Addiction: Science Drives New & Novel Treatments

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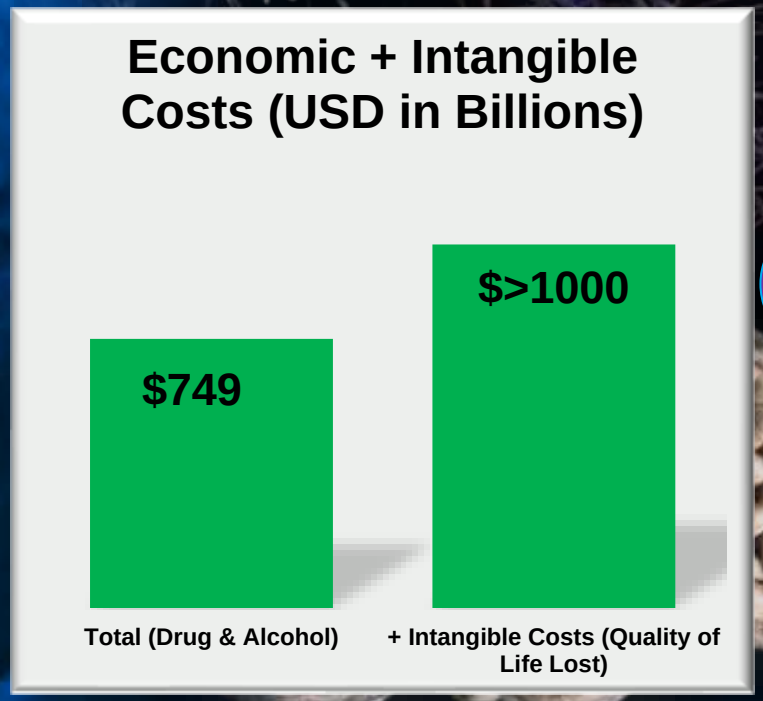
ADDICTION AND AMERICA



OVERDOSE DEATHS

STIGMA

OPIOIDS

STIMULANTS

HEALTHCARE SYSTEM UNDER SEIGE

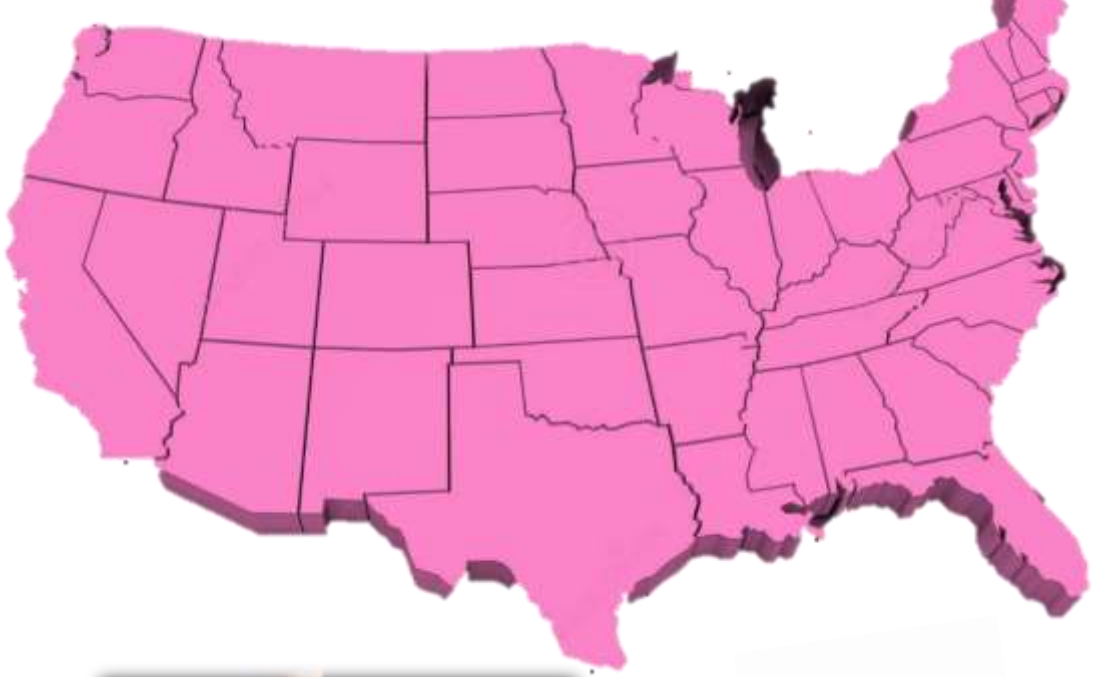
CANNABIS

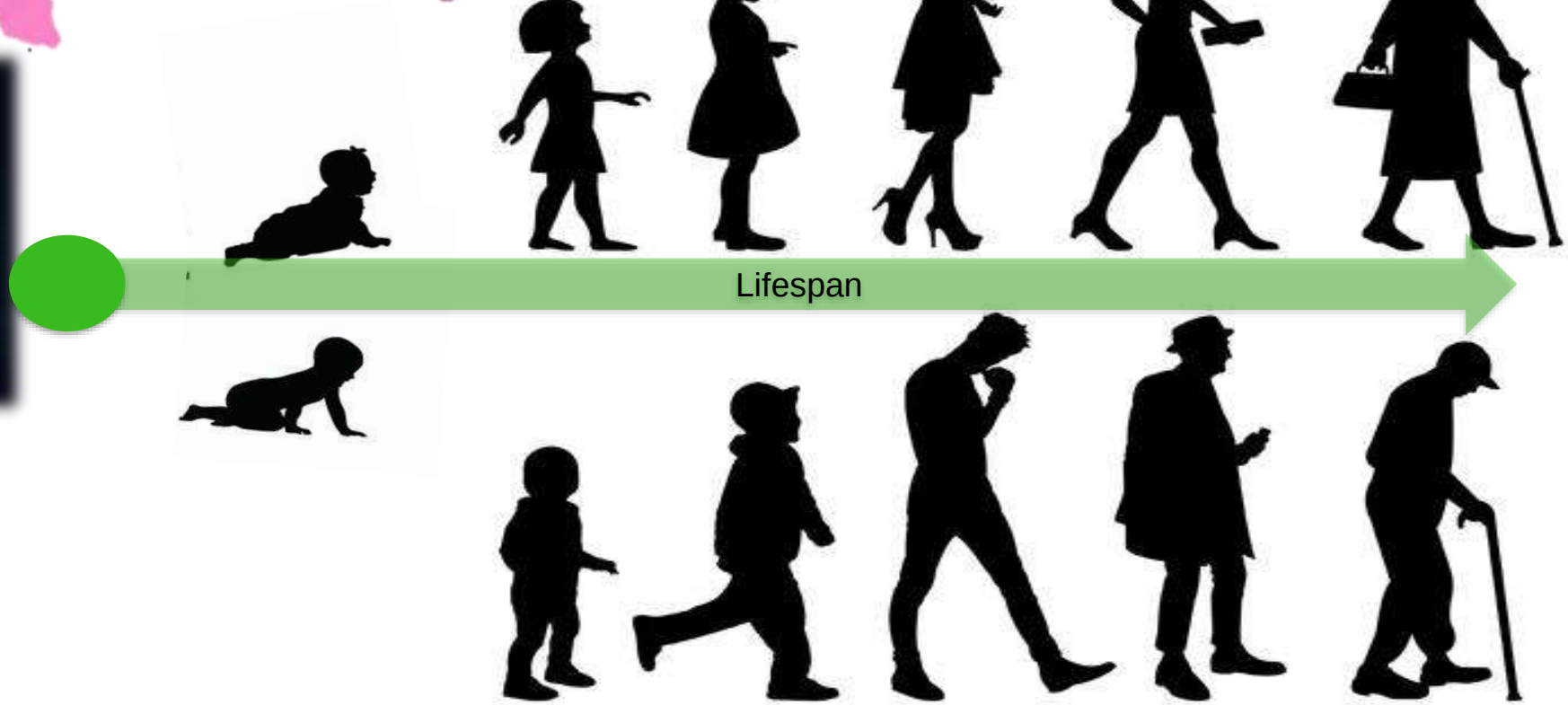
synthetics

ECONOMIC BURDEN

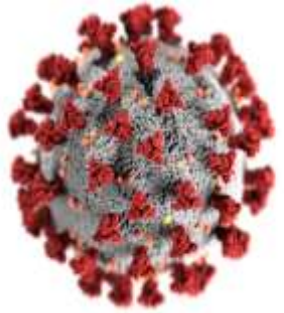
tobacco

Alcohol

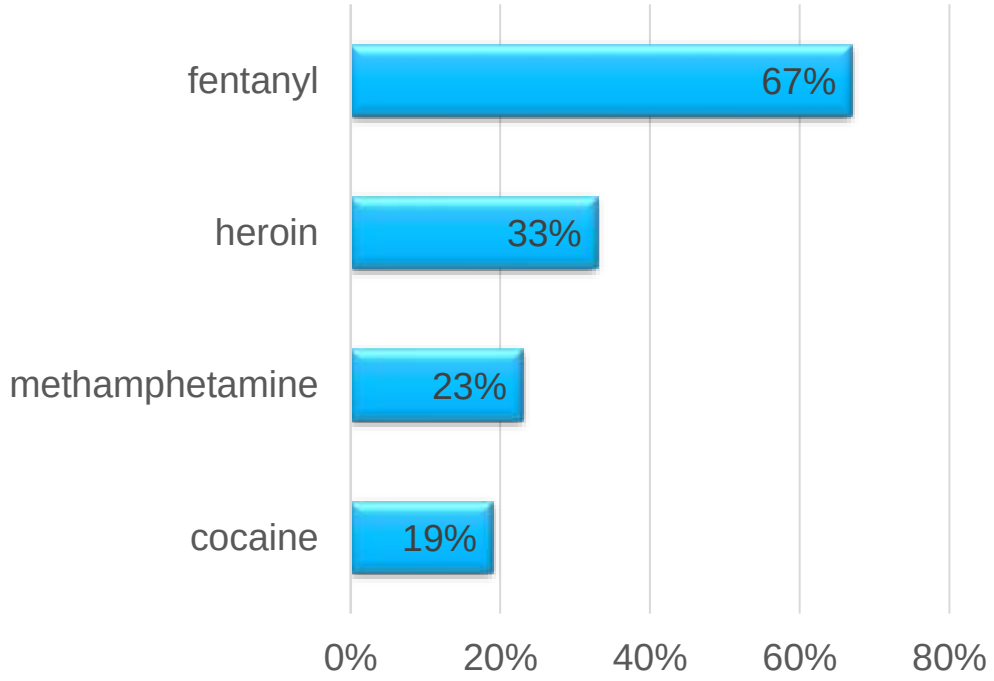



Lifespan

COVID: stress, social isolation and drug use



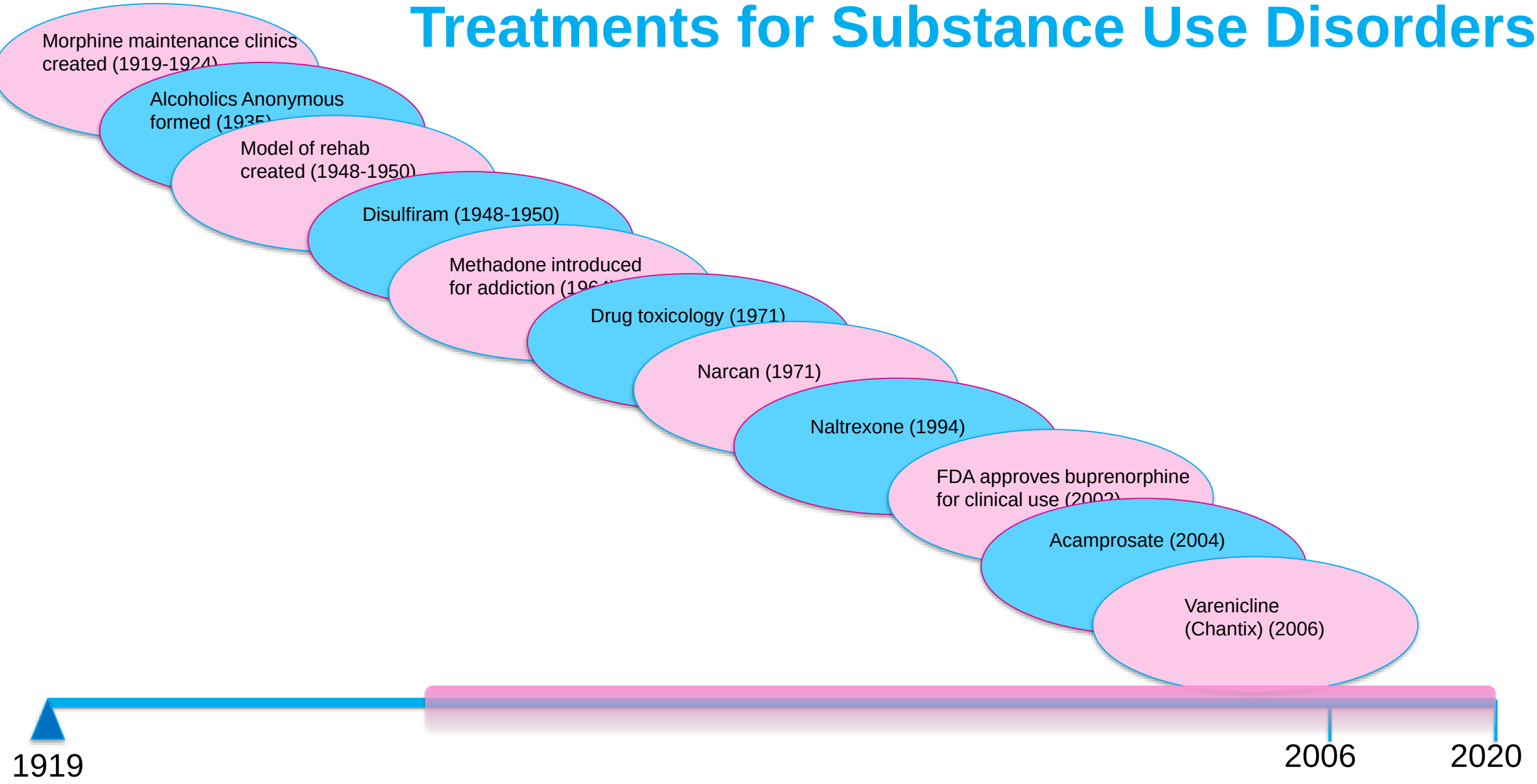
National increase in urine drug test positivity rates during COVID-19



