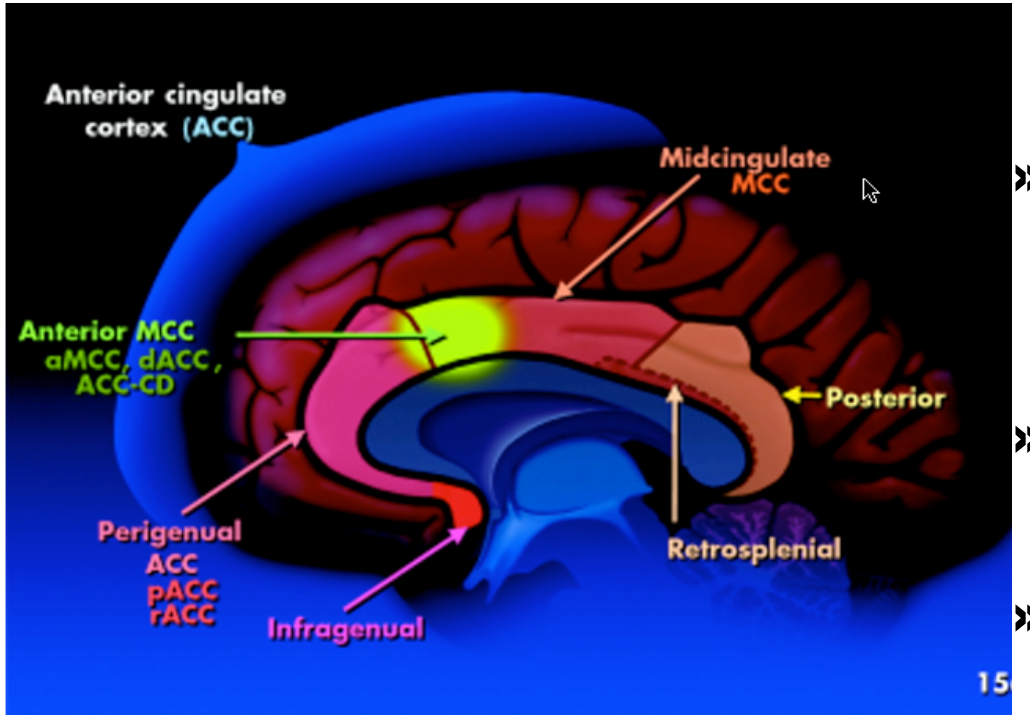
Gives us the capacity to use past experience and knowledge to make sense of our current behavior

Orbitofrontal Cortex (OFC)



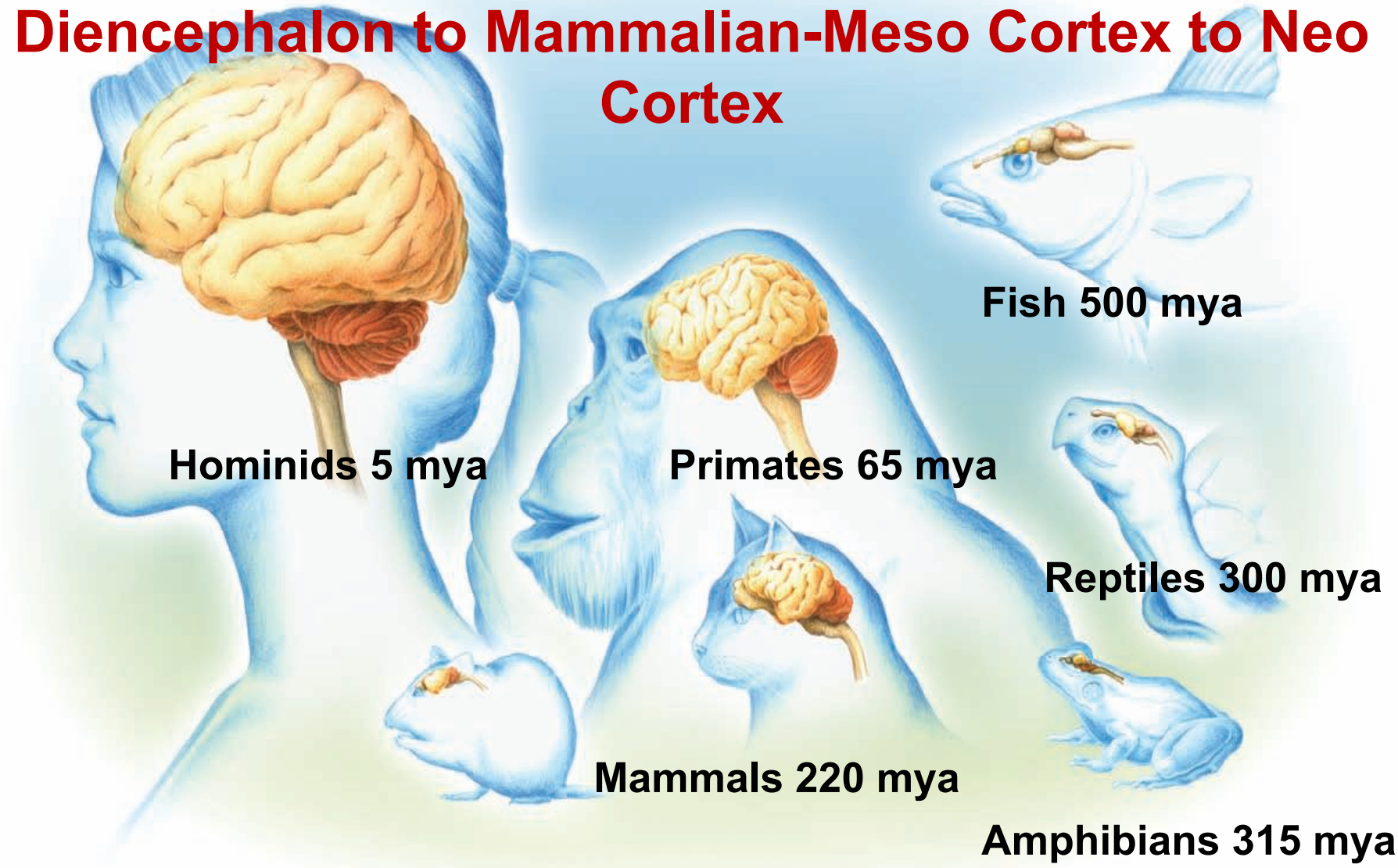
- Decision-making guided by rewards
- Integrates sensory and emotional information from lower limbic structures
- Flexible assignment of value to environmental stimuli to motivate or inhibit choices & actions
- Self-monitoring and social responding

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 requiring empathy and trust

Neurons in Earth's Fossil Record: Spinal Cord to Diencephalon to Mammalian-Meso Cortex to Neo Cortex



Earth 4.5 Billion Years, Life from 4 Billion Years

Last Area of Brain to Develop is Prefrontal Cortex

Medial PFC = Value
Lateral PFCs = Costs or consequences

Functional at age 25!

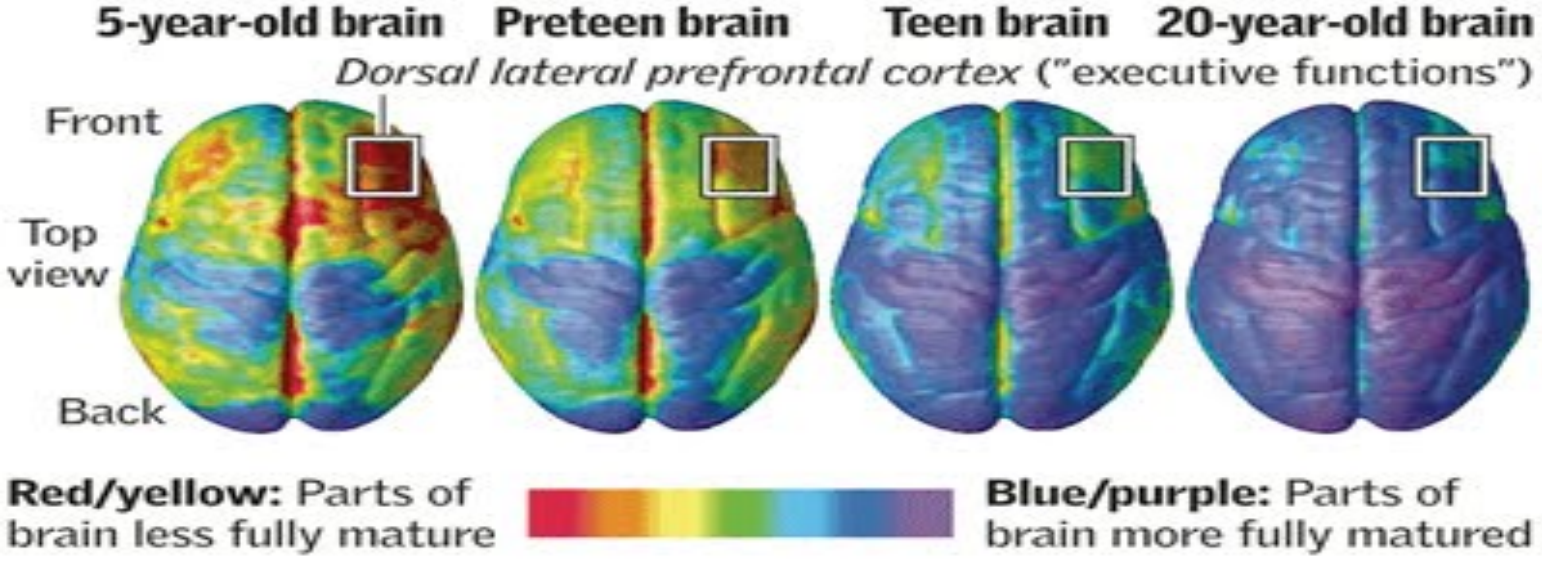
Fully Developed At age 40+

Reasoning, Impulse Control, Temporal Processing, Planning, Judgment

Why we all make such “great” decisions before age 25

Judgment last to develop

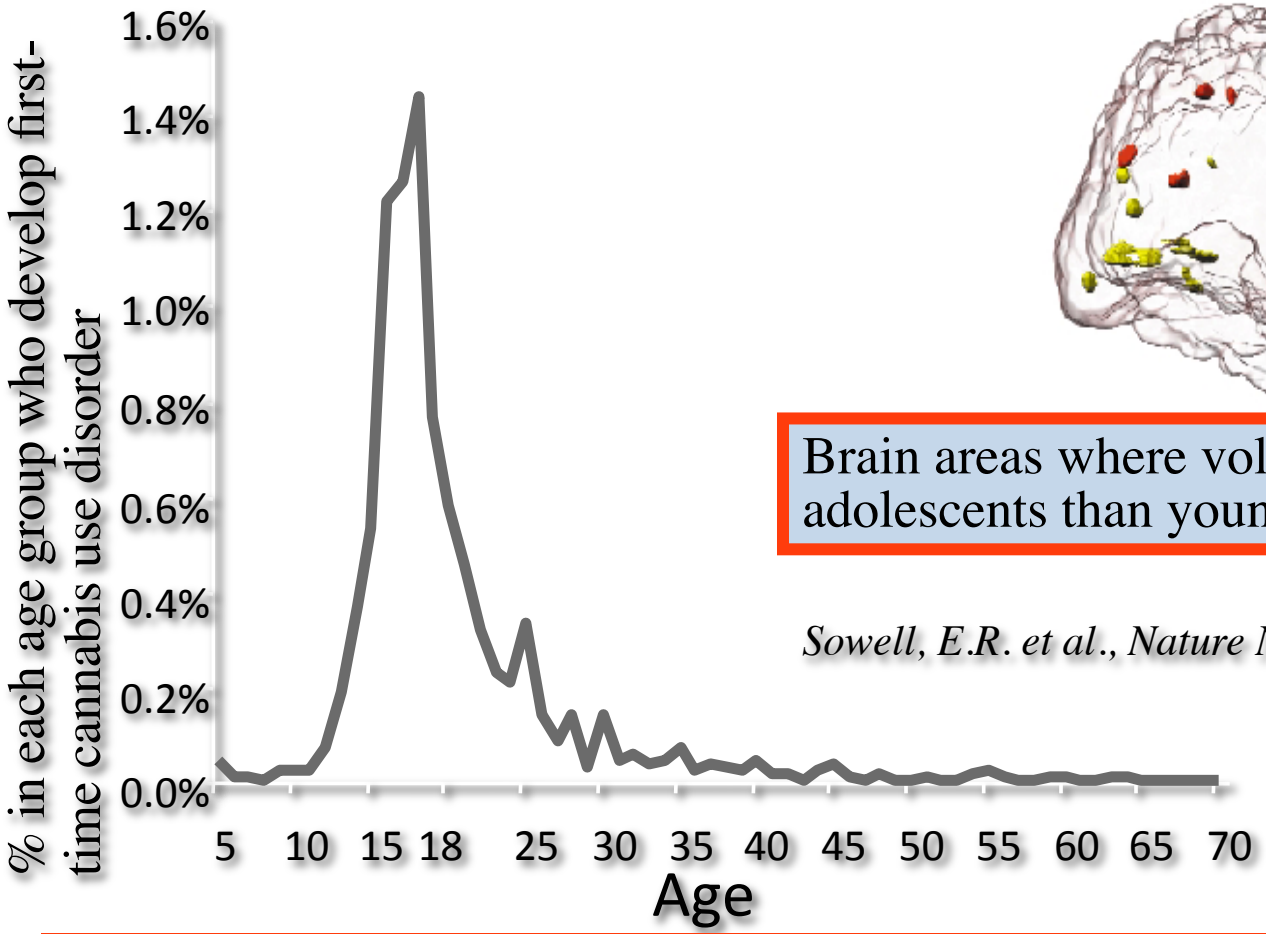
The area of the brain that controls "executive functions" — including weighing long-term consequences and controlling impulses — is among the last to fully mature. Brain development from childhood to adulthood:

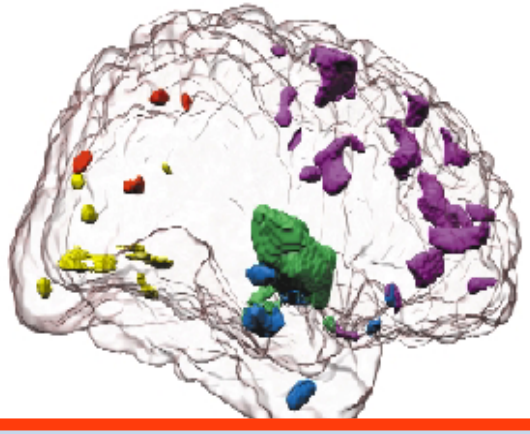


Sources: National Institute of Mental Health; Paul Thompson, Ph.D., UCLA Laboratory of Neuro Imaging

Thomas McKay | The Denver Post

Drug Addiction is a Developmental Disease that Starts in Adolescence and Childhood





Brain areas where volumes are smaller in adolescents than young adults.