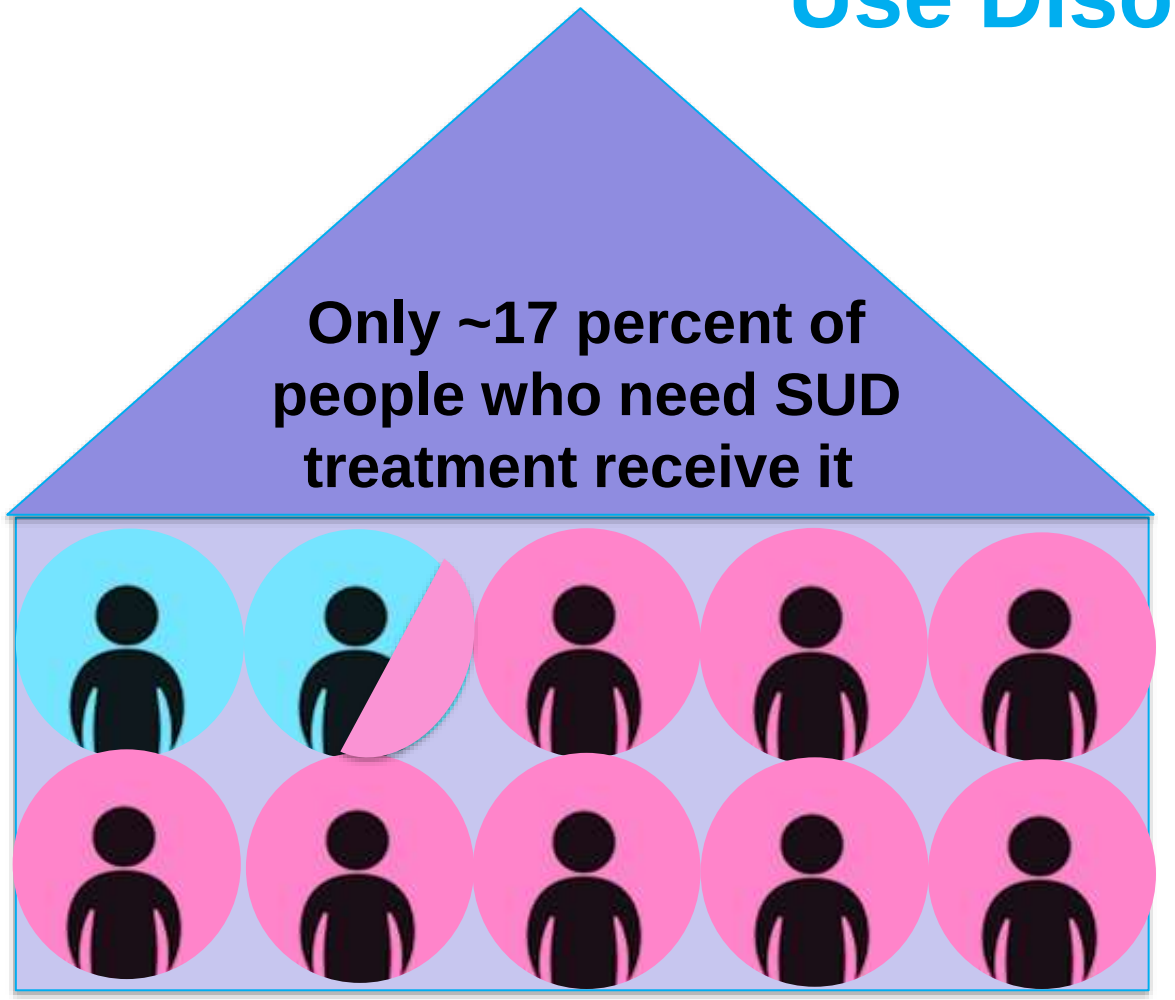
~85,000 drug overdose

Wainwright et al., JAMA. 2020;324(16):1674-1677.

Treatments for Substance Use Disorders



Medications Used To Treat Substance Use Disorder



Barriers:

Stigma

Governmental regulation

Science-based novel treatments

Behavioral Therapies

Cognitive Behavioral Therapy

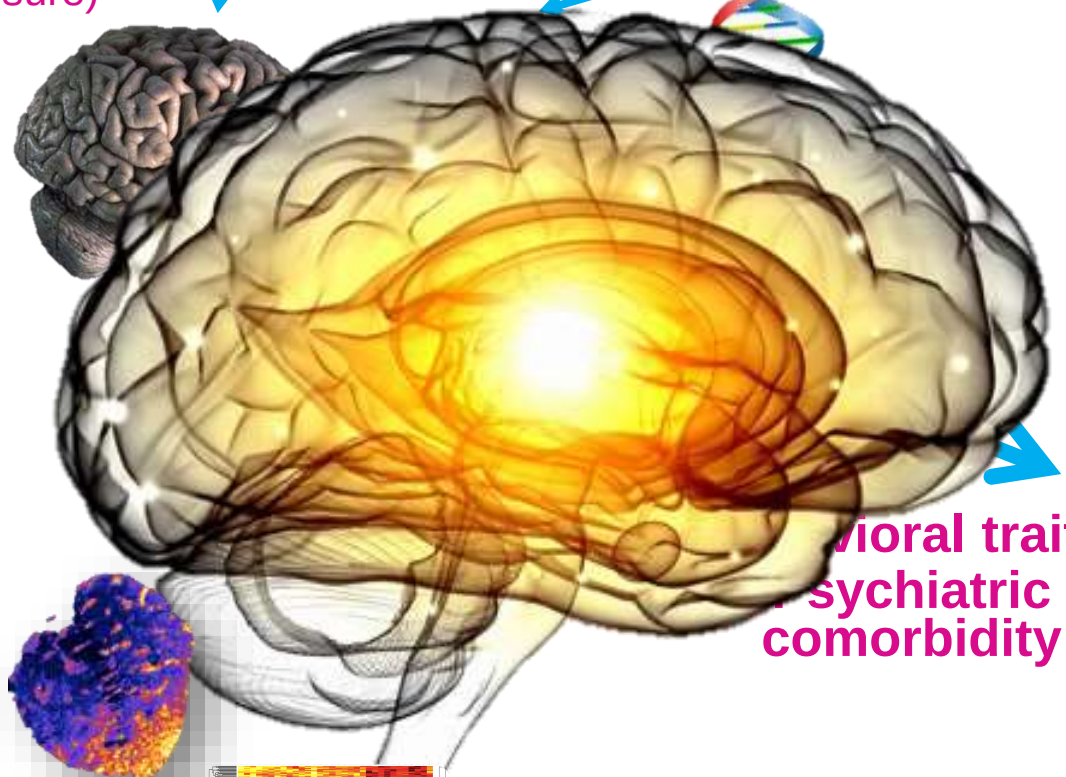
Contingency Management

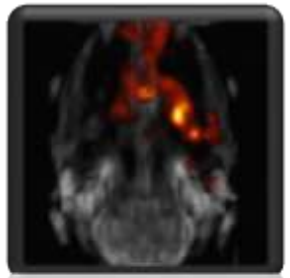
Motivational Enhancement Therapy Group/ *Family Therapy*

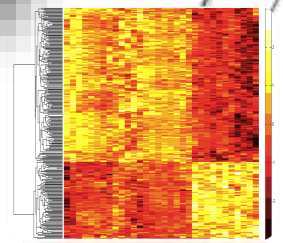
Neurodevelopment

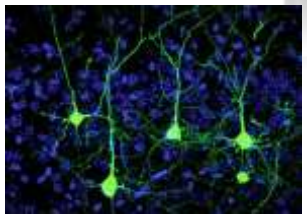
Environmental factors
(e.g., stress, impoverished conditions, early drug exposure)

Genetics









Drug use

…vioral traits/ …sychiatric comorbidity

Addiction risk

Neurobiology of Addiction

NAc (ventral striatum; Nucleus accumbens): reward expectation; goal-directed behavior

DS (Dorsal striatum): habit formation

PFC (Prefrontal cortex): cognitive control

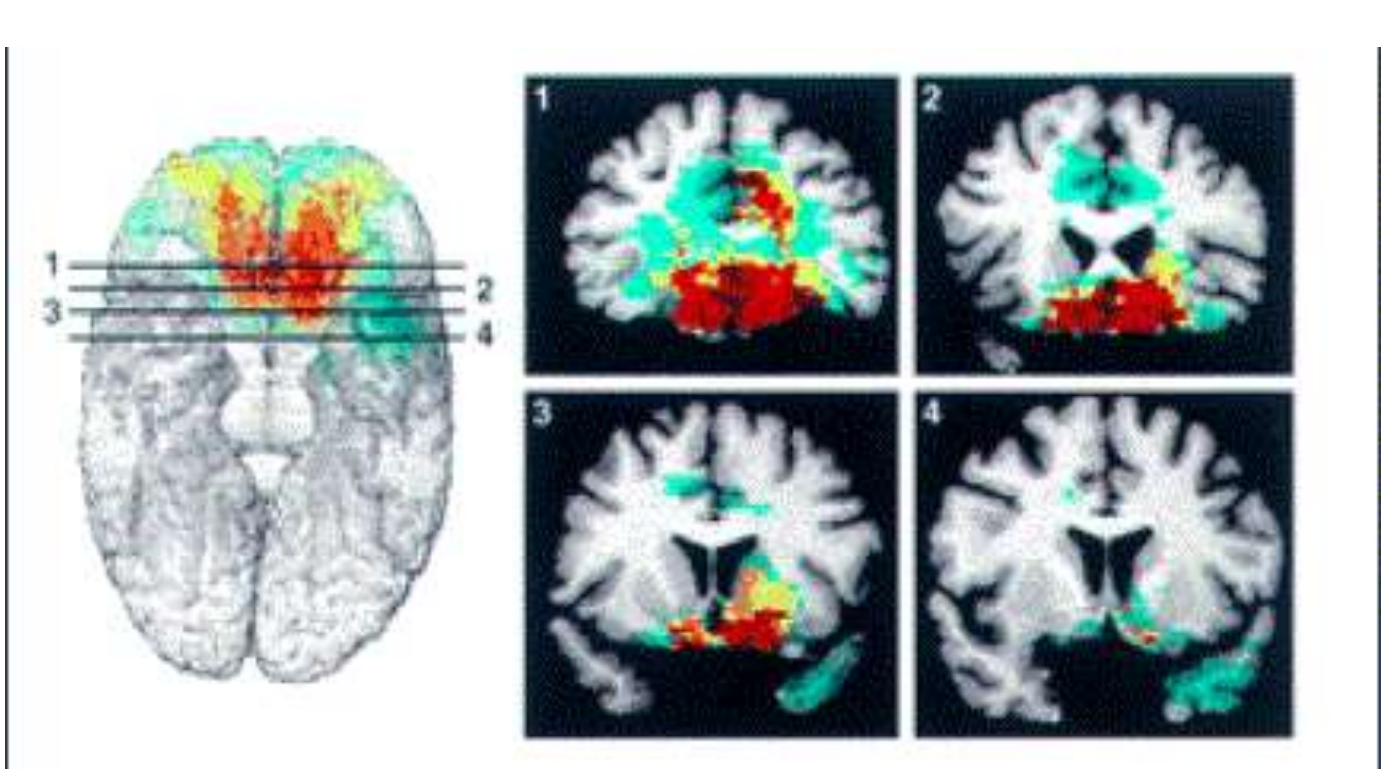
OFC (orbitofronal cortex): goal-directed behavior, motivational drive; cognitive flexibility

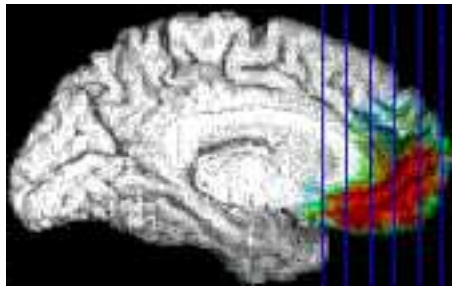
AMG (amygdala): emotional regulation; drug-seeking behavior

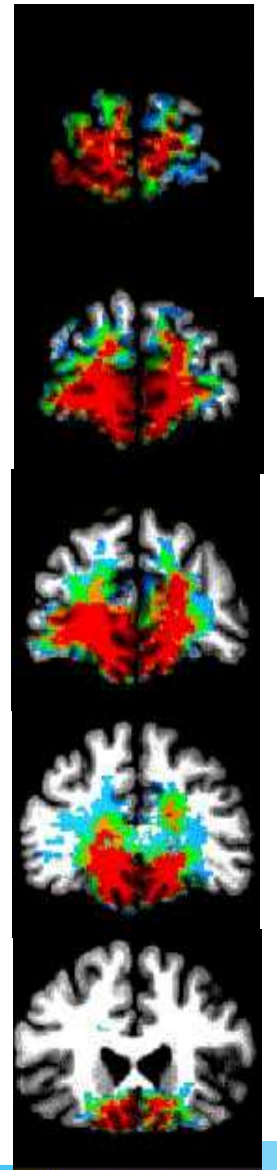
HIPP (hippocampus): memory

VTA (ventral tegmental area): reward, cognition, emotional regulation

Impaired Cortical Function in Drug-Addicted Subjects and Individuals With Orbitofrontal Cortical Lesions

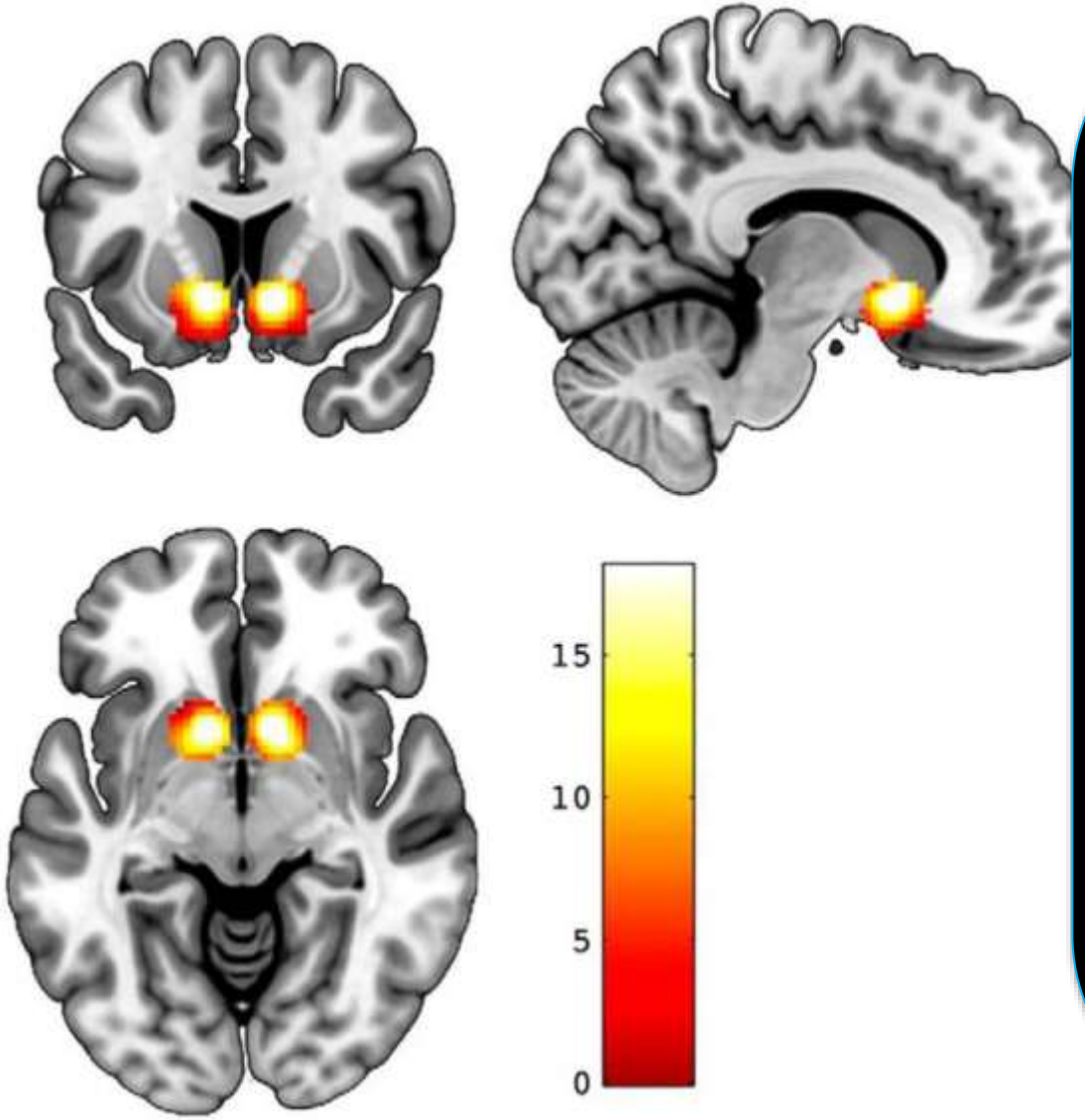






- Poor decision
- Poor impulse control
- Emotional lability
- Rapid temporal discounting of rewards

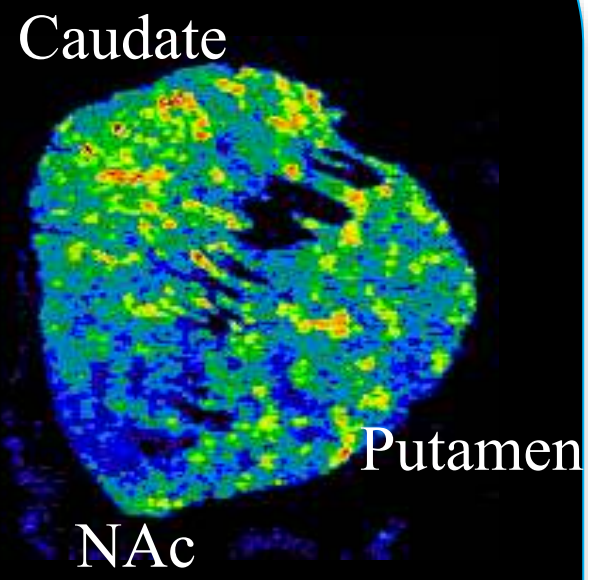
Ventral Striatum (nucleus accumbens and reward)



Dorsolateral Striatum = responsible for the stimulus–response (S–R) associations; habitual responding

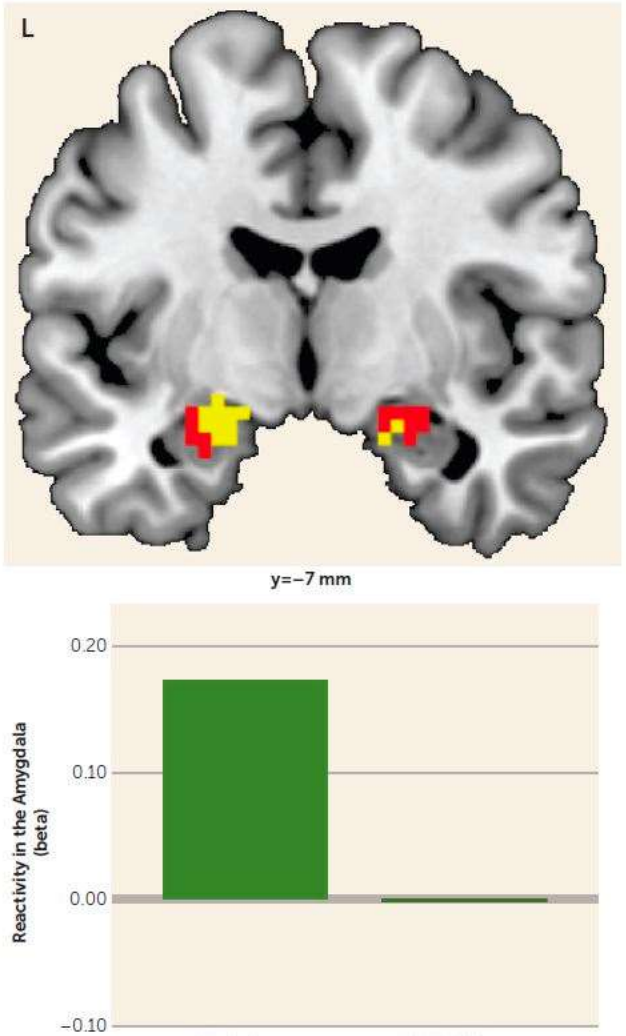
Associative striatum (caudate nucleus) = Crucial for the learning and expression of goal-directed actions; involved in the selection of actions that lead to reward

Ventral striatum (NAc) = Reinforcement



Reut Avinun et al. J. Neurosci. 2017;37:9724-9729

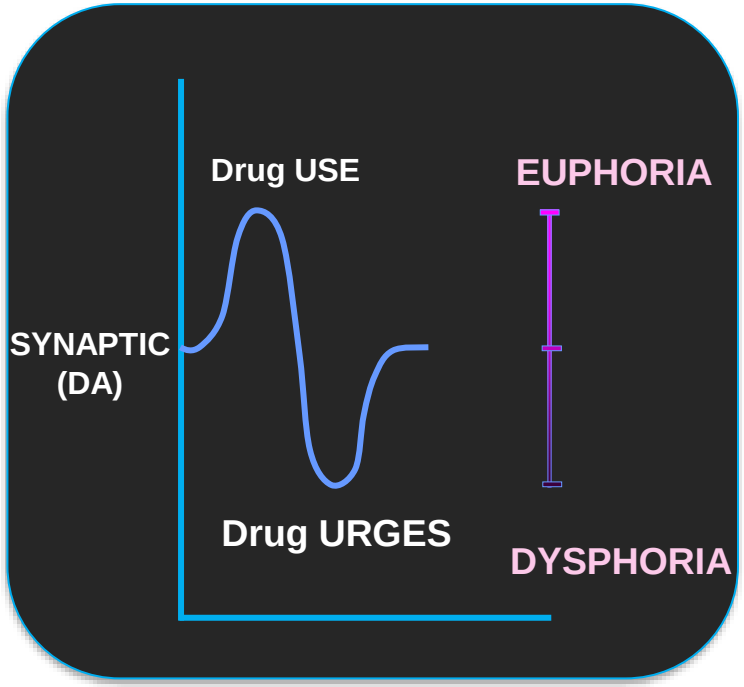
Amygdala

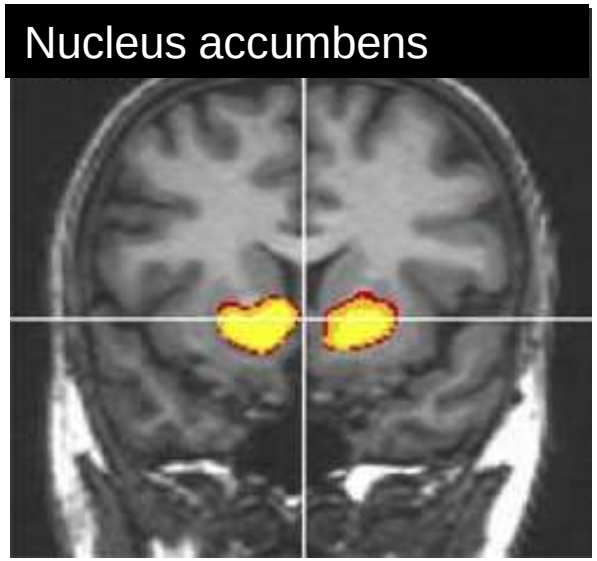


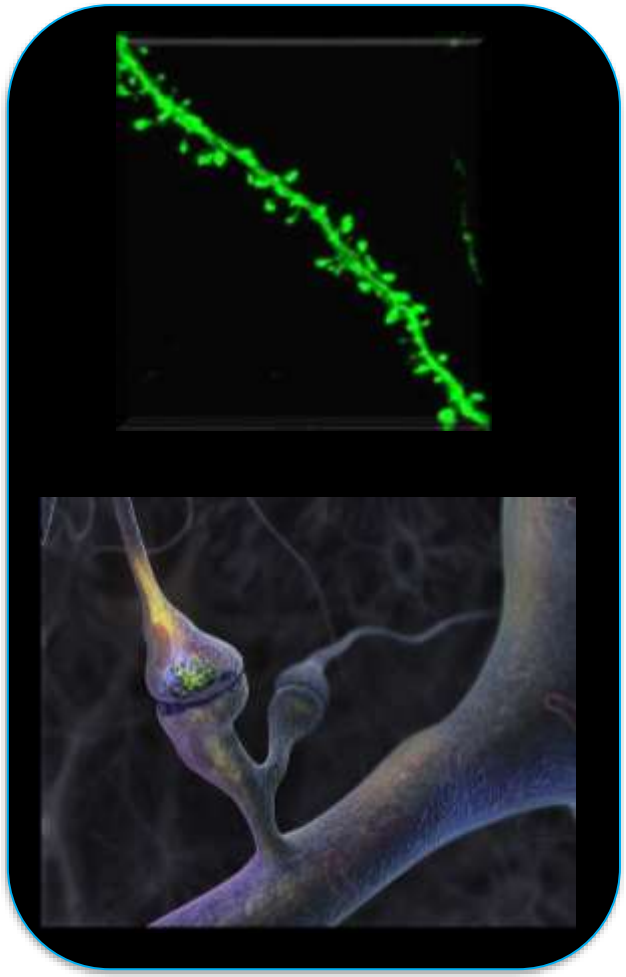
Craving
Cue reactivity
Emotional regulation