Sowell, E.R. et al., Nature Neuroscience, 2: 859-861, 1999

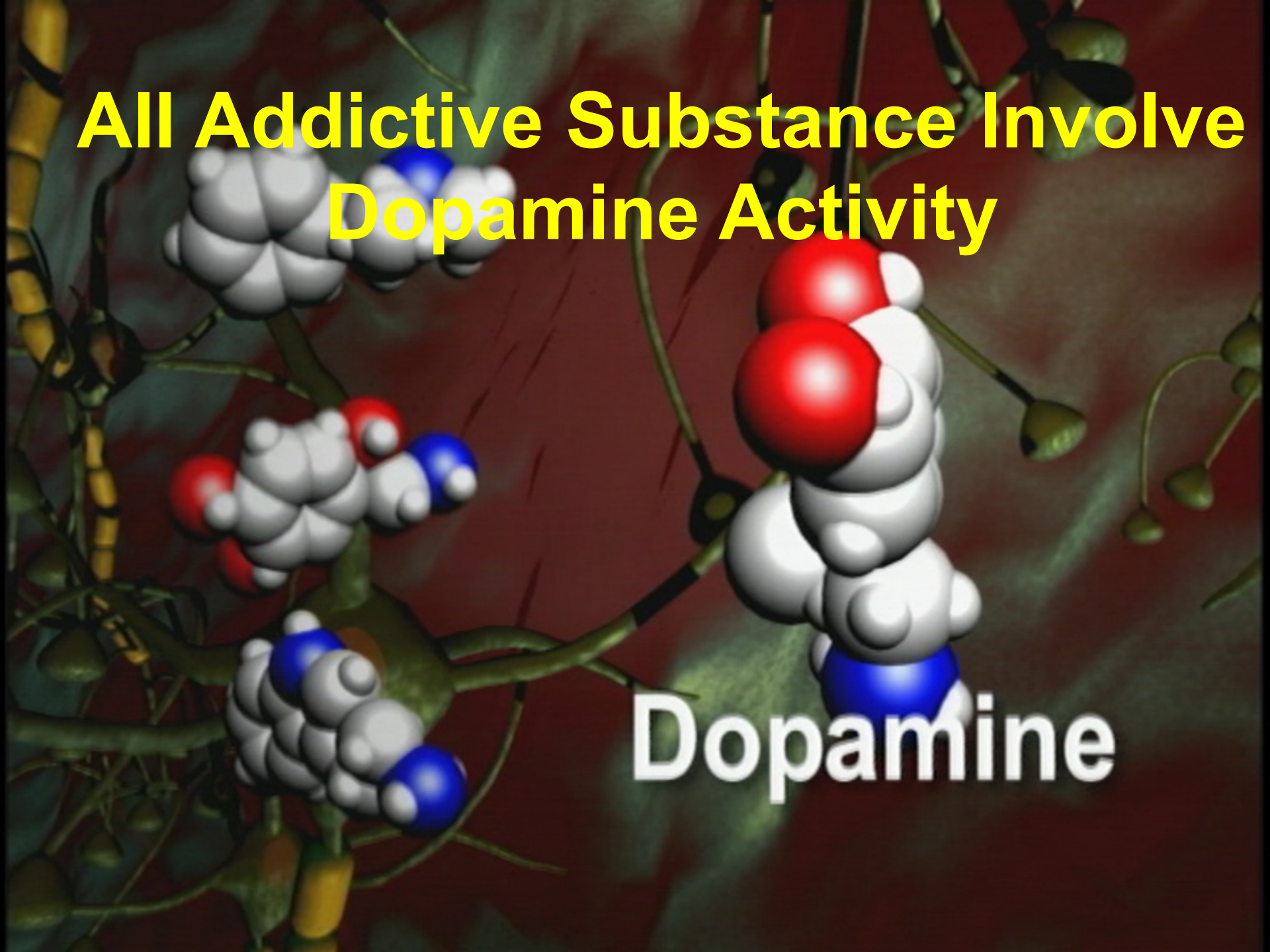
Age at cannabis use disorder as per DSM IV

NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003

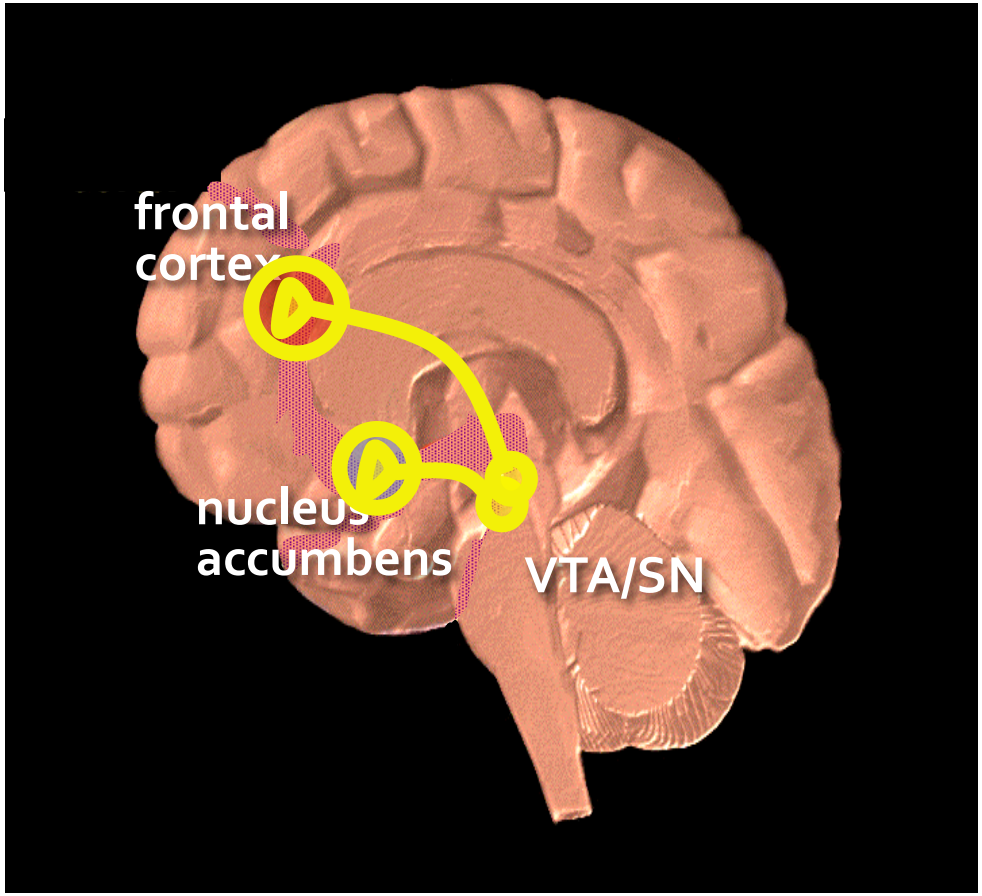
Stages of Addiction + Recovery

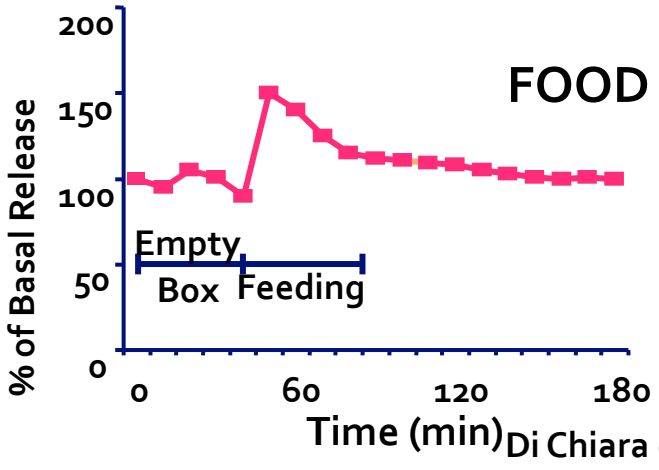
- Like — Exposure
- Want — Experimentation
- Get — Planning and drug seeking
- Need — Self Medication-withdrawal prevention

- Don't Need — Detox and mood stabilization
- Don't Get — Trigger and urge control
- Don't Want — Relapse prevention skills
- Don't Like — Recovery and self exploration

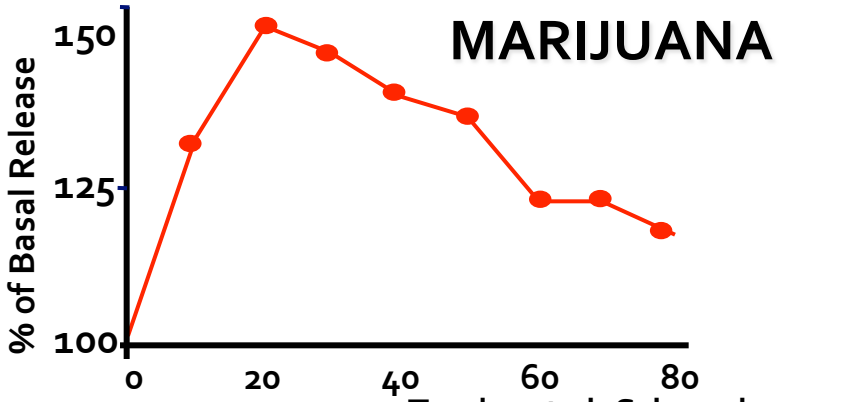

All Addictive Substance Involve Dopamine Activity
Dopamine

Natural and Drug Reinforcers Increase Dopamine in NAc

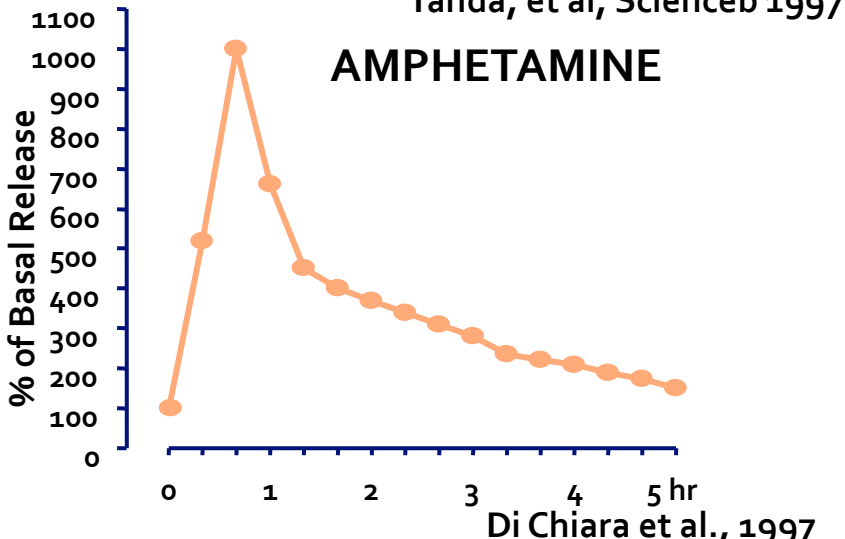




Di Chiara et al., 1997



Tanda, et al, Scienceb 1997



Di Chiara et al., 1997

Drugs of abuse increase DA in the Nucleus Accumbens, which is believed to trigger the neuroadaptions that result in addiction

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

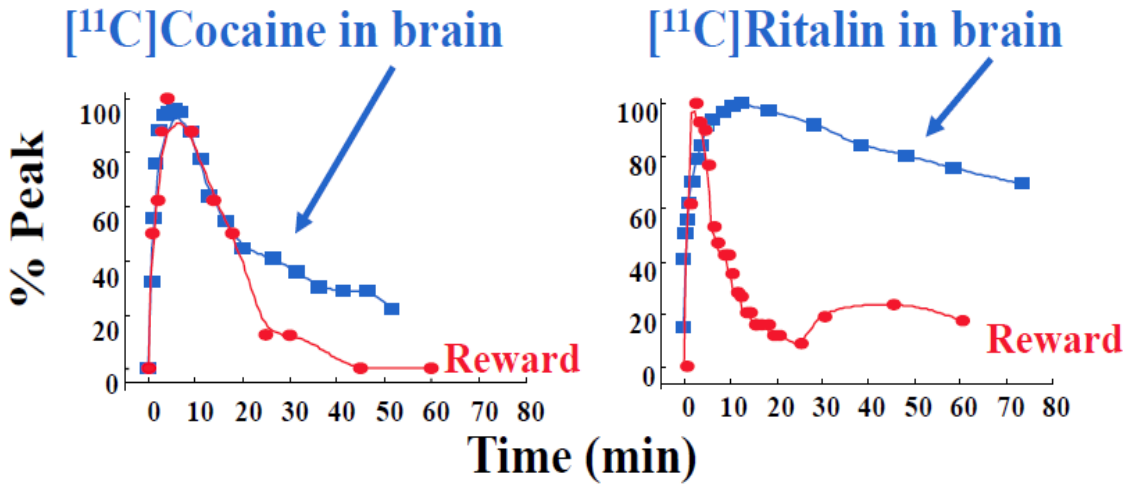
Addiction is a disorder of …

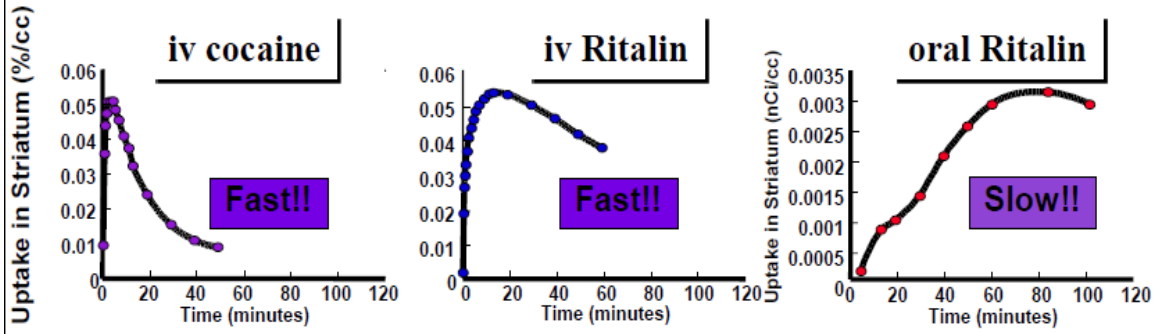
5. … CHOICE (motivation)
4. … STRESS (anti-reward system)
3. … MEMORY (learning)
2. … REWARD (hedonic system)
1. … GENES (vulnerability)

With permission from Dr. Kevin McCauley

Pharmacokinetics : Route of Administration

Rewarding Effects of Drugs Depend on How Fast they Get into the Brain



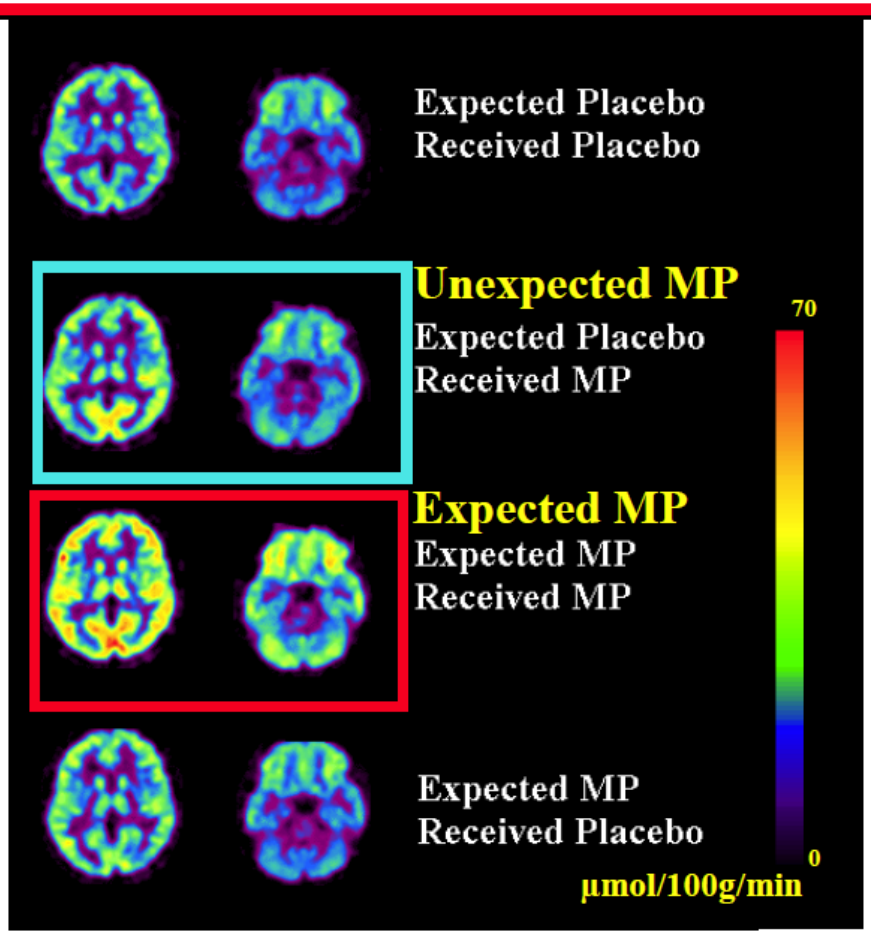


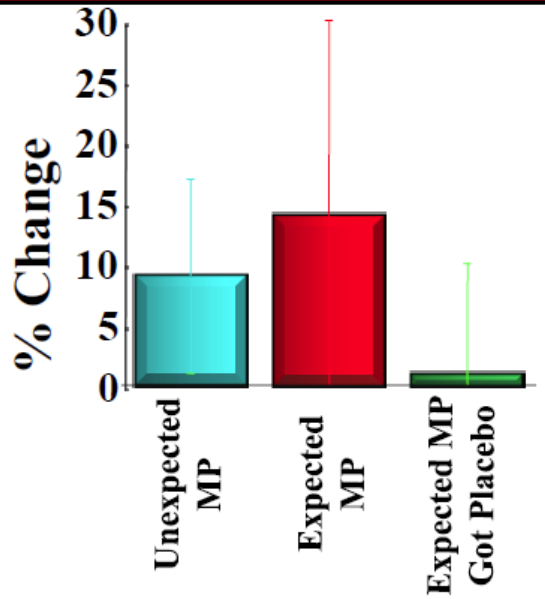
Cocaine (iv) and Ritalin (iv) are rewarding but Ritalin (oral) is not.

The slow brain uptake of oral Ritalin allows treatment without reward

"Want" & Expectation

Glucose Metabolism Was Greatly Increased By the *Expectation* of the Drug

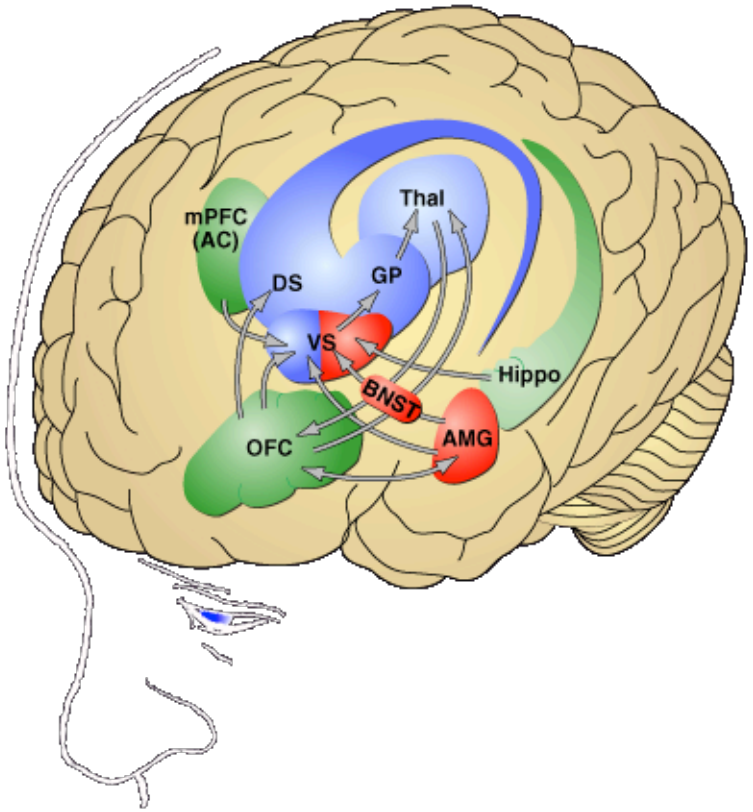


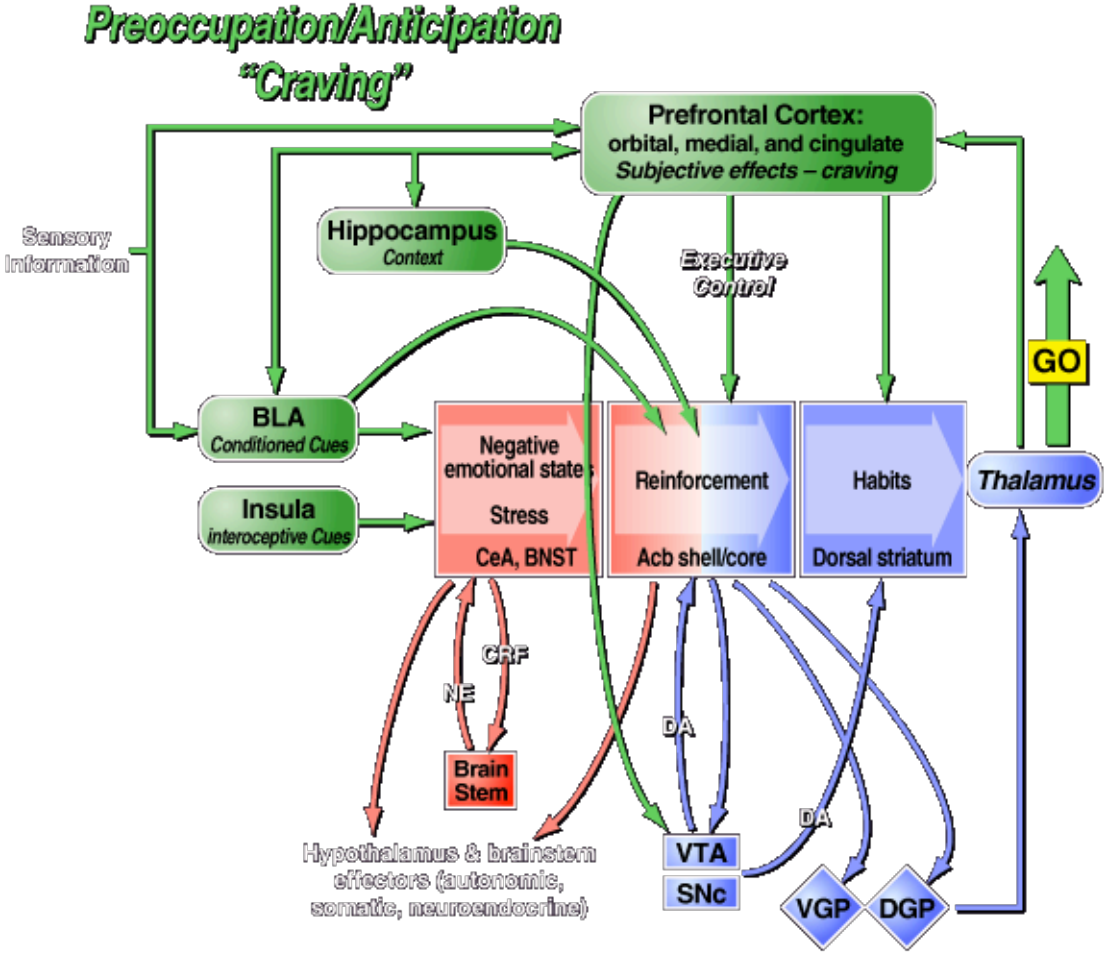


Increases in Metabolism Were About 50% Larger When MP Was Expected Than Unexpected

Source: Volkow, ND et al., Journal of Neuroscience, 23, pp. 11461-11468, December 2003.

Neurobiology of Addiction





Koob, G. F. and Volkow. N. D. Neurocircuitry of Addiction, Neuropsychopharmacology reviews 35 (2010) 217-238

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

Amygdalar-Cortical Circuit

- "GO!"
- Impulsive
- Non-reflective
- Poorly conceived
- Socially inappropriate

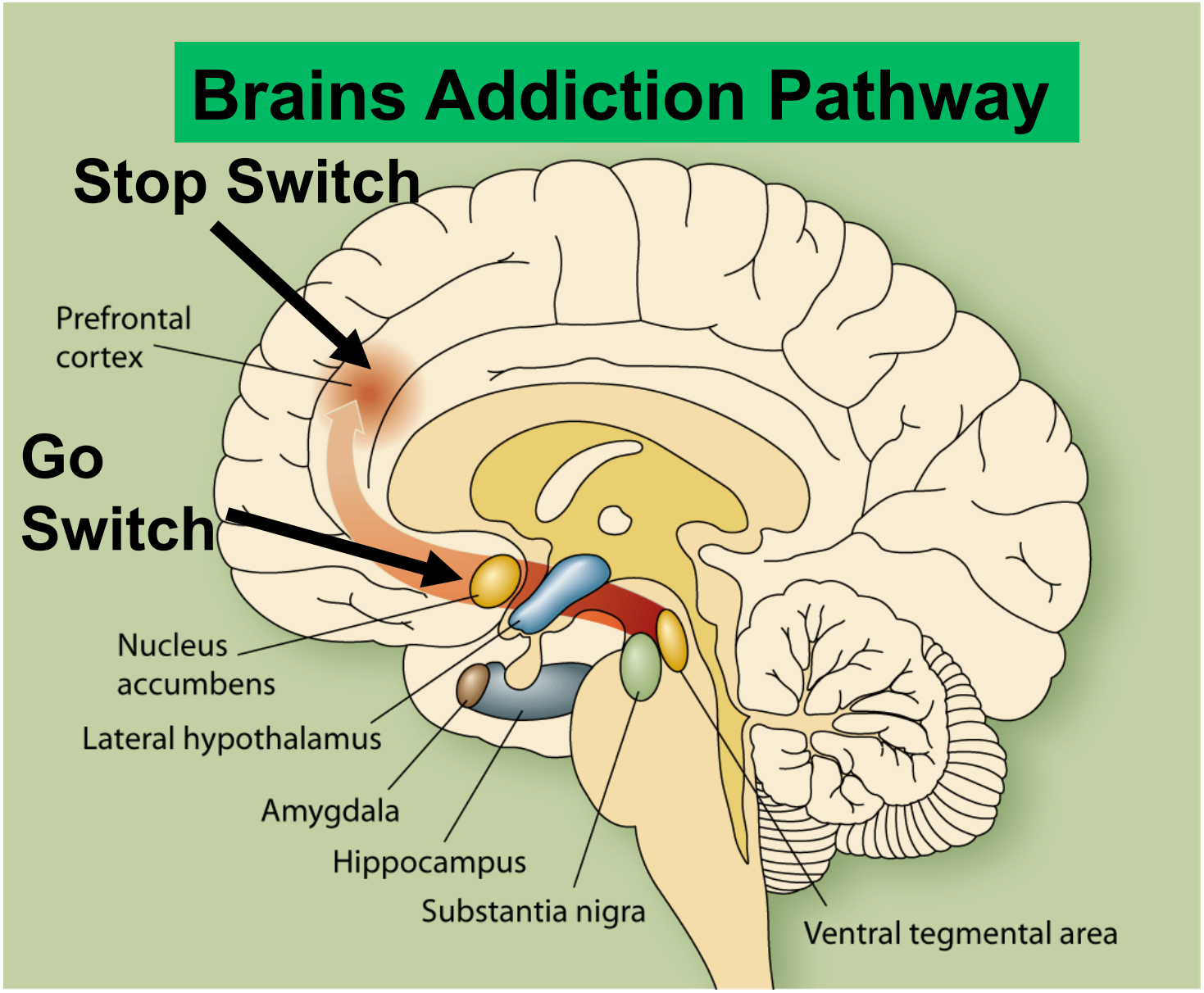
THERE'S TOO MUCH OF THIS

Cortico-Striatal Circuit

- "NOT GO!"
- Organized, Attentive
- Sensitive to consequences
- Well-planned
- Socially appropriate

THERE'S TOO LITTLE OF THIS

Brains Addiction Pathway



Addiction is a Brain Disease

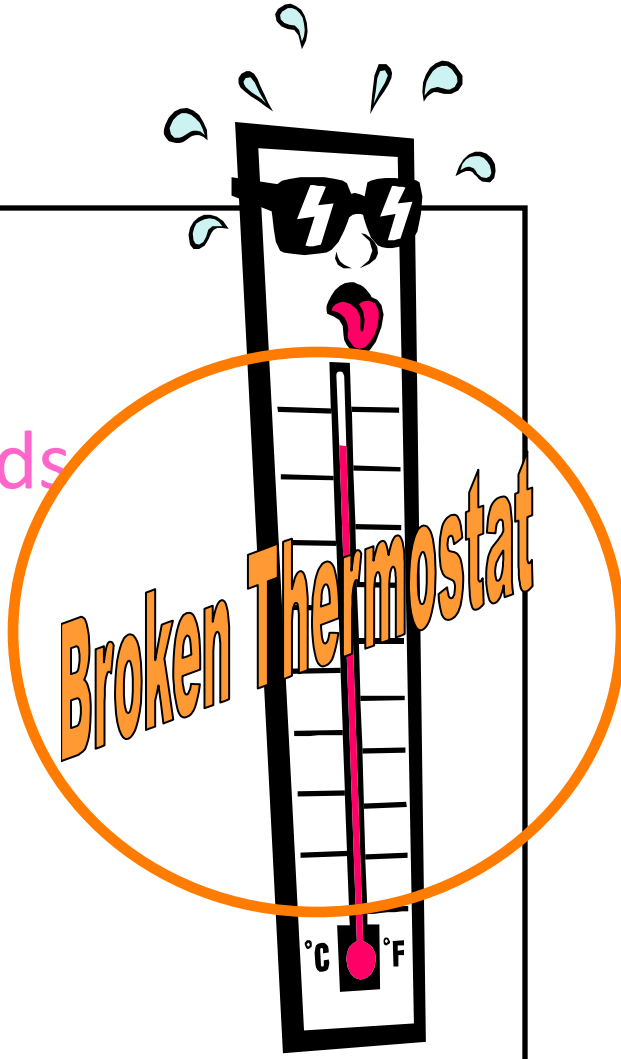
Repeated Drug Exposure...