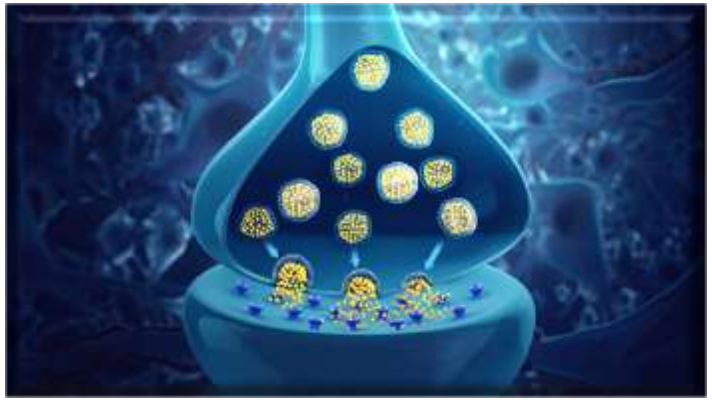
Wiers et al., Am J Psychiatry, 2015

Neurobiology of Addiction









Dopamine
Glutamate
GABA
Opioid
Endocannabinoid

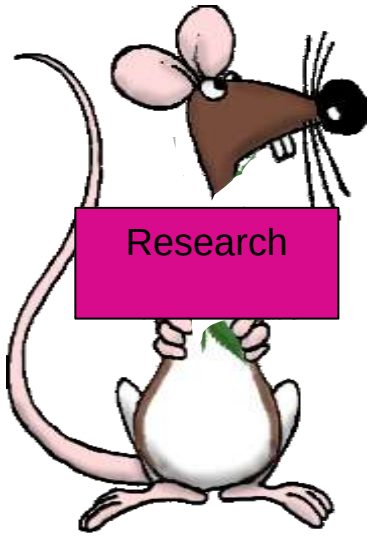
Treatment Development

Human molecular studies

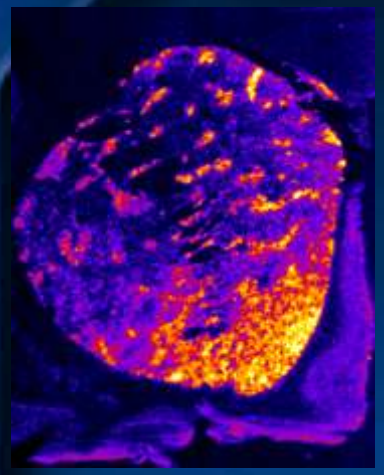
Preclinical Animal Models

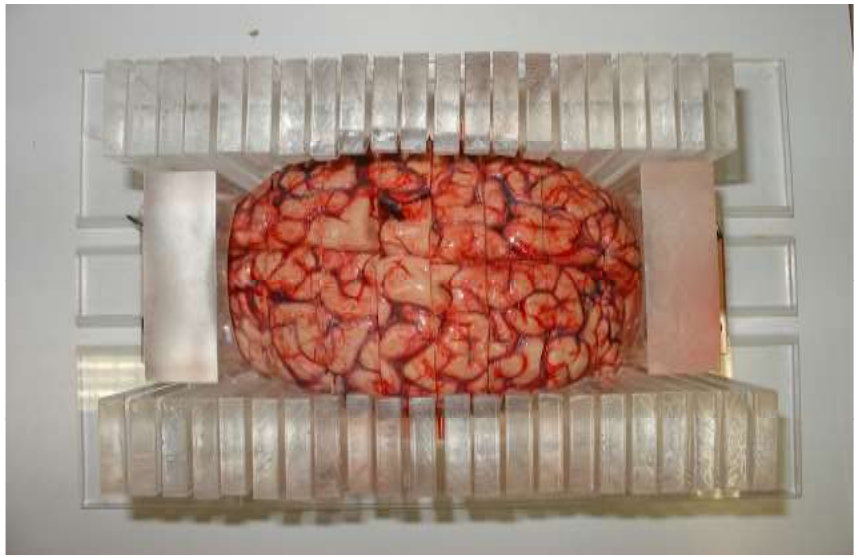
Neurobiological targets

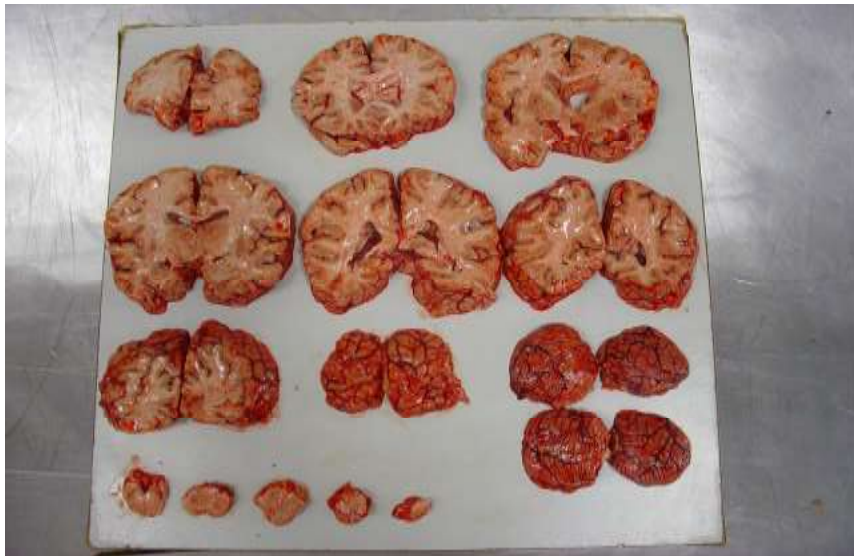
Clinical Studies



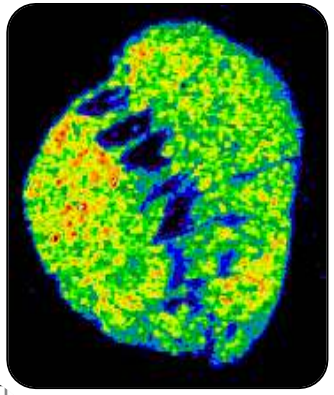
Molecular Insights: Human Brain

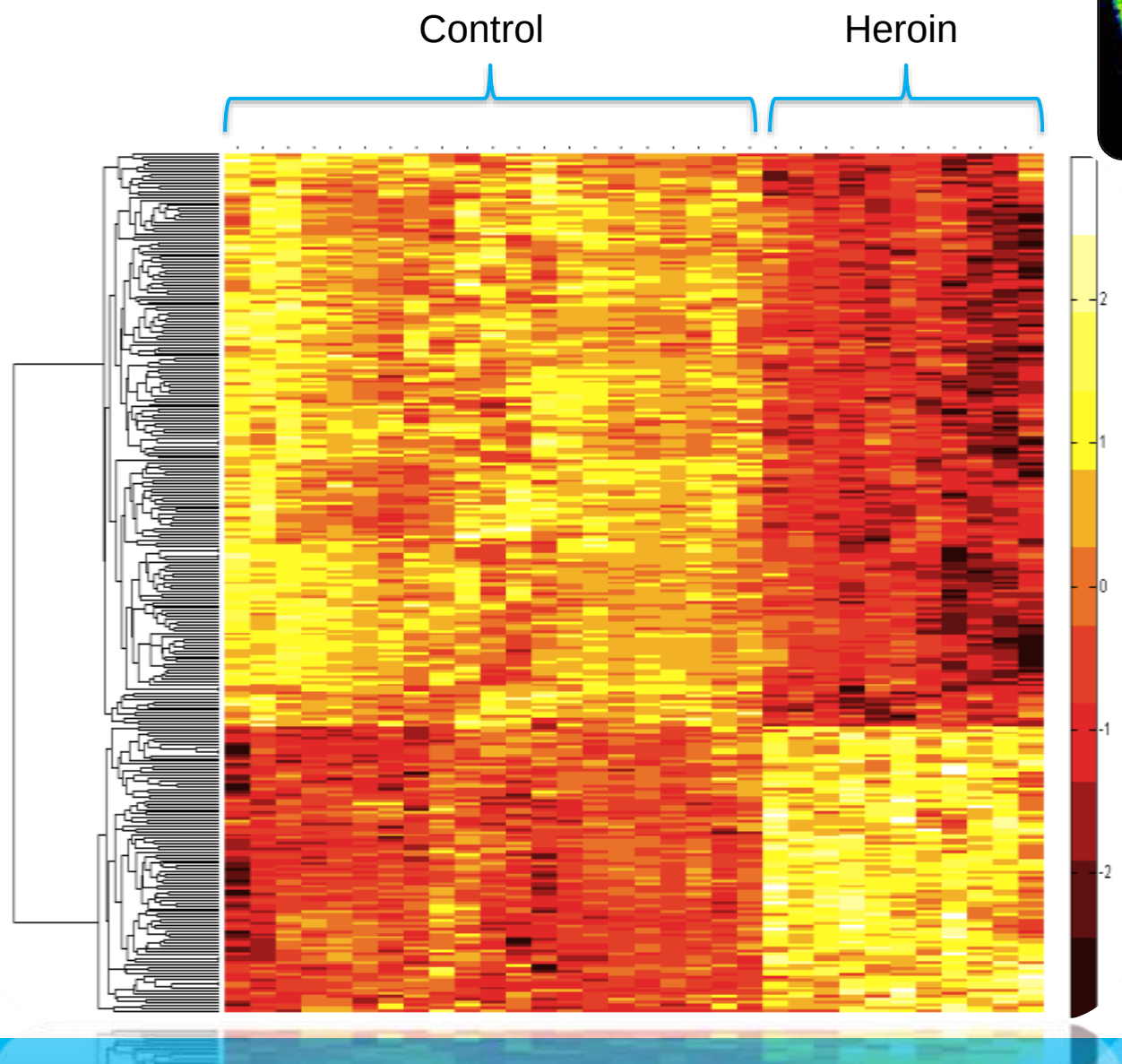






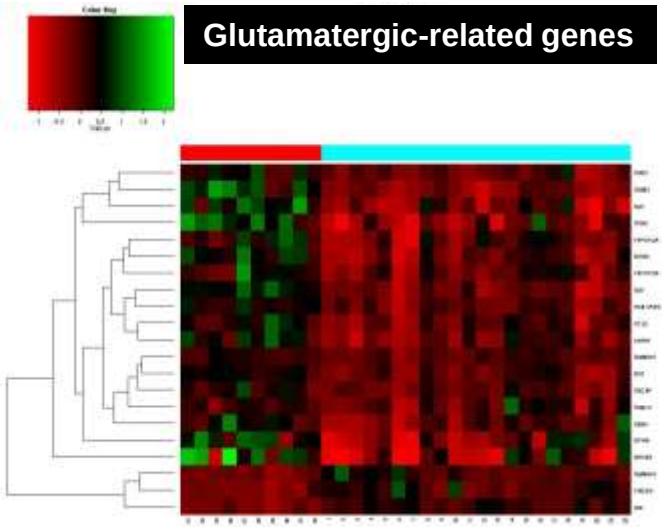
Transcriptional Profile of Heroin Abusers



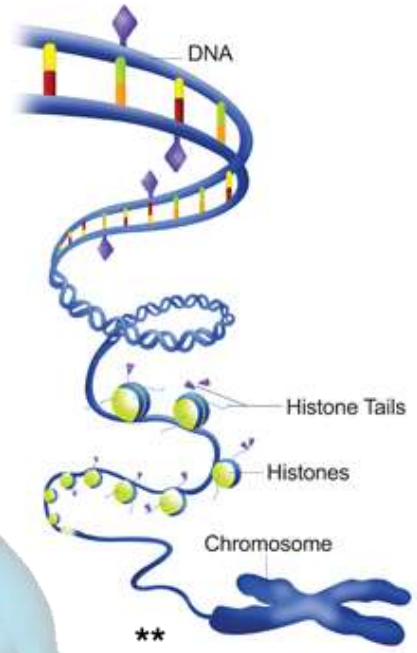


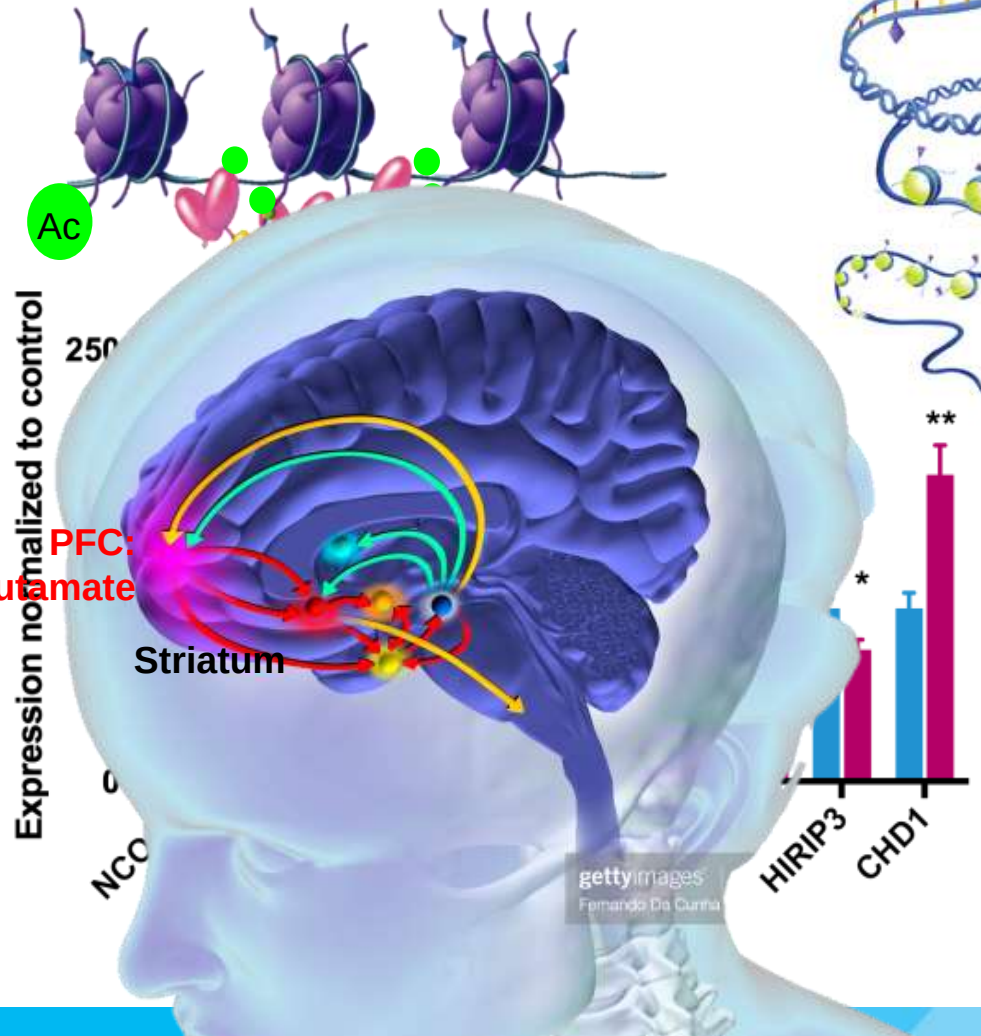
Dysregulation of Glutamatergic Genes and Epigenetic Remodelers in the Striatum of Human Heroin Abusers