- Changes "Reward" Set-Point
- Prolonged Dysregulation leads to vulnerability to

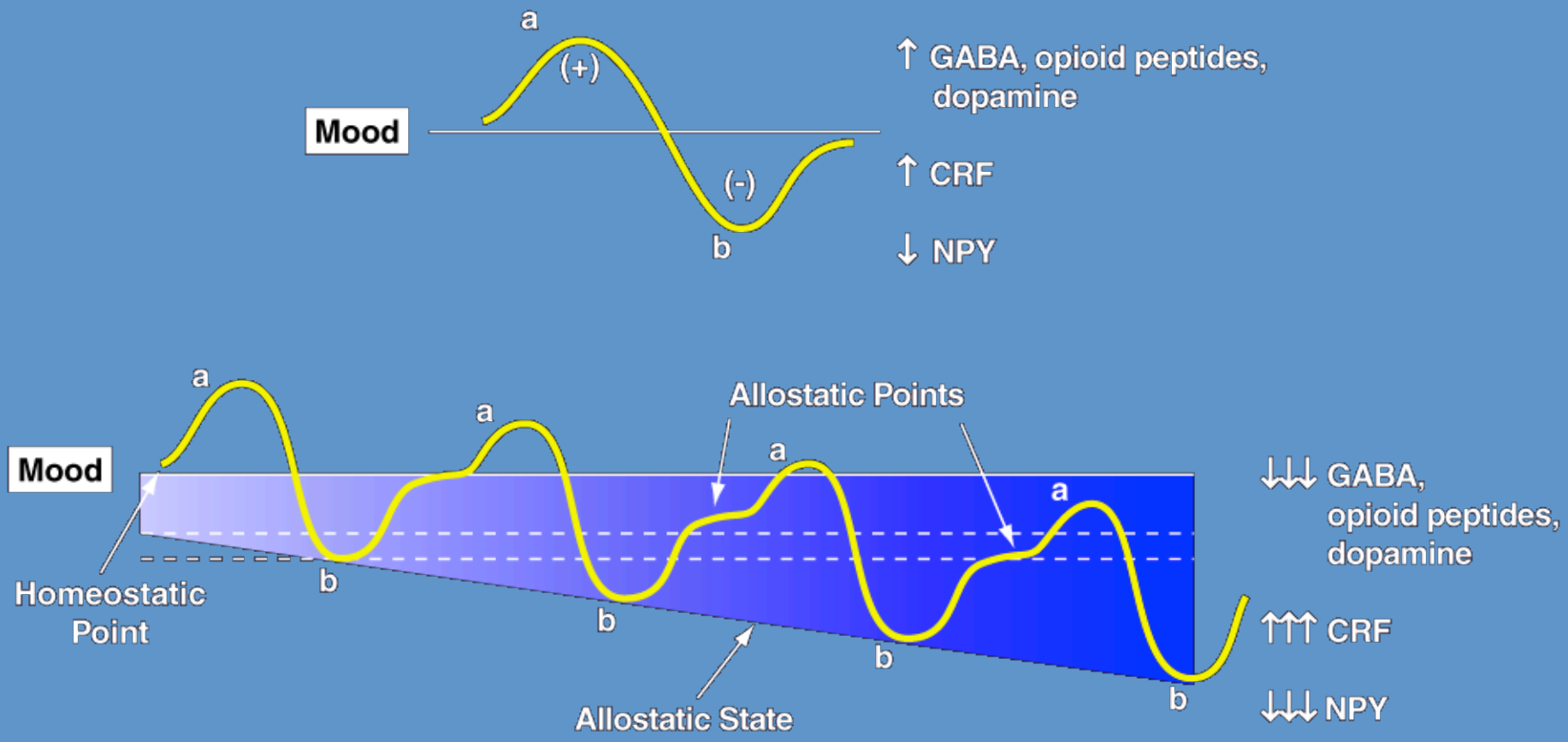
drug use behavior,

long after acute withdrawal.

(Koob, Neuron, 1998)



Allostatic Change in Emotional State associated with Transition to Drug Addiction



Adapted from: Koob GF and Le Moal M, Neuropsychopharmacology, 2001, 24:97-129.

"Both Steering and Brakes Fail"

Four circuits:

1. Reward

Overvaluation of drug/decreased value of natural reinforcers

2. Motivation/Drive

Immediate rewards > delayed gratification

3. Memory

Hypersalience of drug-related cues

4. Control

Impaired self-awareness, bodily awareness, problem recognition

disruptive to social relationships

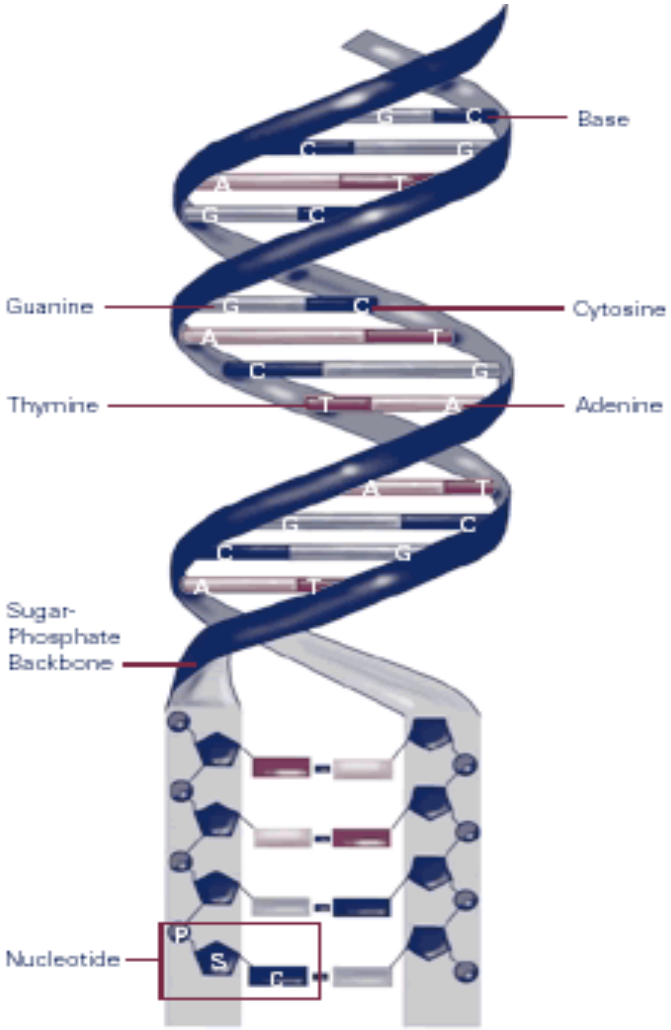
Diminished social competence/cognition

Impaired behavioral inhibition / impulse control

Volkow ND et al. Addiction: pulling at the neural threads of social behaviors. Neuron 69: 599-602 (2011)

I can't Help It; its in my Genes

Single Nucleotide Polymorphism



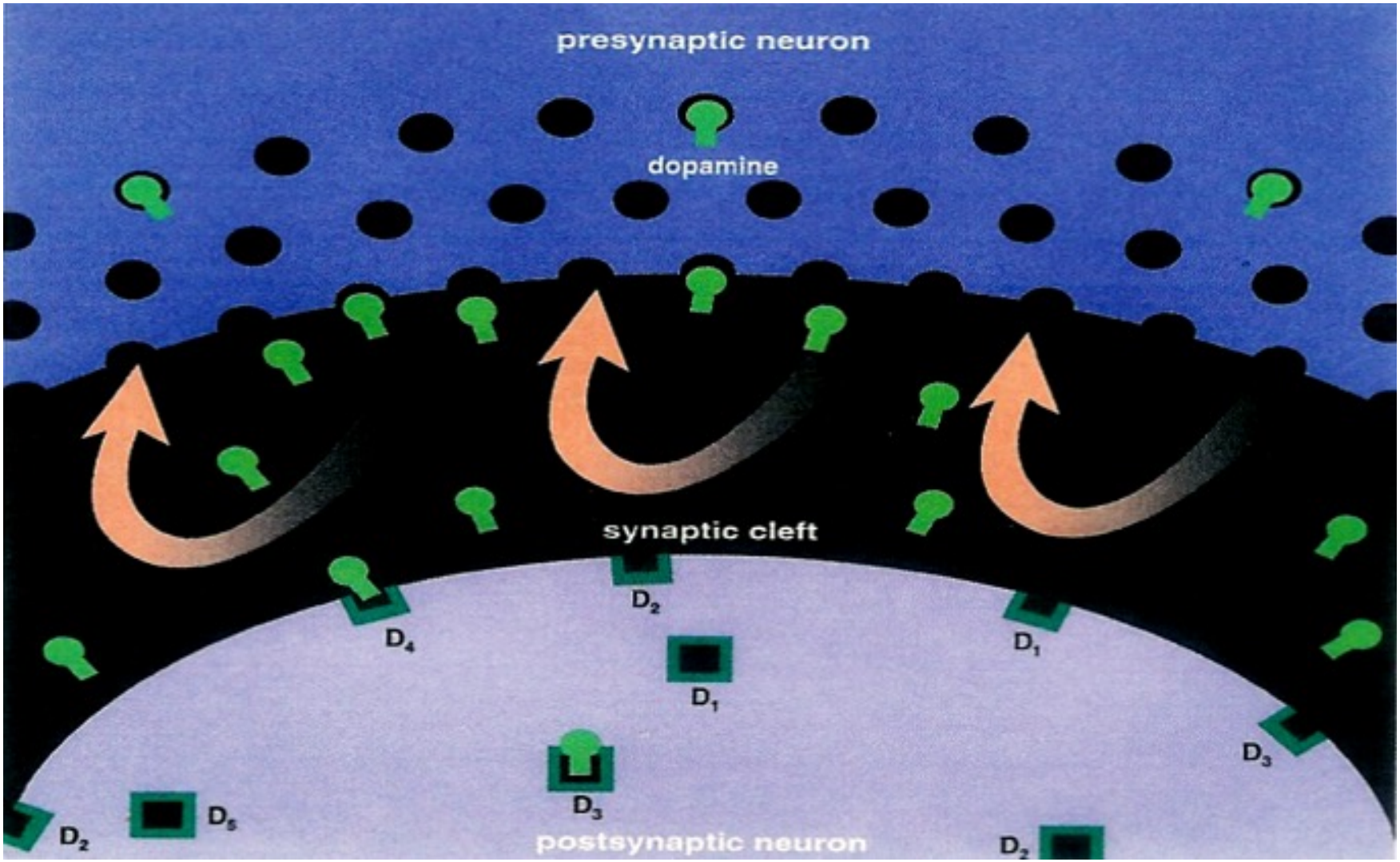
- SNP-single nucleotide polymorphism
- Allelic Frequency:

<1%	low or rare
1–5%	intermediate
>5%	high, frequent

Kreek (Rockefeller University) & Hassin (Columbia P&S), 2004

A_1 Gene = 1/3 Lower D_2 Receptors

Equates to 100,000,000 people living in the USA



A1 = Dopamine Resistance

- **Hypodopaminergic Function**
  - **“I’m a normal person minus two drinks”**
- **Lower number of dopamine receptors**
- **Reduced dopamine release**
- **Impaired dopamine function**
- **Attraction to fix imbalance by using drugs/behaviors that increase dopamine**
- **Commonality among addictions – cross addiction, behavioral addictions and eating disorders**

Inherited Differences in Drug Effect

“Hollow Leg”

Can drink more than others and show less effect

“Hangover Less”

Minimal hangovers compared to amount of drinking / drugging

“Atypical response”

Energizing effect from opioids, slowing from stimulants

“Risk taking”

Use in hazardous situations with deadened “stop signal”

“Early onset addiction”

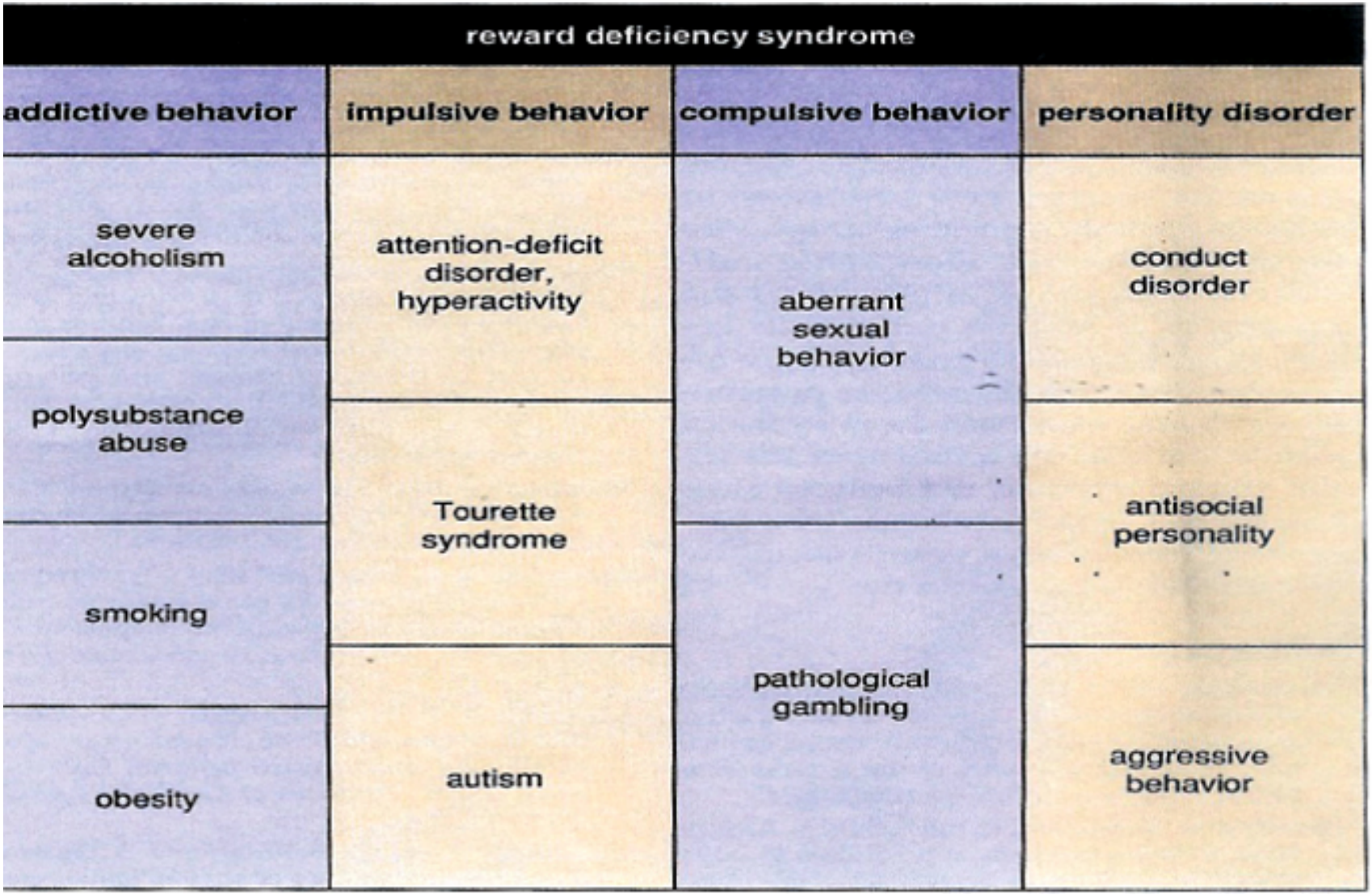
Antisocial behavior, high tolerance, risk tolerance, high “like” index

Hypodopaminergic Function Impairs Reward-Dependent Behaviors

- Inability to cope with stress
- Reduction of energy expenditure
  - Lower BMR (Energy Conservation) and Fatigue
- Increased carbohydrate & fat cravings
- Increased food intake
  - Energy consumption
- Increased blood pressure
- Increased % body fat
- Higher Body Mass Index

- Blunted reward response to pleasurable experiences
- Intensified bingeing behavior
- Addictive behaviors
- Thrill-seeking behaviors
- Impulsive behaviors
- Compulsive behaviors
- Personality disorders
- Poor executive function
- Reduced global cognition

Reward Deficiency Syndrome



GARS Study: Candidate Genes

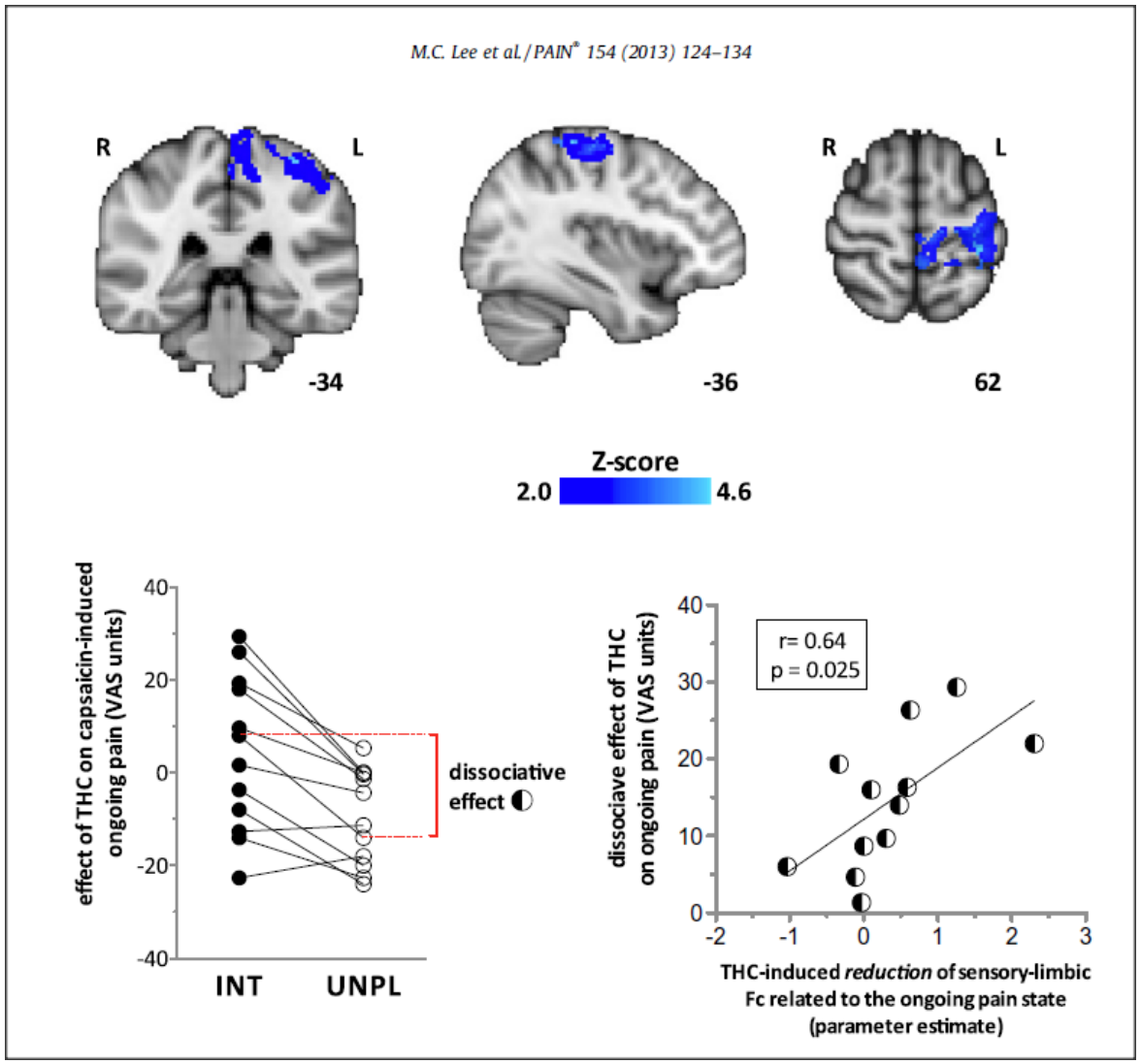
GENE/ALLELE
Caspi MAOA uVNTR
Caspi MAOA uVNTR
DRD4
DAT
5HTTLLR dialletic
COMT
DRD2 Taq1
DRD3
OPRM1
GABRA3
GABRA3

Number of Subjects	Percentage of Low Risk	Percentage of Moderate Risk	Percentage of High Risk	ASI Lifetime Risk Composite
70	14	81	5	

Conditions associated with deficits in impulsive control

- Adolescence
- Alcohol use disorders
- Substance abuse
- ADHD
- Conduct disorder / Anti-social personality disorder
- Depression

THC: Effect on Functional Connectivity

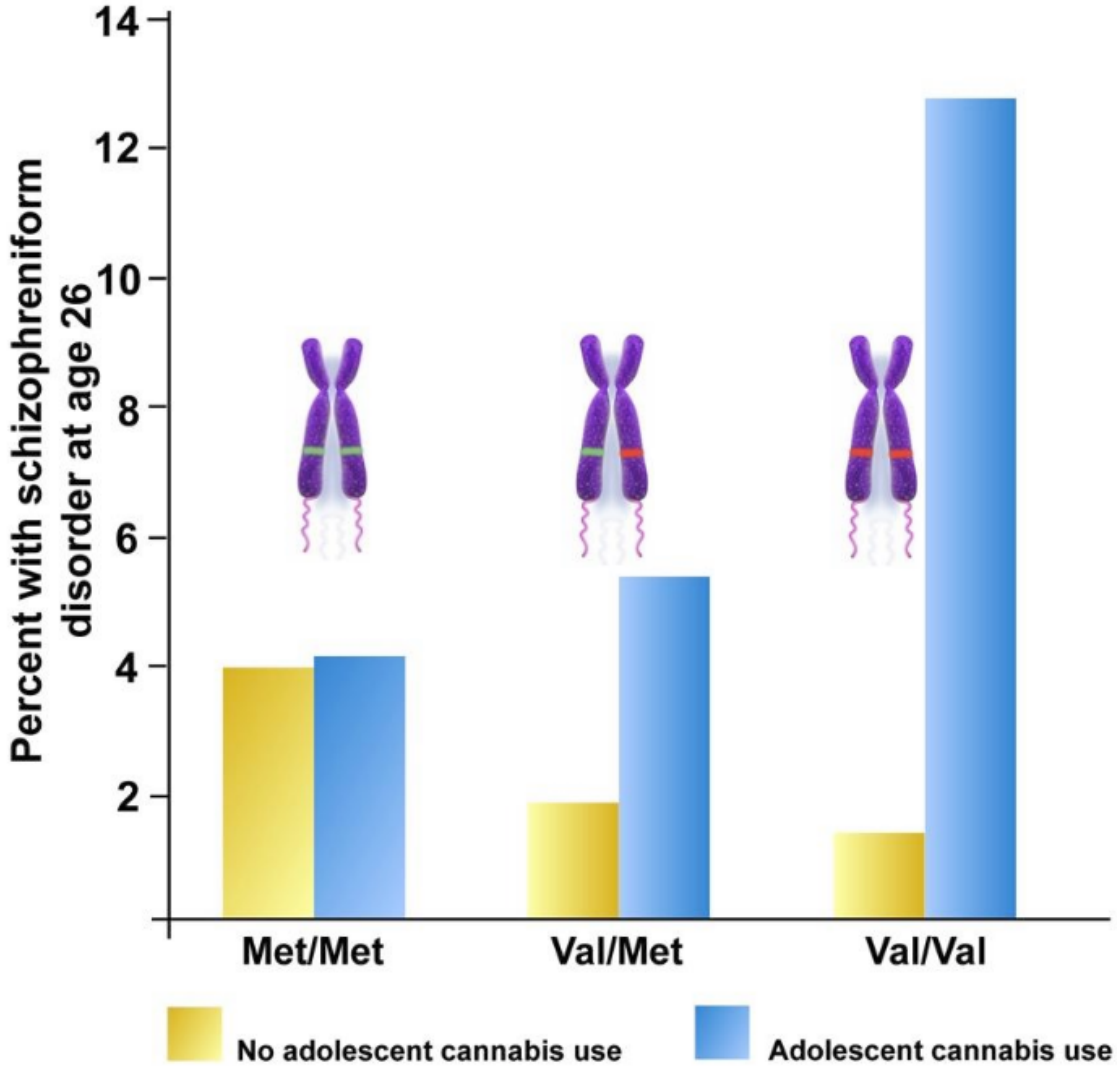


M.C. Lee et al. / PAIN 154 (2013) 124–134

Individual characteristics that predict high vulnerability to drug-seeking behavior

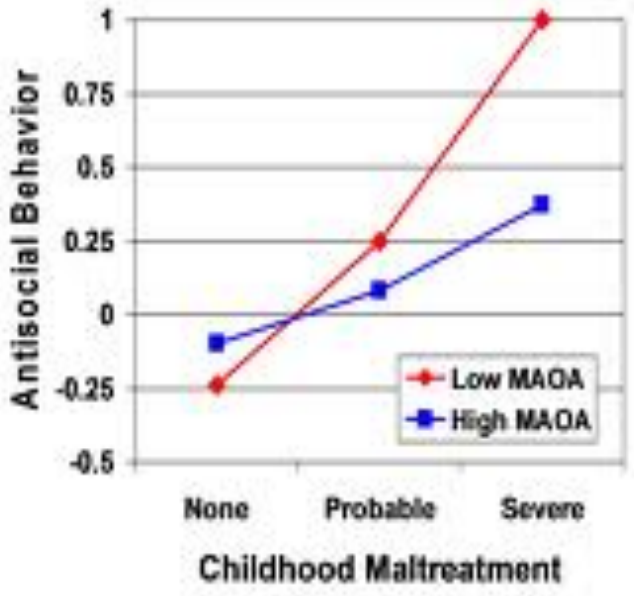
- High stress reactivity
- High novelty-induced locomotor activity
- High novelty-seeking
- High trait impulsivity

Adolescents who Smoke Cannabis have Increased Risk of Schizophreniform Disorder, Depending on the COMT Gene



Caspi et al., 2005

MAOA Gene Expression, Childhood Trauma and Antisocial Behavior



MAOA gene related to improved Neural transmission in the brain

Risk Factors : ASAM Dimension of Care

Dimension 1 – Substance Use

- Early childhood exposure to substances
  - Marijuana teas, cannabis candy, sipping alcohol
  - Fetal exposure of alcohol, cannabis, opioids, cocaine
- Atypical responses to medications
  - Stimulation by opioids, and sedatives
  - sedation by stimulants
- Parental approval of substance use at home
- Parental substance use in home
- Drug using siblings, family members, friends

Risk Factors : ASAM Dimension of Care

Dimension 2 – Medical Problems

- Family history of alcohol and drug problems
- Atypical responses to medications
- ADD/ADHD
- Anxiety and depression
- Eating disorder and body image
- Inherited drug metabolism
- Physical and sexual abuse

Risk Factors : ASAM Dimension of Care

Dimension 3 – Behavioral Disorders

- Novelty seeking
- Poor impulse control
- Low harm avoidance
- Early aggressive behavior
- Conduct disorder
- Parent – child attachment and nurturing
- Childhood abuse and neglect
- Domestic violence, PTSD
- Peer abuse – bullying, internet