Glutamatergic system



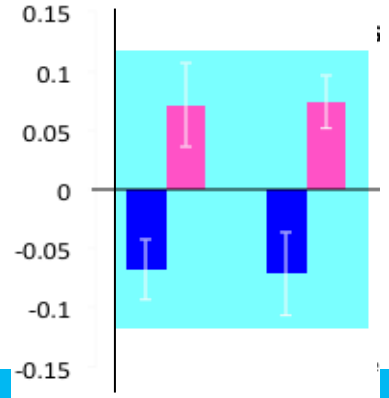
Epigenetic





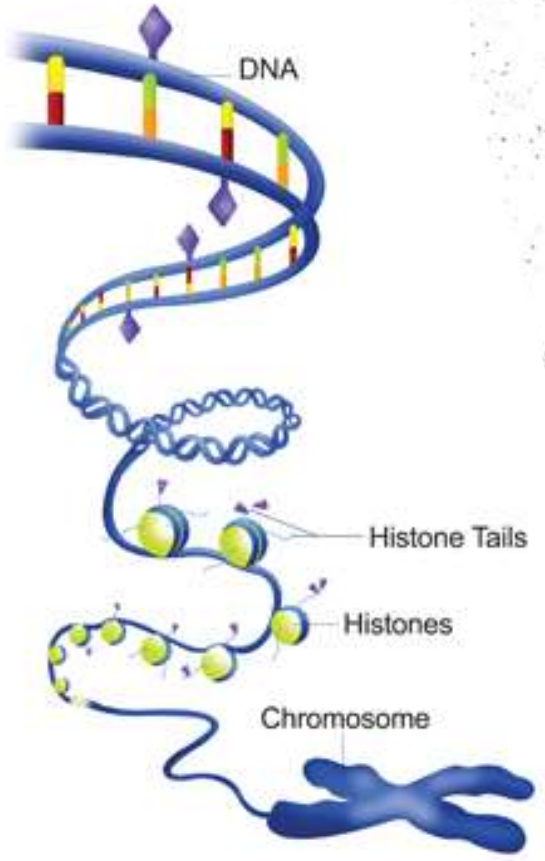
Synaptic plasticity

Whole genome co-expression network analysis



Epi Genetics

Addiction — Complex Disorder



Environment

-control gene activity

Describes the study of mechanisms by which genes are turned on or off without altering their genetic code or DNA sequences.

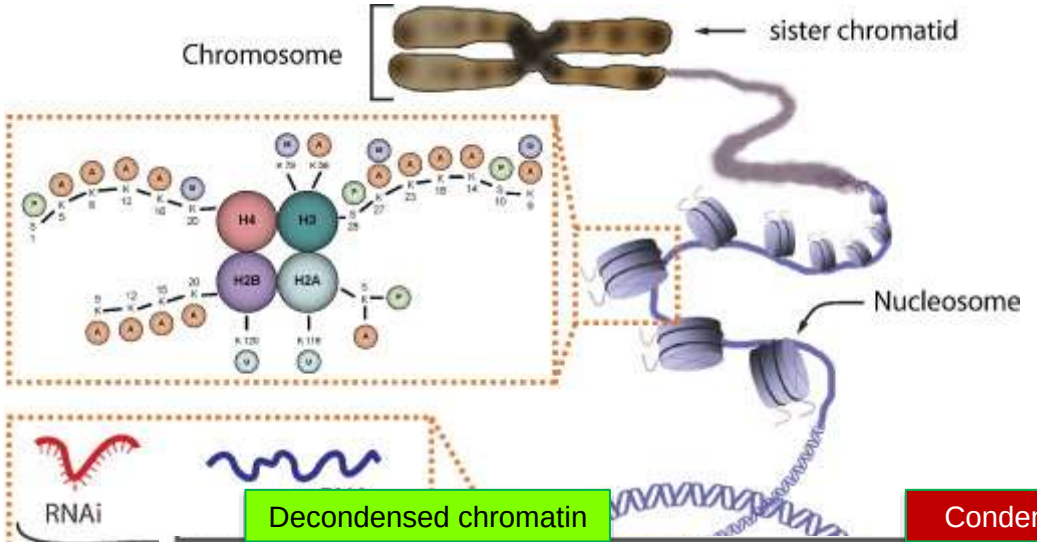
Epigenetics

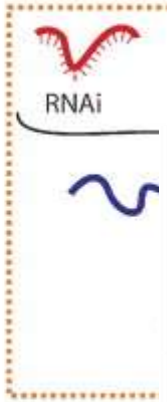
Cellular and physiological trait variations that are *not* caused by changes in the DNA sequence; the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself

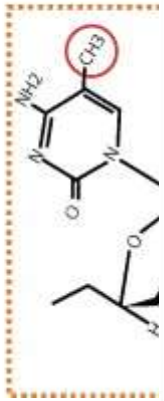
Histone modifications

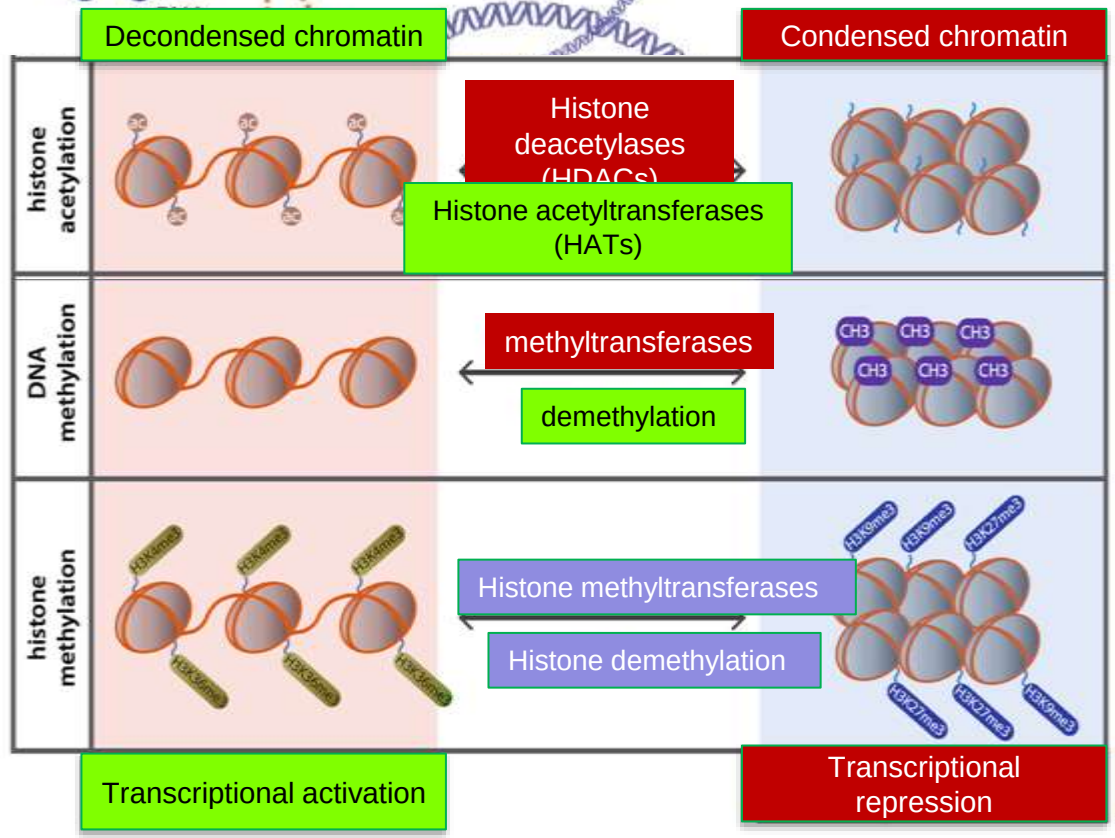
RNA interference

DNA methylation

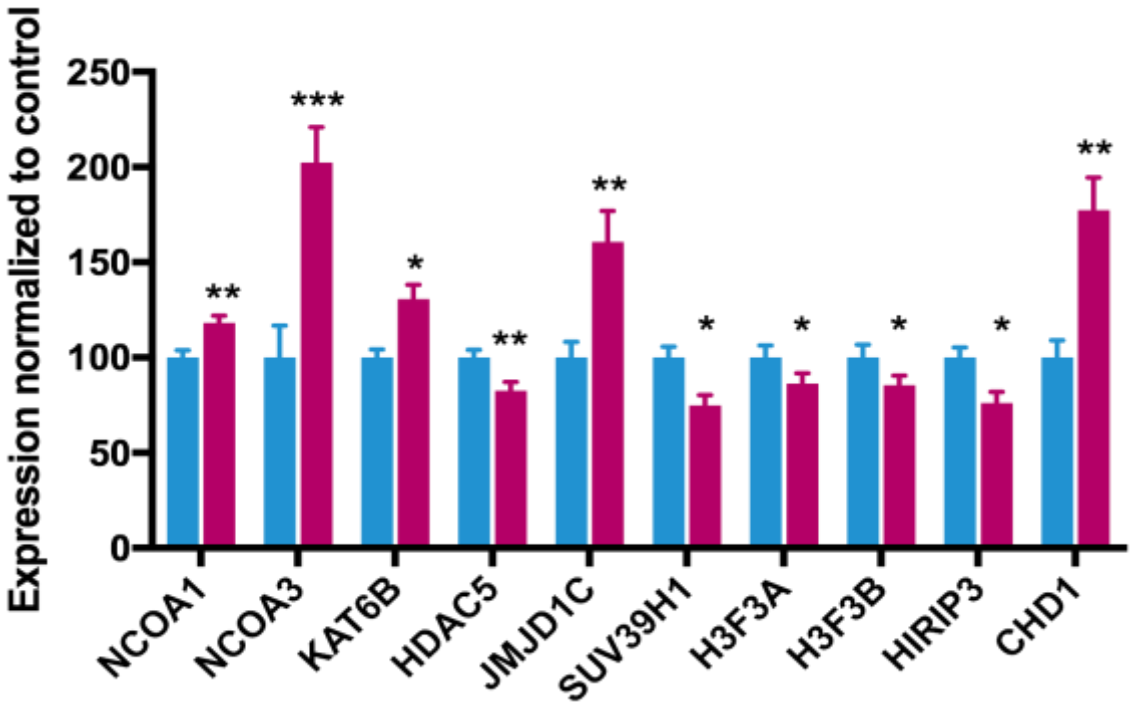


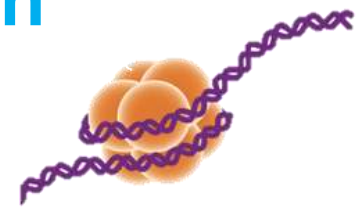






Dysregulation of Epigenetic Remodelers in the Striatum of Human Heroin Abusers Predict Increased Acetylation and Transcription



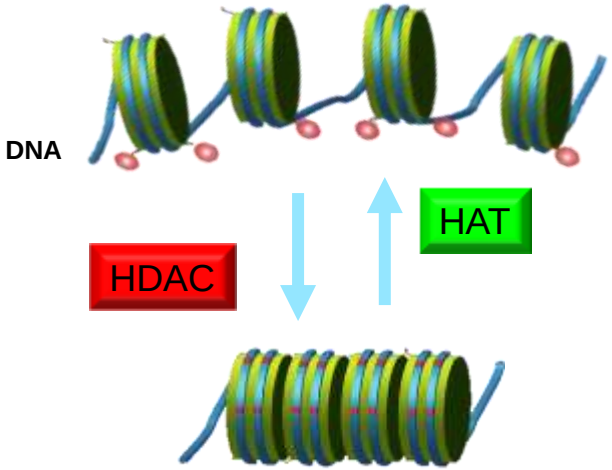


More accessible state of DNA = **enhanced transcription**

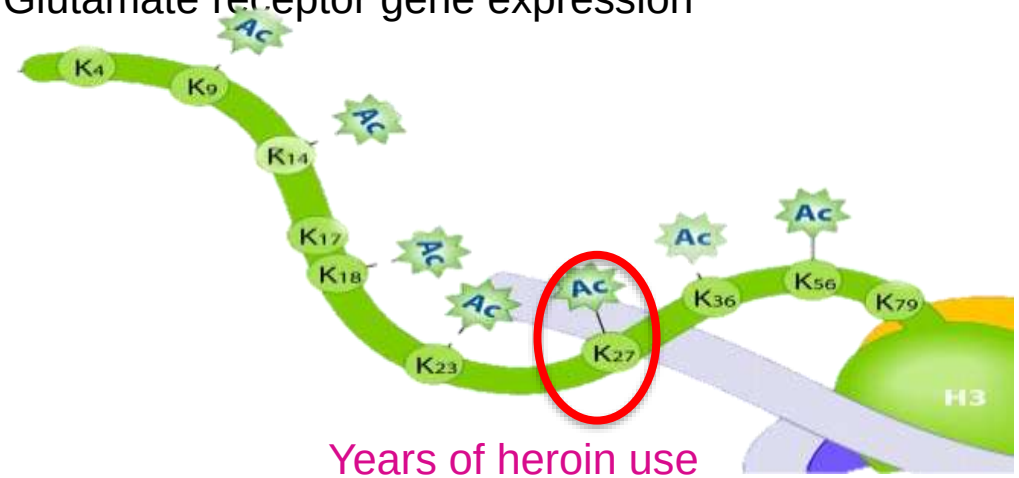
Increased histone H3 acetylation

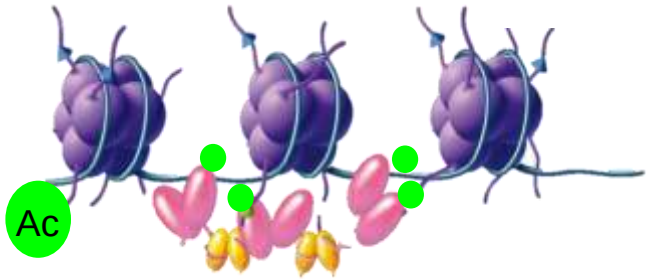
- elevated histone acetyl transferase (HAT) levels (e.g., Ncoa1, Ncoa3)