Risk Factors : ASAM Dimension of Care

Dimension 4 – Attitude and Stage of Change

- Perception of risk
- Youth perception of parental approval of substances
- Availability within home and friends
- Belief that drug use = experimentation
  - Snapshot vs. movie
- Increased knowledge/training from internet
- Advertising by alcohol + cigarette legal dealers
- Perception of invulnerability and peer norms

Risk Factors : ASAM Dimension of Care

Dimension 5 – Continued use and relapse potential

- Perception of parental monitoring
- Inconsistent consequences for behavioral deviations of roles and responsibilities
- High sensation seeking
- Novelty seeking
- Poor prediction of long term risks/consequences
- Changes to decision making when using
- Withdrawal avoidance anti-reward
  - Anxiety as symptom of marijuana withdrawal
  - Opioid use to prevent sickness – maintenance use

Risk Factors : ASAM Dimension of Care

Dimension 6 – Recovery and living environment

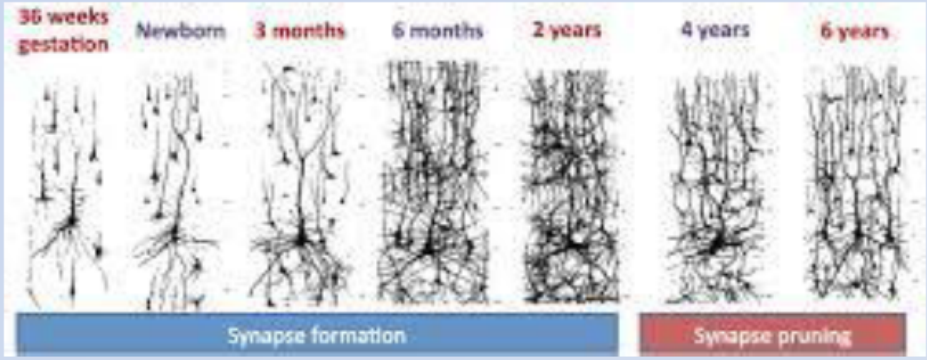
- Use of substances at home and peers
- Poor parental supervision, monitoring, discipline
- Disrupted families and parental conflict
- Poverty and gang participation
- Academic difficulties and dislike of school
- Social norms – advertising and availability
- Lack of sober models and supports for recovery
- Active drug using peer groups
- Decrease in non-drug related activities

Adverse Childhood Experiences (ACE) Study

Almost 2/3 reported at least one ACE; more than 20% reported 3 or more ACEs!

Source: Centers for Disease Control and Prevention

Stress responses:



- Brain stress circuits
  - Plasticity max. @ fetal/early childhood periods
- Hormones and neurochemical systems
  - Cortisol –
    - Short Term -mobilizes energy stores, enhances certain types of memory, activates immune responses
    - Longer term – suppression of immune function, learning and memory; health issues – metabolic syndrome (pre-diabetes), bone mineral loss, muscle atrophy

Cortisol Studies

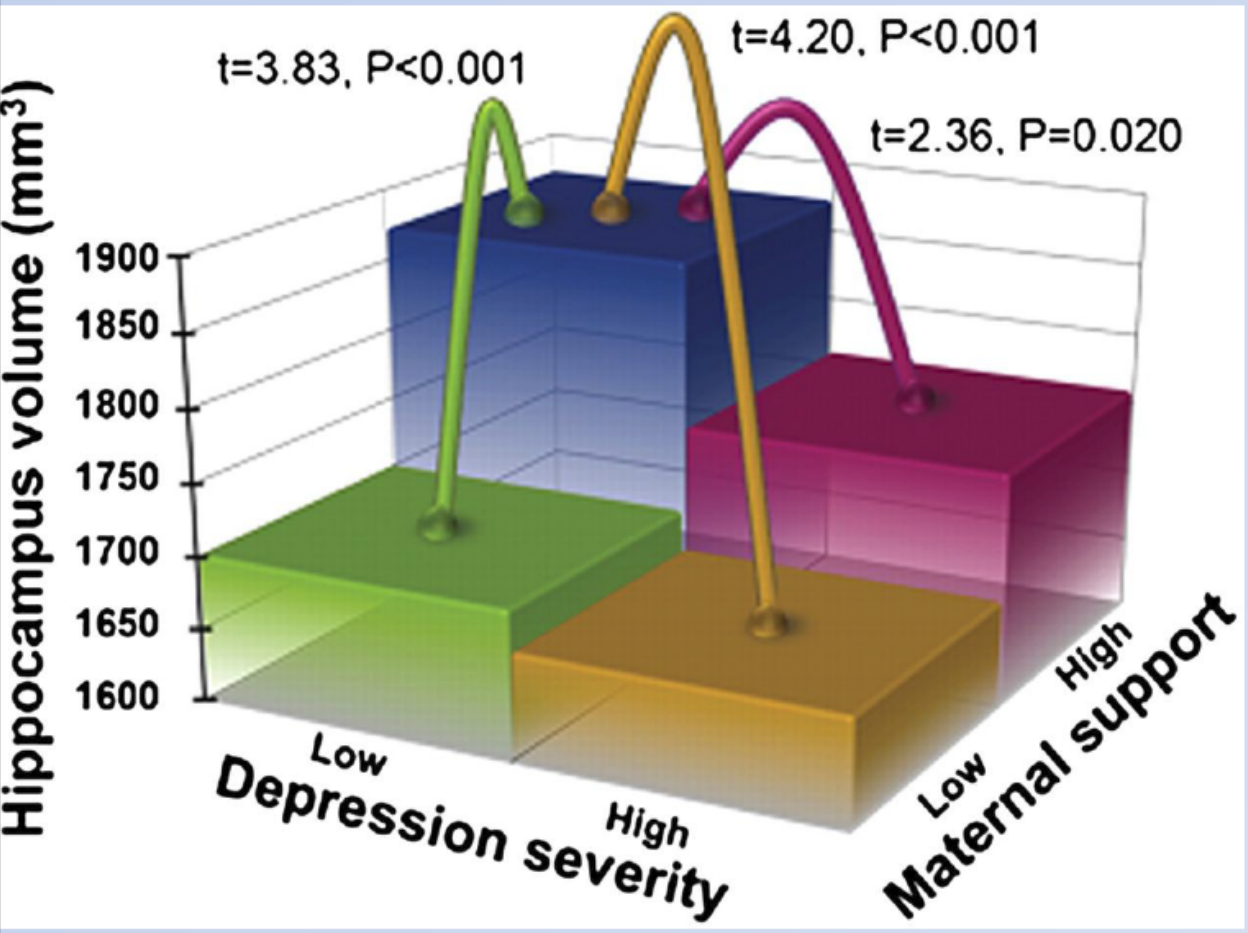
- When faced with a scary situation, the child will show fright and seek proximity to his or her parent or other supportive caregiver, but there will be no rise in cortisol.
- Toddlers exposed to clowns, all showed the same frightened behavior, but
  - Children in secure attachment relationships did not register a rise in cortisol,
  - Children in insecure attachment relationships showed elevated cortisol

The difference between the two groups was the children's expectation of supportiveness from the parents in the room with them.

Megan Gunnar, PhD
University of Minnesota

Regents Professor, Distinguished McKnight University Professor of Child Development and Director of the Institute of Child Development, University of Minnesota. Dr. Gunnar's main interest area is stress and coping in infants and young children. Her work documents the importance of sensitive and responsive care by adults in the modulation and buffering of stress physiology in the developing child. She is director of the NIMH Center on Early Experience, Stress and Neurobehavioral Development and is a member of the National Scientific Council on the Developing Child and of the Canadian Institute for Advanced Research's program on Experience-based Brain and Biological Development.

Hippocampus Volume by Preschool Depression Severity and Maternal Support



Hippocampus region is key to memory and stress regulation.

- Children of nurturing mothers had hippocampal volumes 10% larger than children whose mothers were not so nurturing

- Note the effect of maternal support even in 'low severity depression'!!!

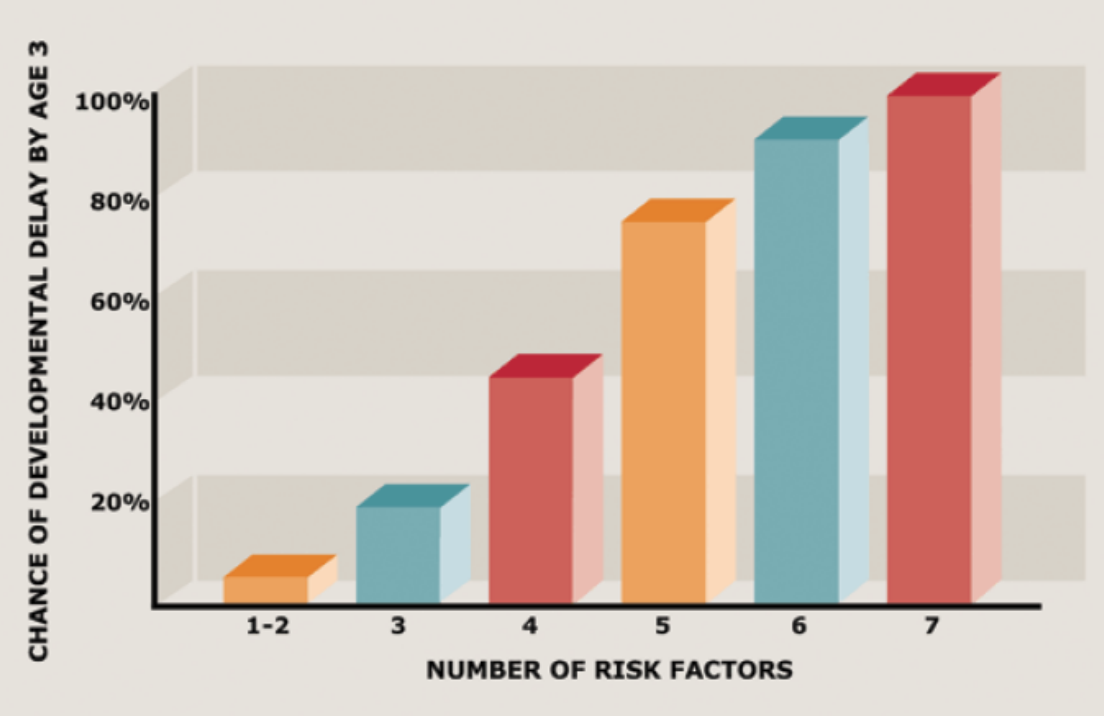
Luby J L et al. Maternal support in early childhood predicts larger hippocampal volumes at school age. Proceedings of the National Academy of Science. 2012;109:2854-2859

92 children in longitudinal study of preschool depression

PNAS

Early Brain and Child Development
BUILDING BRAINS, FORGING FUTURES

Adverse Childhood Experiences and Developmental Delay



- Physical, sexual or emotional abuse
- Physical or emotional neglect
- Household mental illness
- Living in a household with substance abuse
- Having a parent/caregiver divorce or separate
- Exposure to domestic violence
- Living in a household where a member was or has been incarcerated

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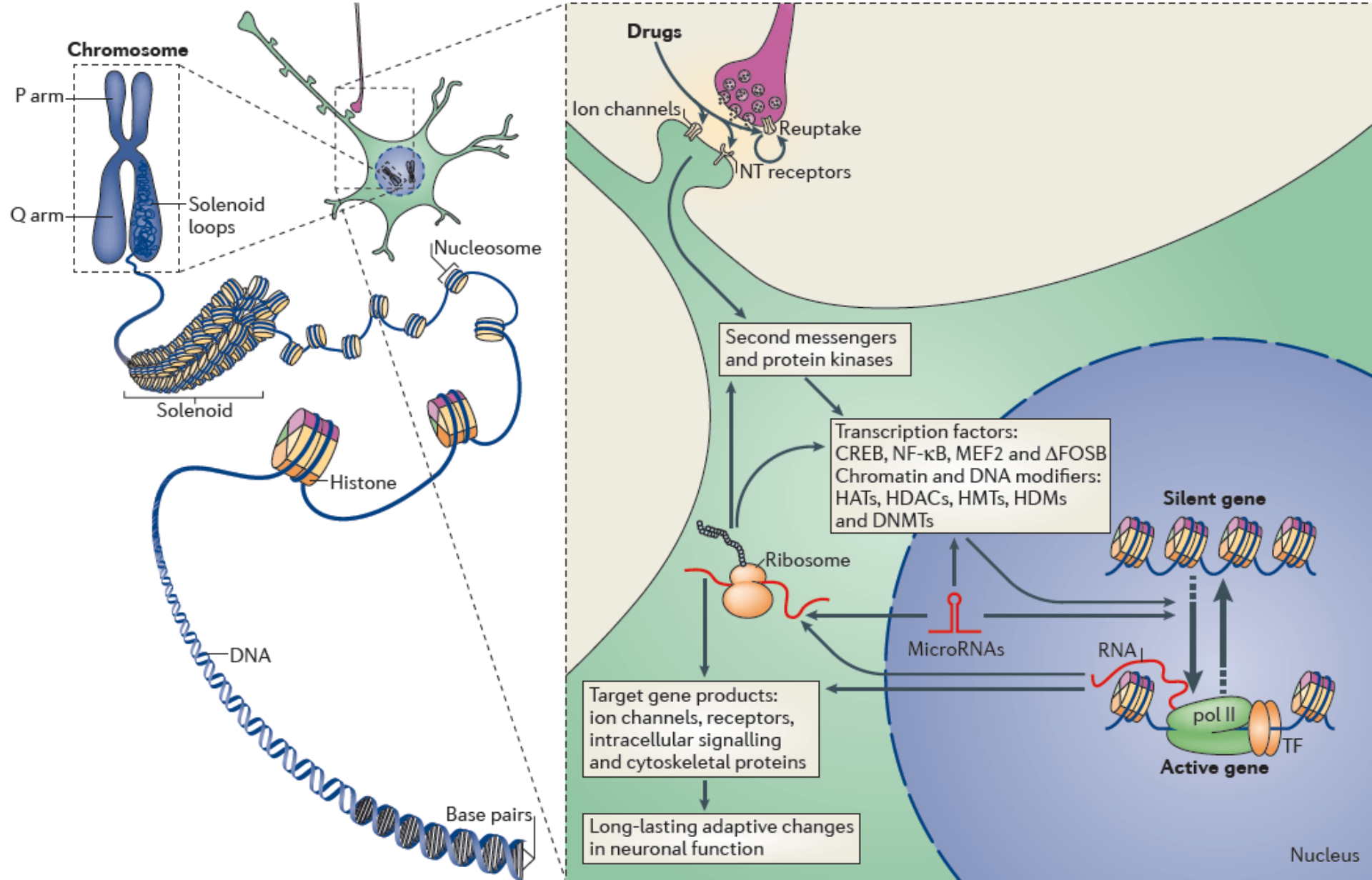
Epigenetics

- 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

Epigenetic effects of drugs



Future of Neurobiology : Biology

- Genotype & Phenotype Analysis

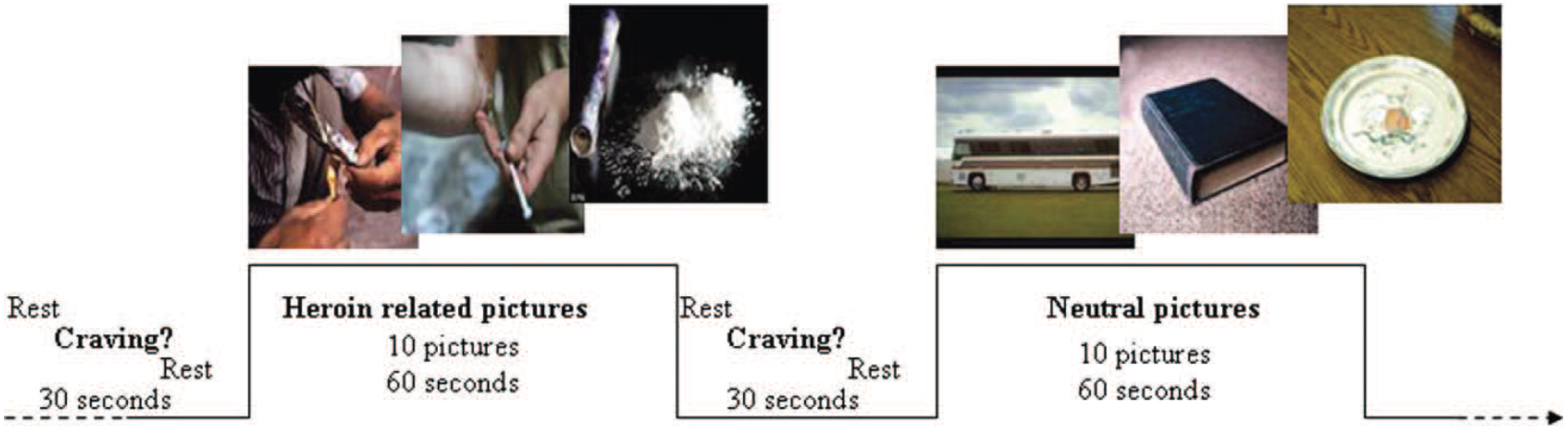
  Diagnostic tests

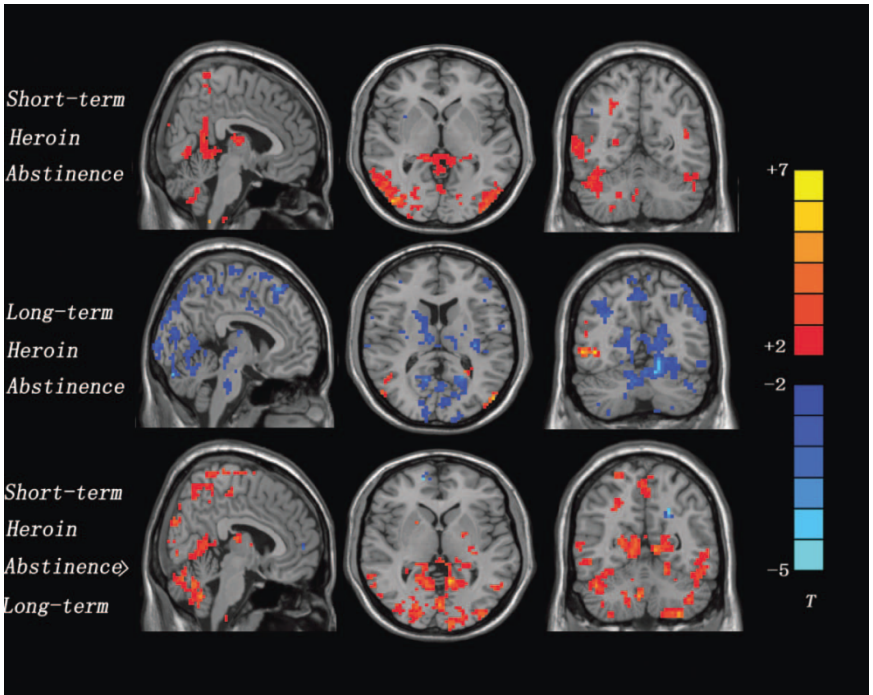
  - Genetic testing - GARS
  - Imaging
  - EEG – Electroencephalographic
  - Biofeedback
  - Psychological and Neuro-psychological testing - CPT
  - Addiction severity measurement
  - Urine Drug Testing and Report Analysis

Future of Neurobiology : Diagnostic Testing

- Functional tests
  - Audio analysis – emotion detection
  - EEG mapping
  - Functional Imaging – fMRI, Spect, PET scans
  - Metabolic analysis
    - Proteinomic measurement of tolerance
    - P450 analysis of metabolism
    - Pharmacokinetic - metabolism
  - Cue Reactivity Assessment and Monitoring
    - fMRI – measure brain functioning
    - Transcranial Magnetic treatments

fMRI response: Stage of Recovery





Occipital-temporal-posterior cingulate
visual spacial and information processing

Anterior cingulate
Emotional processing

Hippocampus and thalamus
Learning, memory and emotional

Dorsal striatum
Drug seeking and wanting

Insula
Emotional wanting

ORIGINAL ARTICLE

OPEN ACCESS

An initial fMRI study on neural correlates of prayer in members of Alcoholics Anonymous

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ABSTRACT

Background: Many individuals with alcohol-use disorders who had experienced alcohol craving before joining Alcoholics Anonymous (AA) report little or no craving after becoming long-term members. Their use of AA prayers may contribute to this. Neural mechanisms underlying this process have not been delineated. *Objective*: To define experiential and neural correlates of diminished alcohol craving following AA prayers among members with long-term abstinence. *Methods*: Twenty AA members with long-term abstinence participated. Self-report measures and functional magnetic resonance imaging of differential neural response to alcohol-craving-inducing images were obtained in three conditions: after reading of AA prayers, after reading irrelevant news, and with passive viewing. Random-effects robust regressions were computed for the main effect (prayer > passive + news) and for estimating the correlations between the main effect and the self-report measures. *Results*: Compared to the other two conditions, the prayer condition was characterized by: less self-reported craving; increased activation in left-anterior middle frontal gyrus, left superior parietal lobule, bilateral precuneus, and bilateral posterior middle temporal gyrus. Craving following prayer was inversely correlated with activation in brain areas associated with self-referential processing and the default mode network, and with characteristics reflecting AA program involvement. *Conclusion*: AA members' prayer was associated with a relative reduction in self-reported craving and with concomitant engagement of neural mechanisms that reflect control of attention and emotion. These findings suggest neural processes underlying the apparent effectiveness of AA prayer.

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KEYWORDS
Alcoholics Anonymous; craving; fMRI; neural correlates; prayer

Effect of AA Prayers on Cravings : fMRI Differences

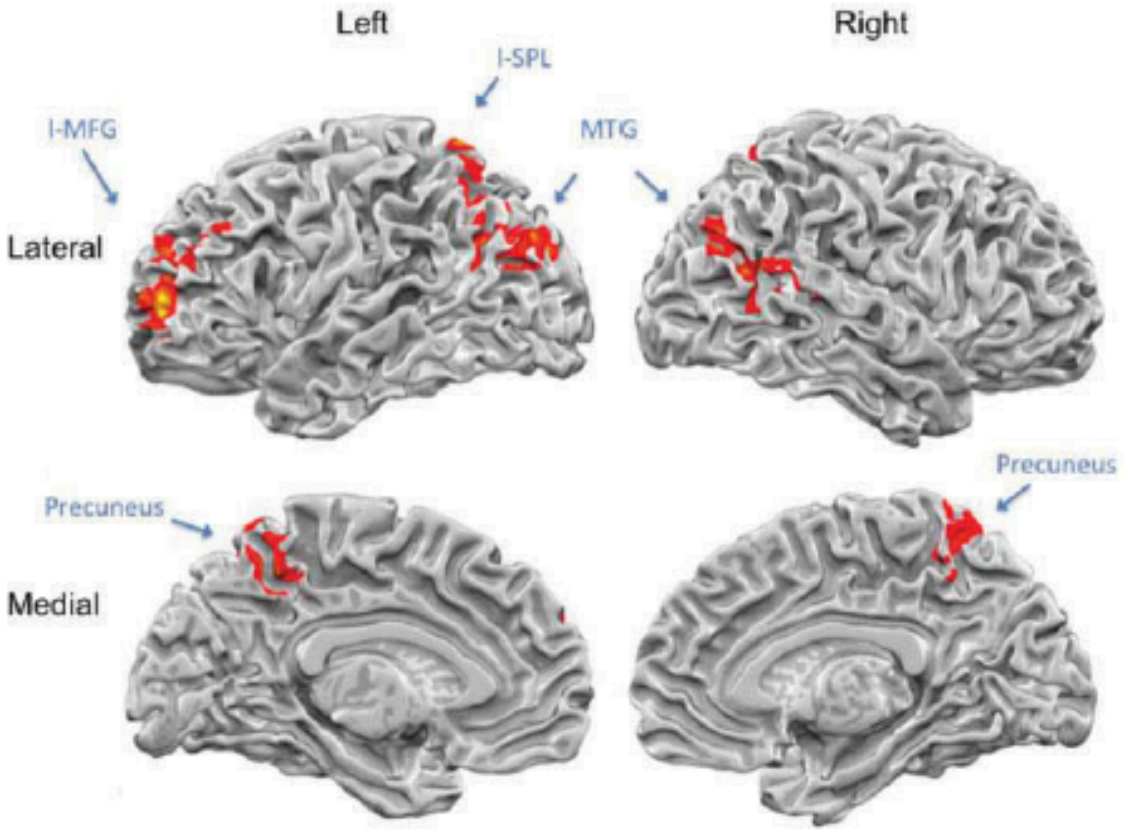


Figure 1. Brain areas activated for main contrast (prayer > passive + news). The left-anterior middle frontal gyrus (l-MFG; BA 10), left-superior parietal lobule (l-SPL; BA 7), bilateral precuneus (BA 7), and bilateral posterior middle temporal gyrus (MTG, BA 39). Two-tail *t*-test (df 17) = 2.56, FWE alphasim $p < 0.05$ corrected, $k = 104$. The brain is displayed in neurological convention (right = right).

From series of papers on Neurobiology of Self Help : Mark Gallanter, MD

fMRI Activation by Brain Region : Reactivity to AA Prayers

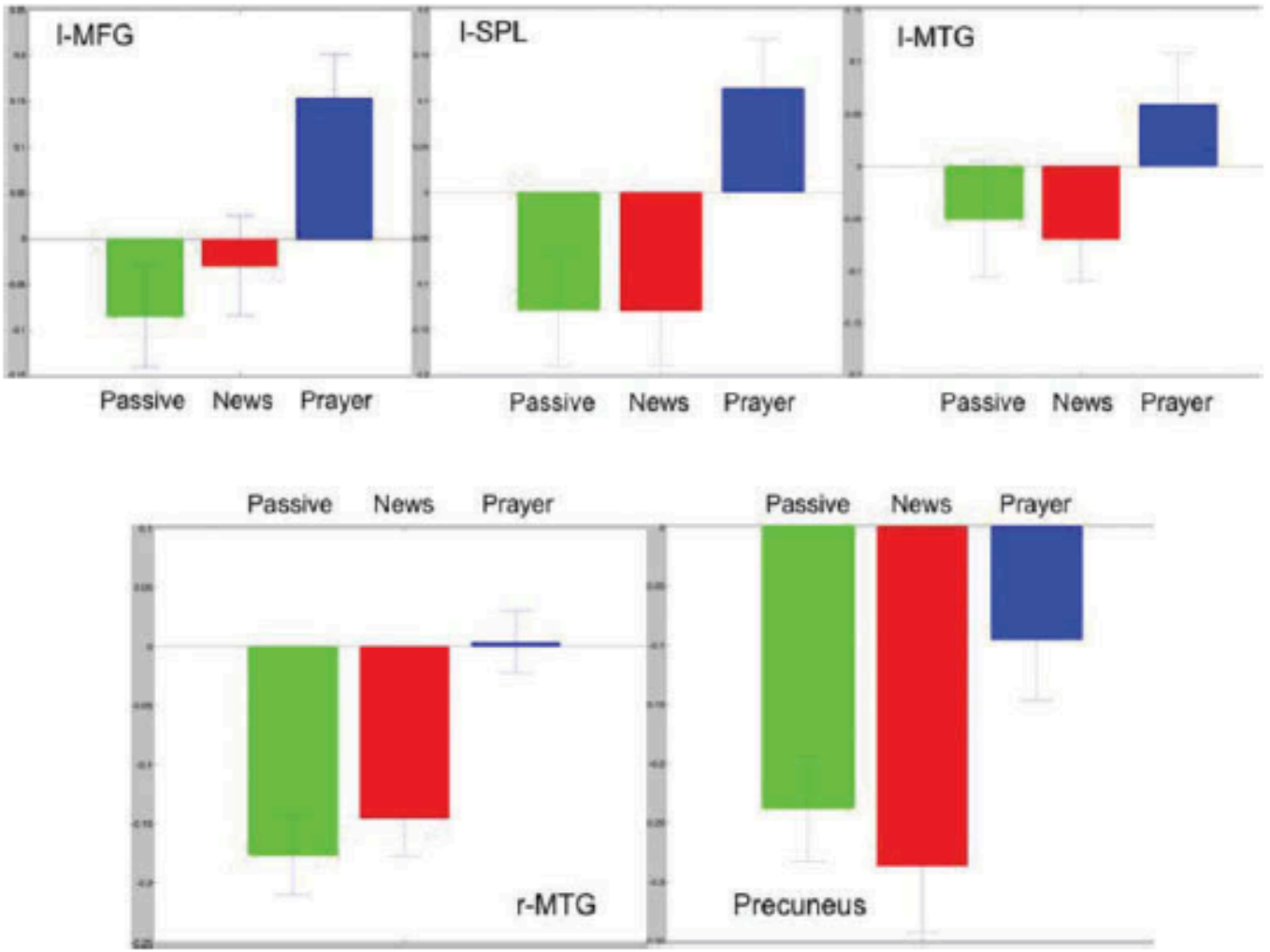


Figure 2. General linear model (GLM) beta plots for the main contrast regions of interest (ROIs). See Table 2 for details. Green – Passive; Red – News; Blue – Prayer. *x*-axis: conditions, *y*-axis: percent BOLD signal change. The left-anterior middle frontal gyrus (l-MFG; BA 10), left-superior parietal lobule (l-SPL; BA 7), left- and right-posterior middle temporal gyrus (l/r-MTG, BA 39), and bilateral precuneus (BA 7).