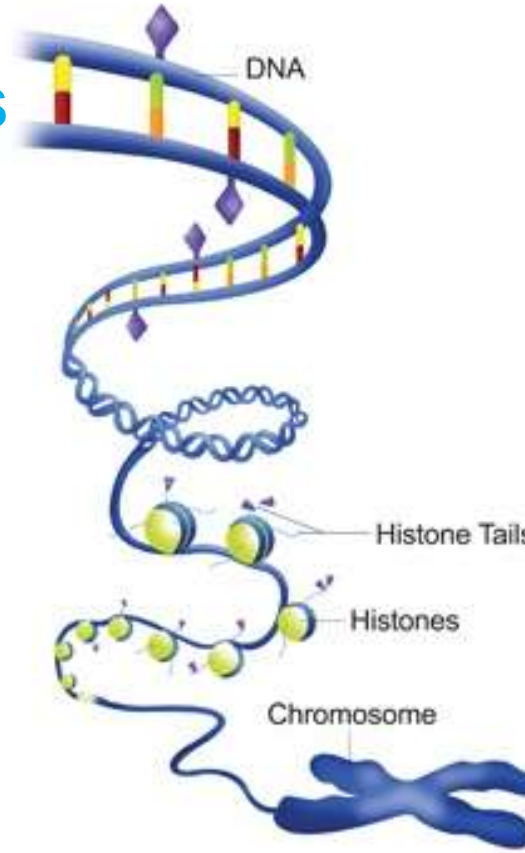
decreased histone deaceylase (HDAC) (e.g., HDAC5)



Epigenetic Marks Related to Transcriptional Activation Correlate to Glutamatergic Impairments

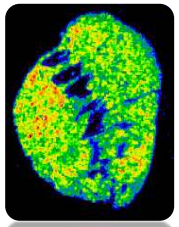


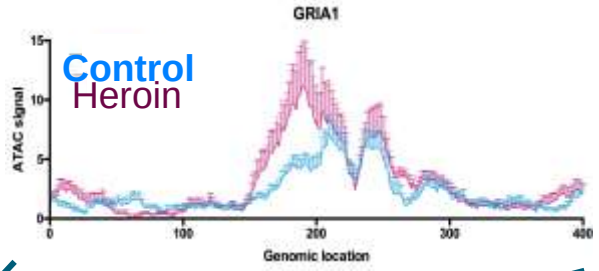


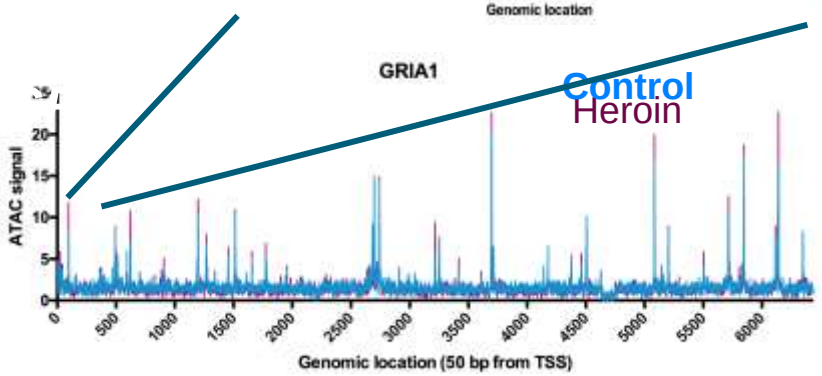


Egervari et al., Biological Psychiatry, 2016

Translational: Consistent Hyperacetylation in the Rat Heroin Self-administration Model







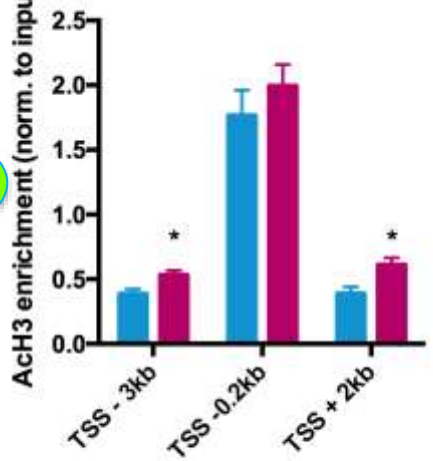
ATAC-seq: Assay for Transposase-Accessible Chromatin with high throughput sequencing

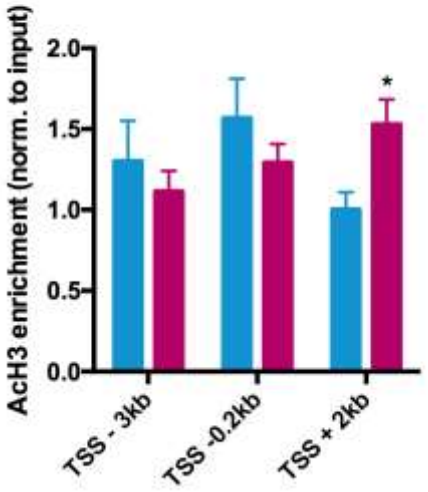
Control
Heroin

AcH3

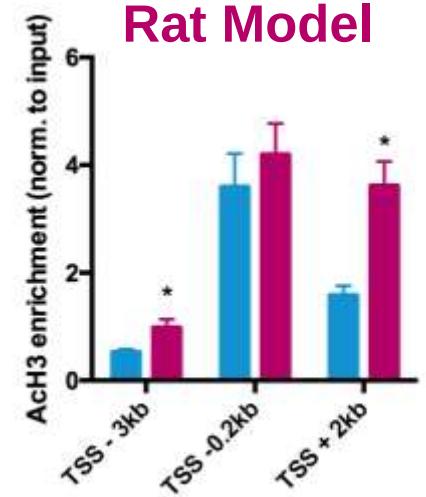
H3K27ac

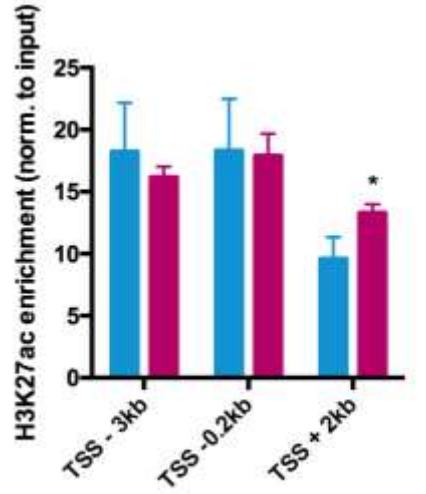
Human





Rat Model

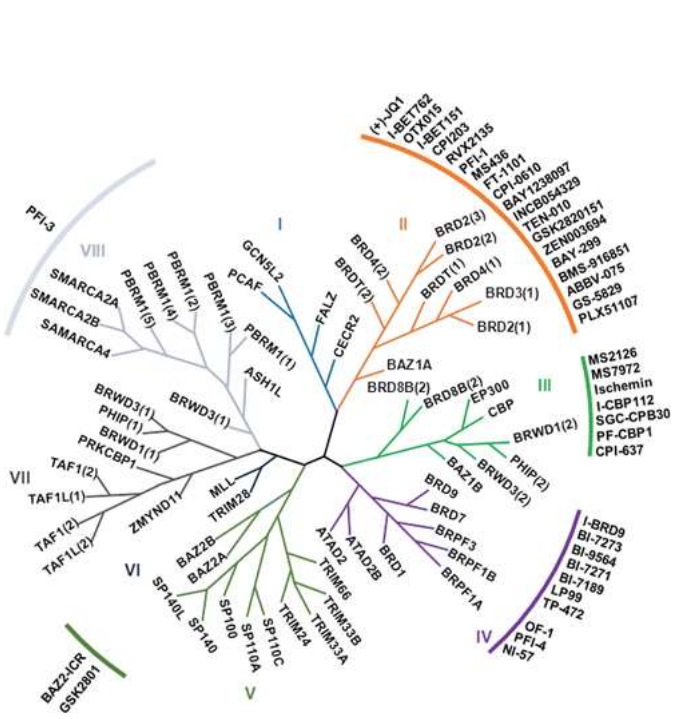


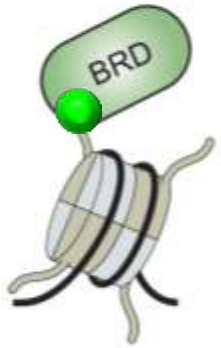


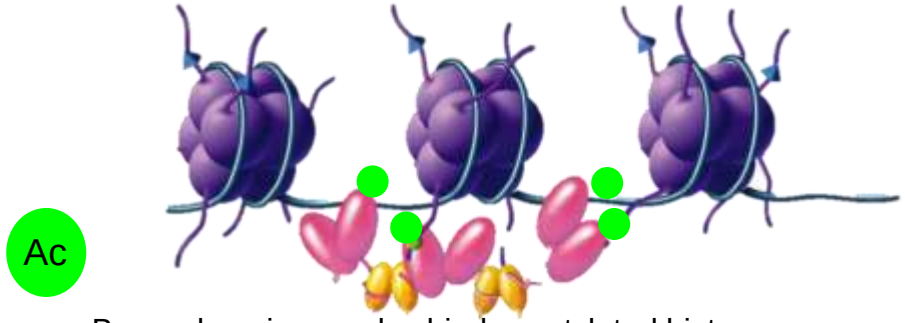
TSS, transcription start site

Egervari et al., Biological Psychiatry, 2016

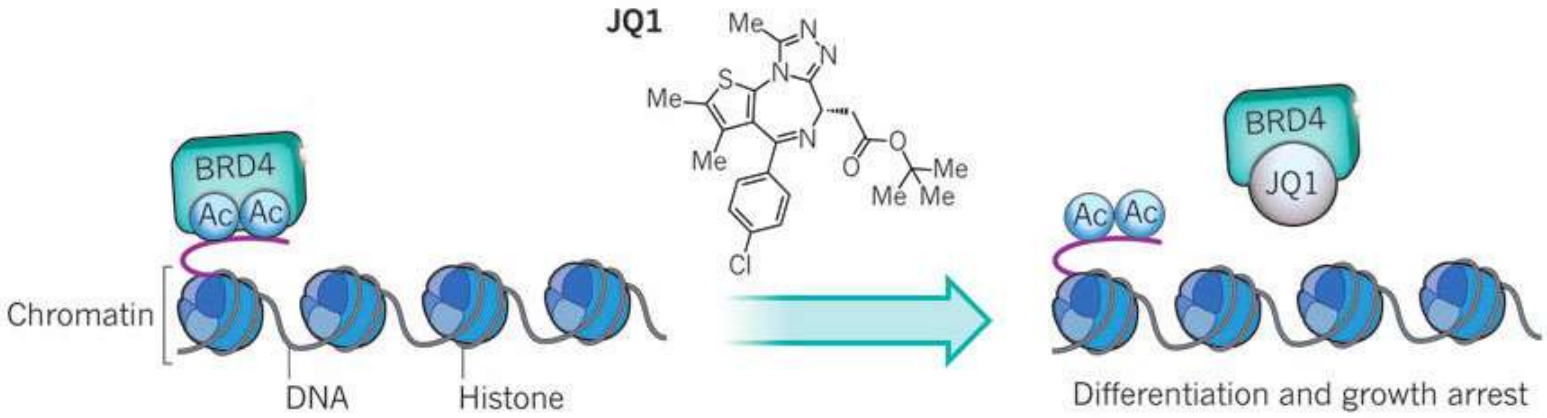
Bromodomain and Extraterminal (BET) Inhibitors - Potential Drug Abuse Treatment?





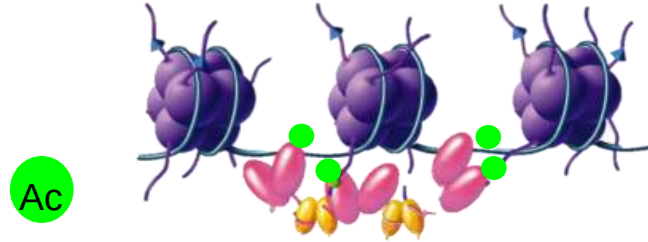


Bromodomain complex binds acetylated histones
BET domain proteins reads acetylated lysine residues



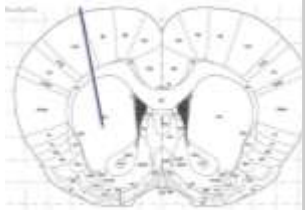
Modified from Taverna and Cole, 2010

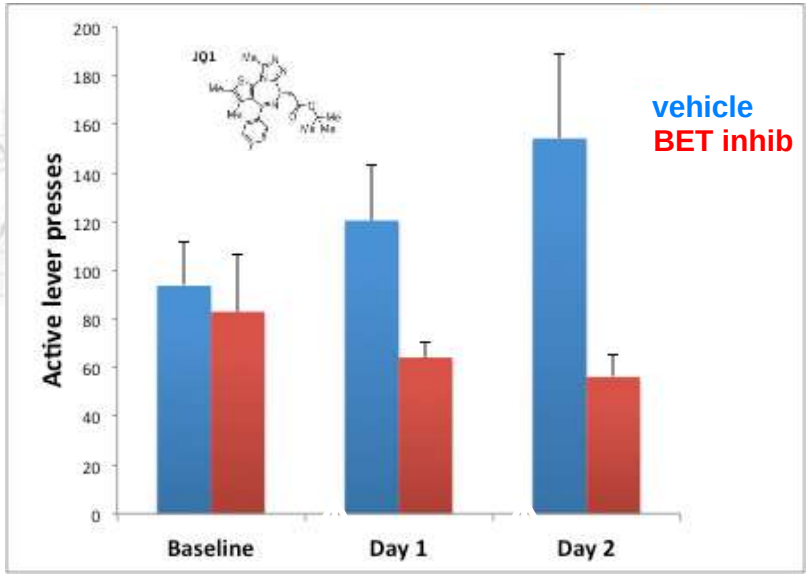
Bromodomain and Extraterminal (BET) Inhibitors - Potential Drug Abuse Treatment

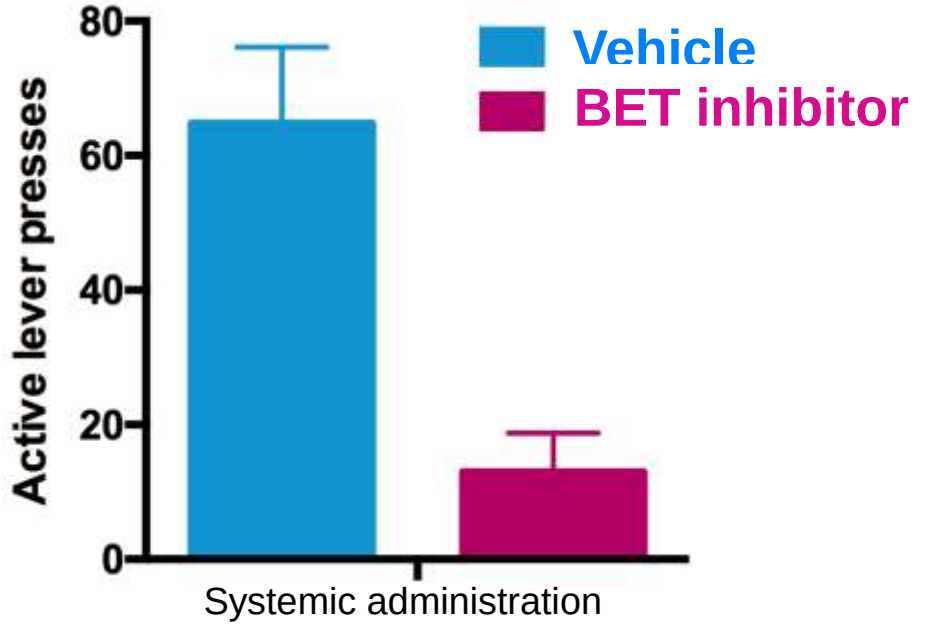


Heroin self-administration behavior can be reduced by specific epigenetic inhibitors

Heroin self-administration







Egervari et al., Biological Psychiatry, 2016

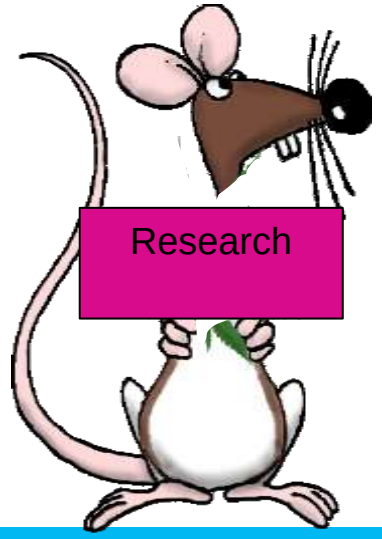
Treatment Development - Part II

Human molecular studies

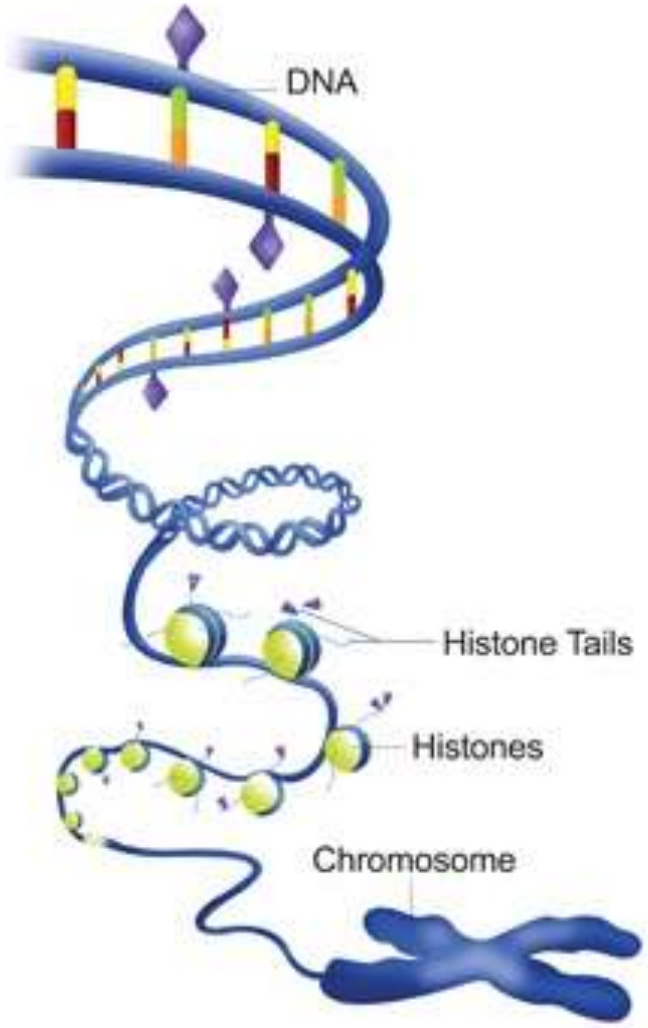
Preclinical Animal Models

Neurobiological targets

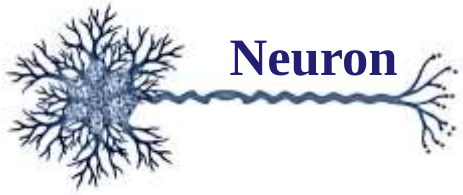
Clinical Studies



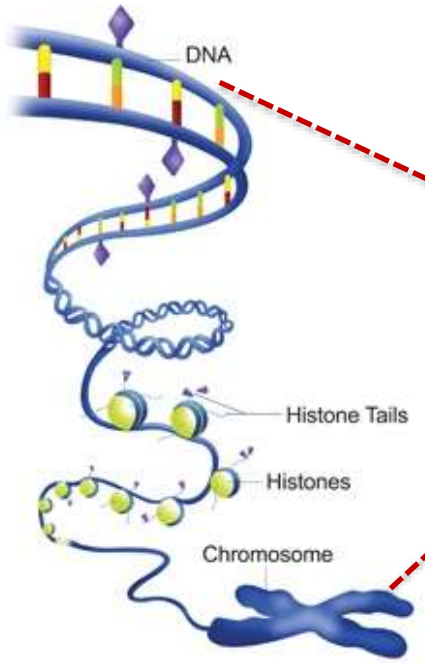
Epigenetics



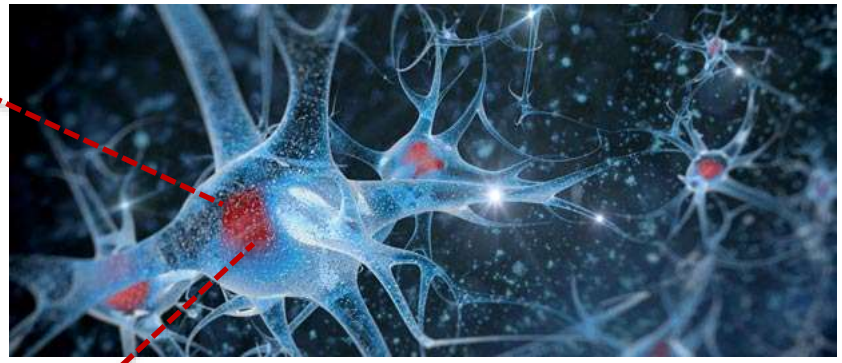
Epigenome sequencing



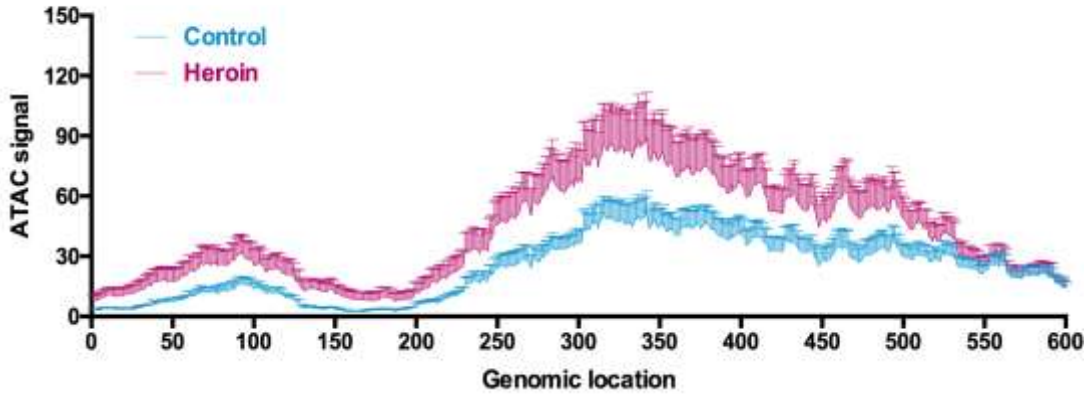
Molecular Neurobiology of Opioid Abuse

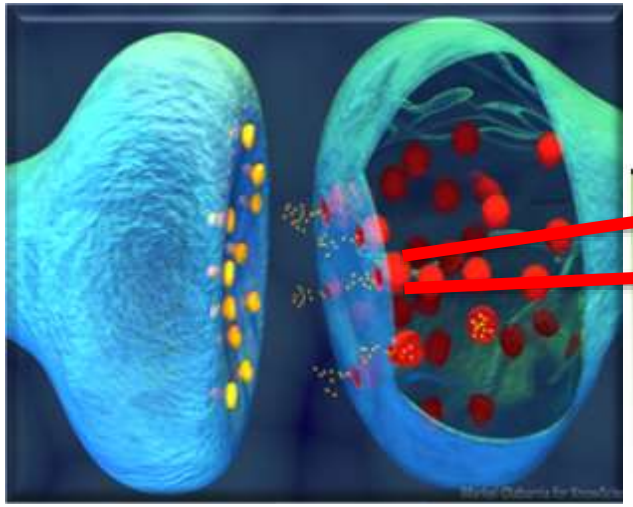


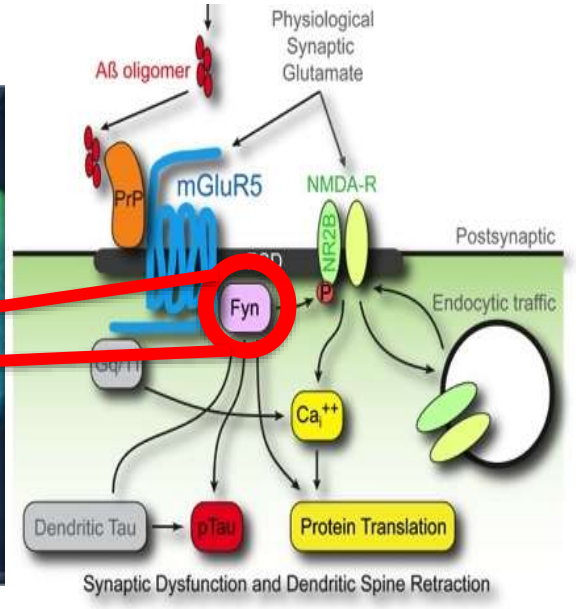
Epigenome



Most significant epigenomic change in neurons relate to the *FYN* gene

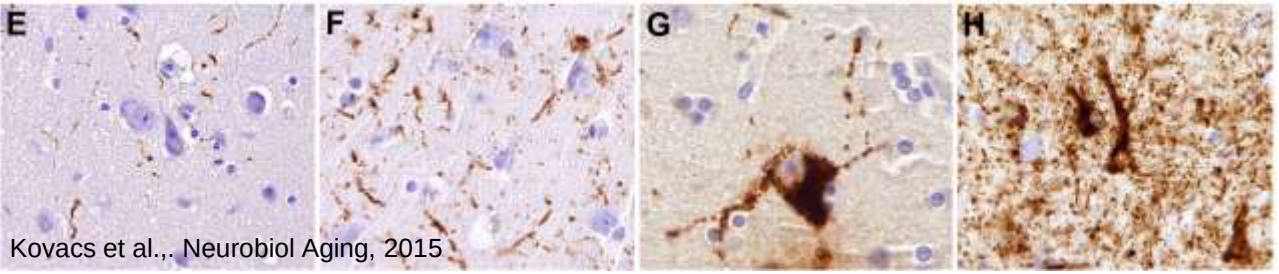




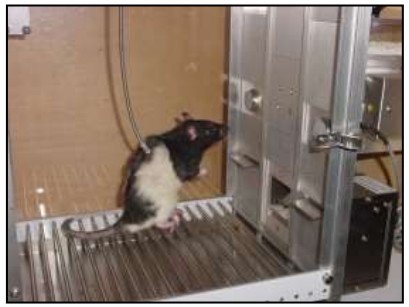


Nygaard et al., Alzheimer's Research & Therapy, 2014

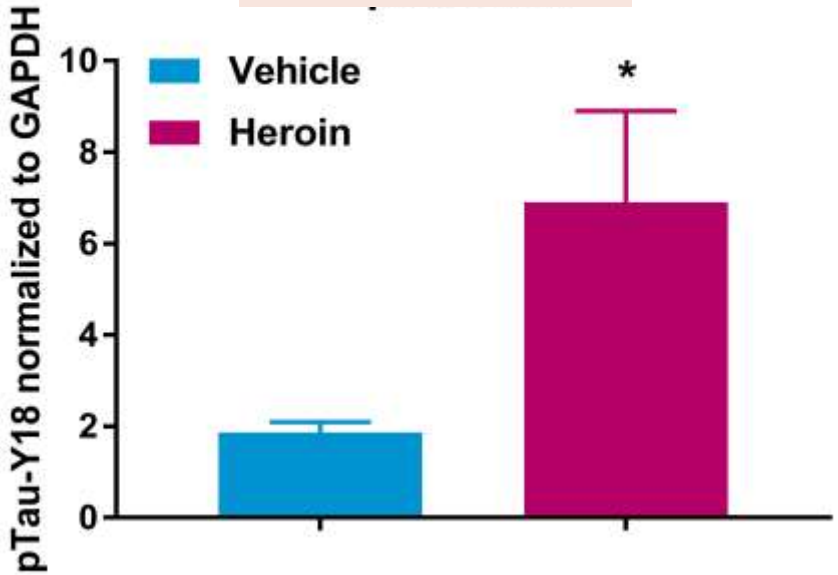
Increased phosphorylated-Tau in the brains of heroin users