Computerized Audio Analysis of Emotions

System says: ***"How are you feeling?"***
Participant says how they feel

Capture emotion express

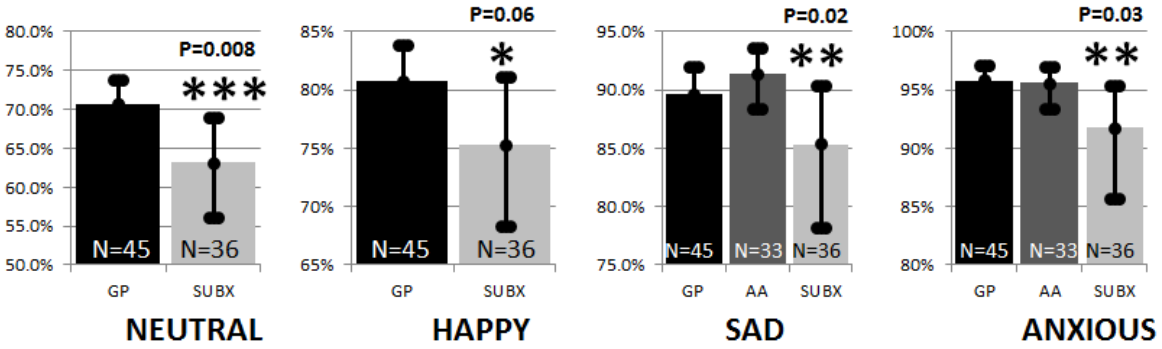
System says: ***"Please classify your mood. Are you happy, angry, sad, nervous, or okay?"***
Participant says one of { okay, happy, sad, angry, anxious}

Capture emotion identify

System says: ***"Guess the emotion of the following speaker"***
System plays a recording from another speaker.
System says: ***"Was the speaker happy, angry, sad, nervous, or okay?"***
Participant says one of {okay, happy, sad, angry, anxious}

Capture emotion relate

Opioid-SUBX patients and self-awareness of emotions compared to GP + AA members.

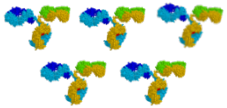


Immunotherapies for Addiction Treatment

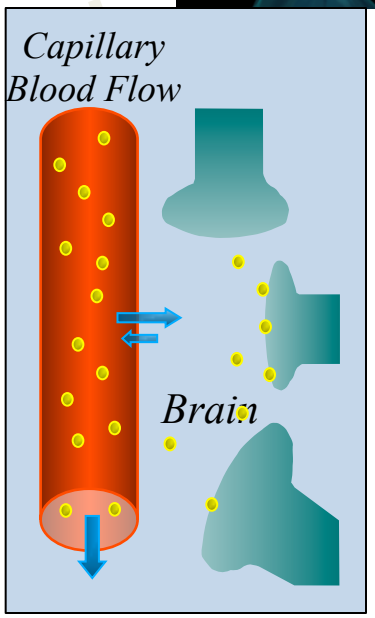
Vaccines : Antibodies Reduce Brain concentrations of Drug

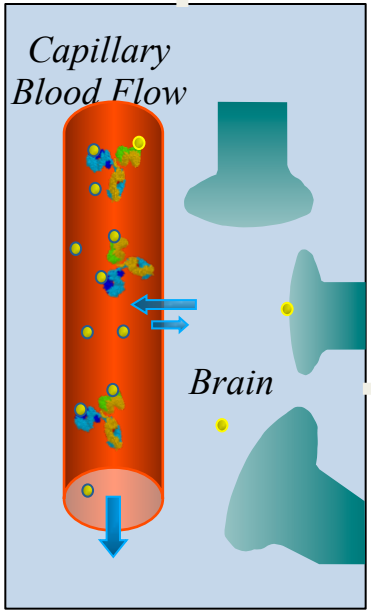
VACCINE

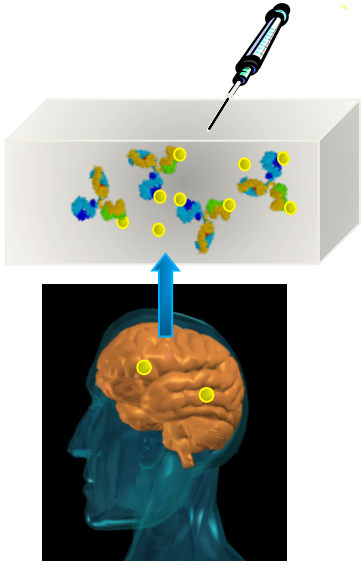
Antibodies



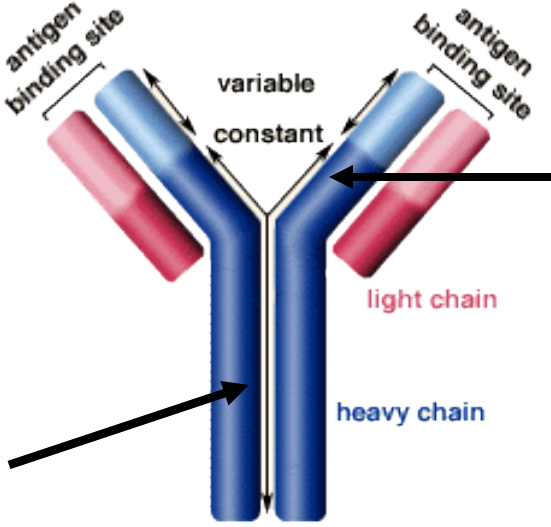
Targeting the drugs, not the receptors







The Antibody: how it works



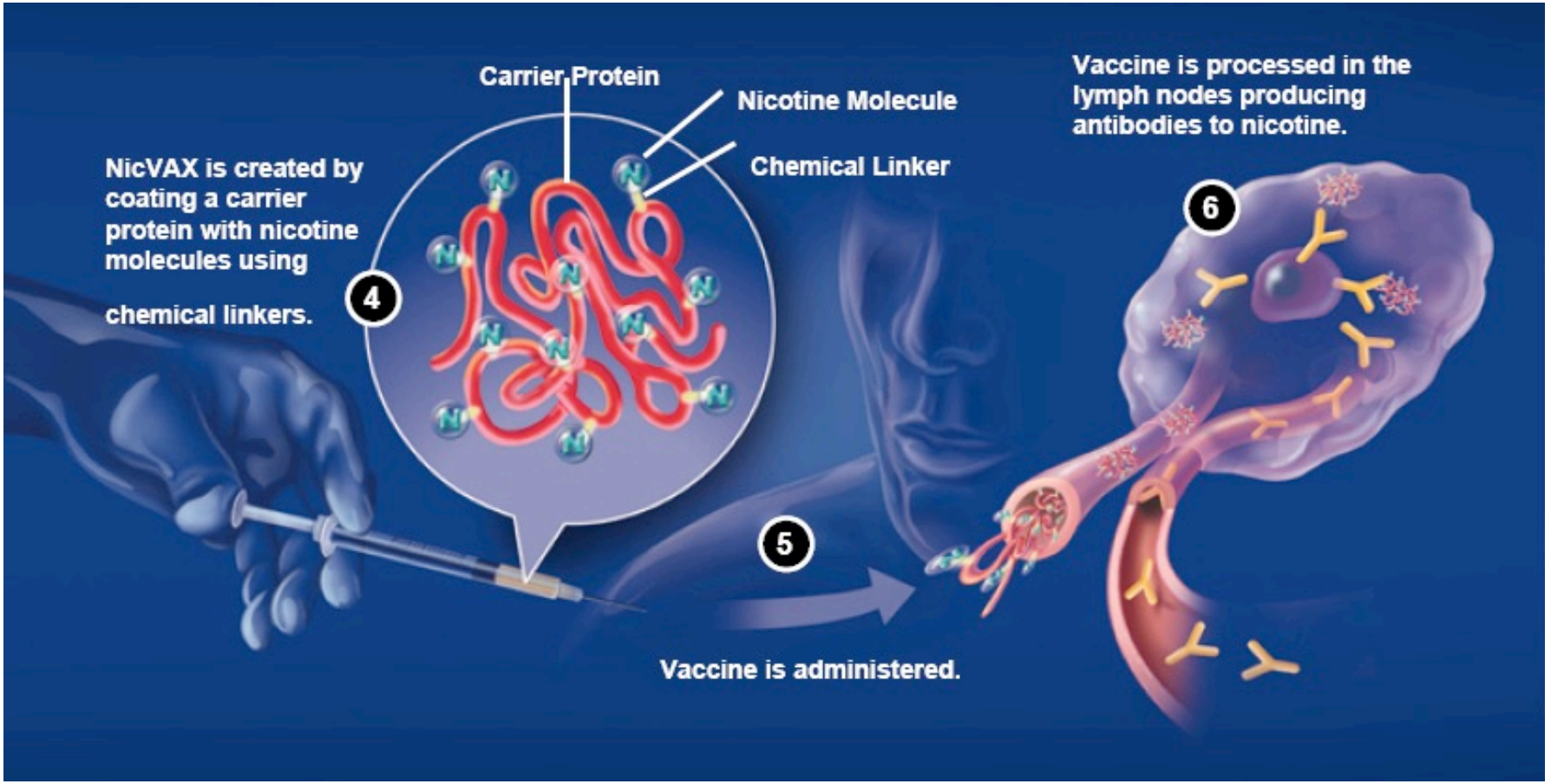
Cocaine binds in variable region

Hinge

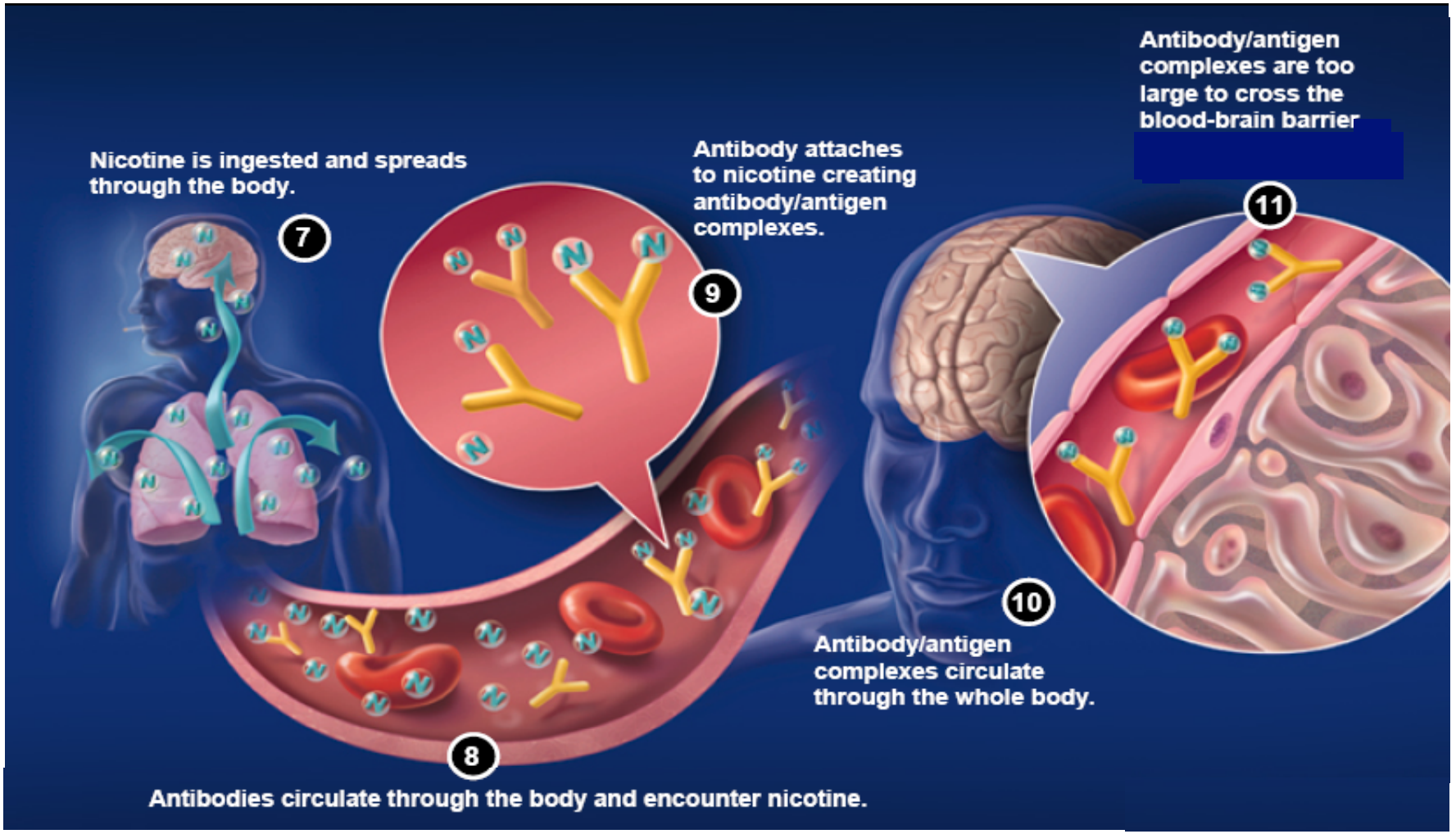
Cocaine Metabolized (cholinesterases)

Antibody free for subsequent binding

NicVAX – the vaccine



Prevent Binding to Brain Receptors



Prevention & Early Identification

- Vaccine development
- Personal risk assessment – portable breathalyzers
- DUI – detection of drugs
- Monitoring abstinence during treatment
- Prevention of drug driving
- Medicalization and monitoring –shift from criminal justice to health care system

Diagnostic & Therapeutic Uses

- Identification of genetic variability
- Assess functioning of neuronal circuits
- Measure severity and reactivity of triggers
- Provide feedback to patient of status
- Biological basis of diagnosis and risk stratification – SBIRT
- Measure effectiveness of drug treatment

Diagnostic & Therapeutic Uses

- Assess readiness to enter high risk situations
- Prevent induction of tolerance and slip to become relapse
- Treat cravings by magnetic
- Predict metabolic alterations of choice and dose of drug prior to prescribing
- Increase use of non-drug nutrigenics

Diagnostic & Therapeutic Uses

- Measure emotional blunting
- Measure executive functioning
- Increase effectiveness of decisions – impulsive reward vs. long term accomplishments
- Demonstrate effectiveness of non-drug interventions – diet, exercise, music, G.O.D.
- Increase monitoring of abstinence