Kovacs et al.,. Neurobiol Aging, 2015

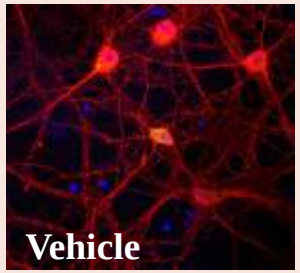


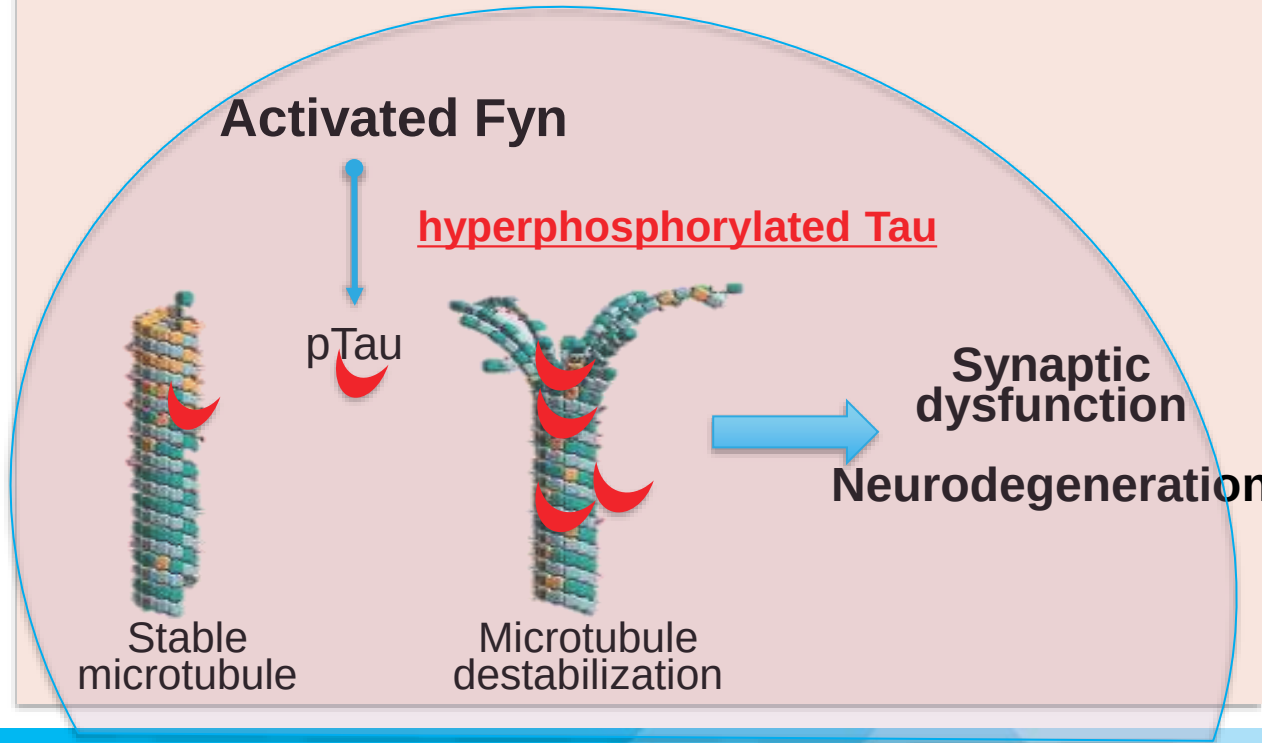
Phosphorylated Tau-Y18

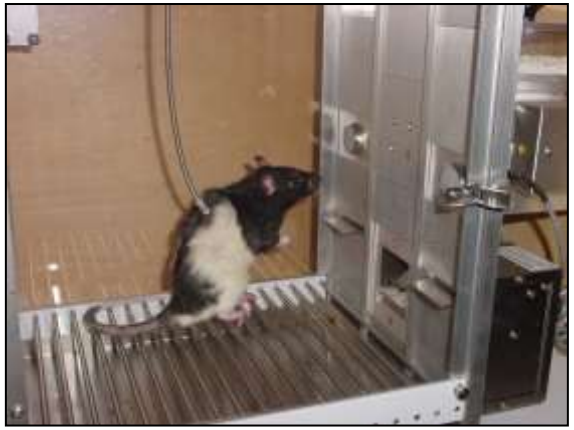


Egervari et al., Nature Communications, 2020

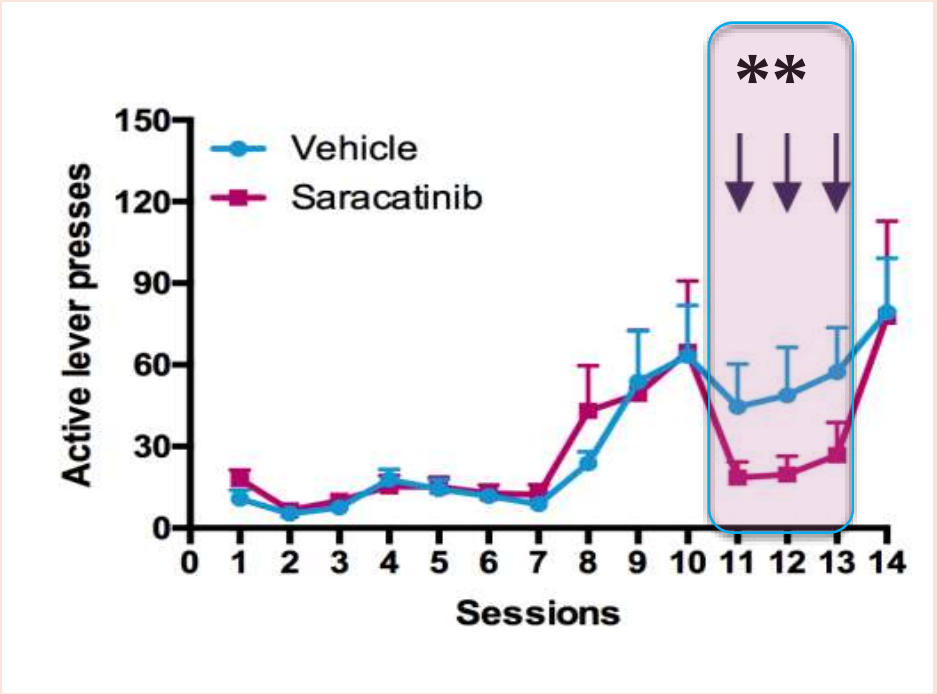
FYN – (tyrosine kinase) is a component of the synaptic machinery that regulates the phosphorylation of Tau; hyperphosphorylated Tau is a pathological feature of neurodegenerative disorders (tauopathies)





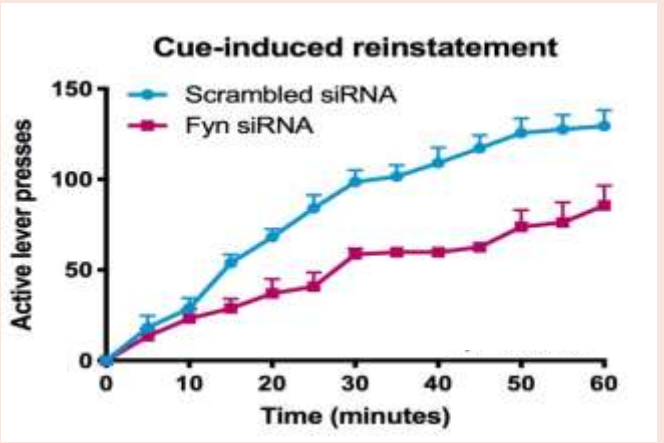


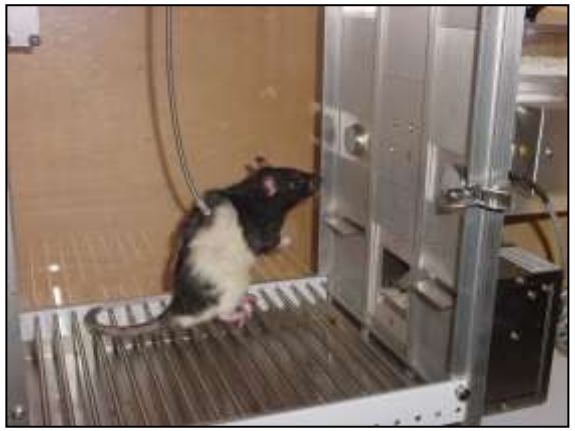
Inhibiting FYN (that reduces pTau) reduces heroin self-administration in animal models



Epigenetic and synaptic regulation target drugs

Clinical Trials

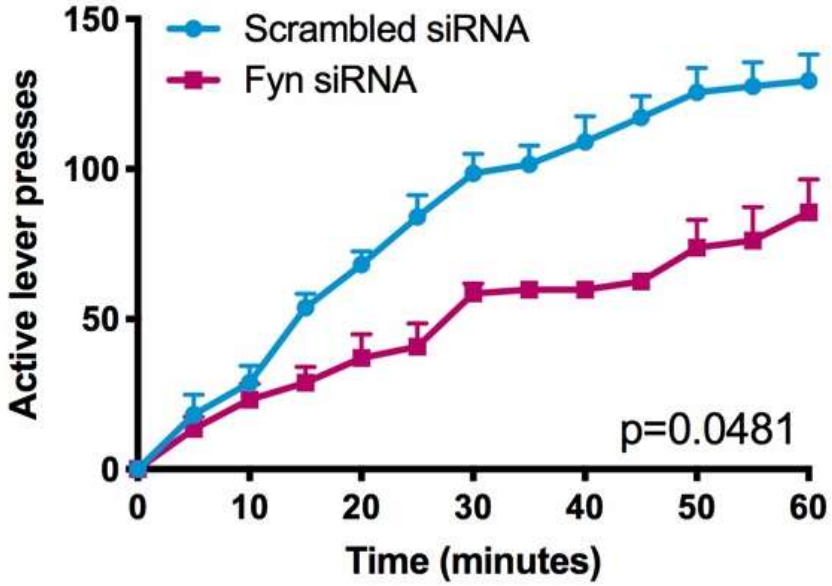




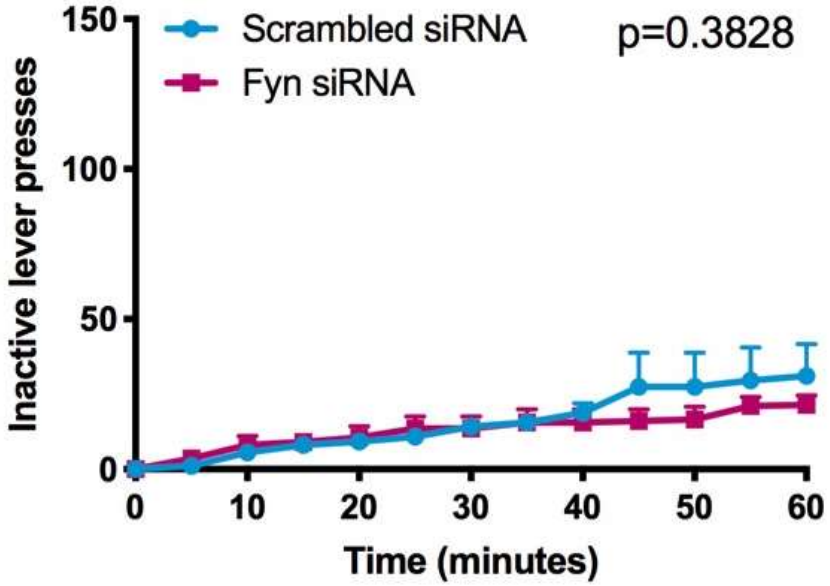
Fyn Expression Regulates Heroin Seeking Behavior

Knockdown of Fyn Reduces Cue-Induced Reinstatement Behavior

Active Lever presses

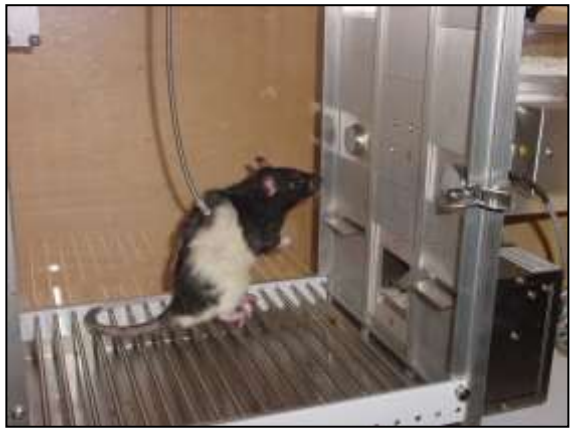


Inactive Lever presses

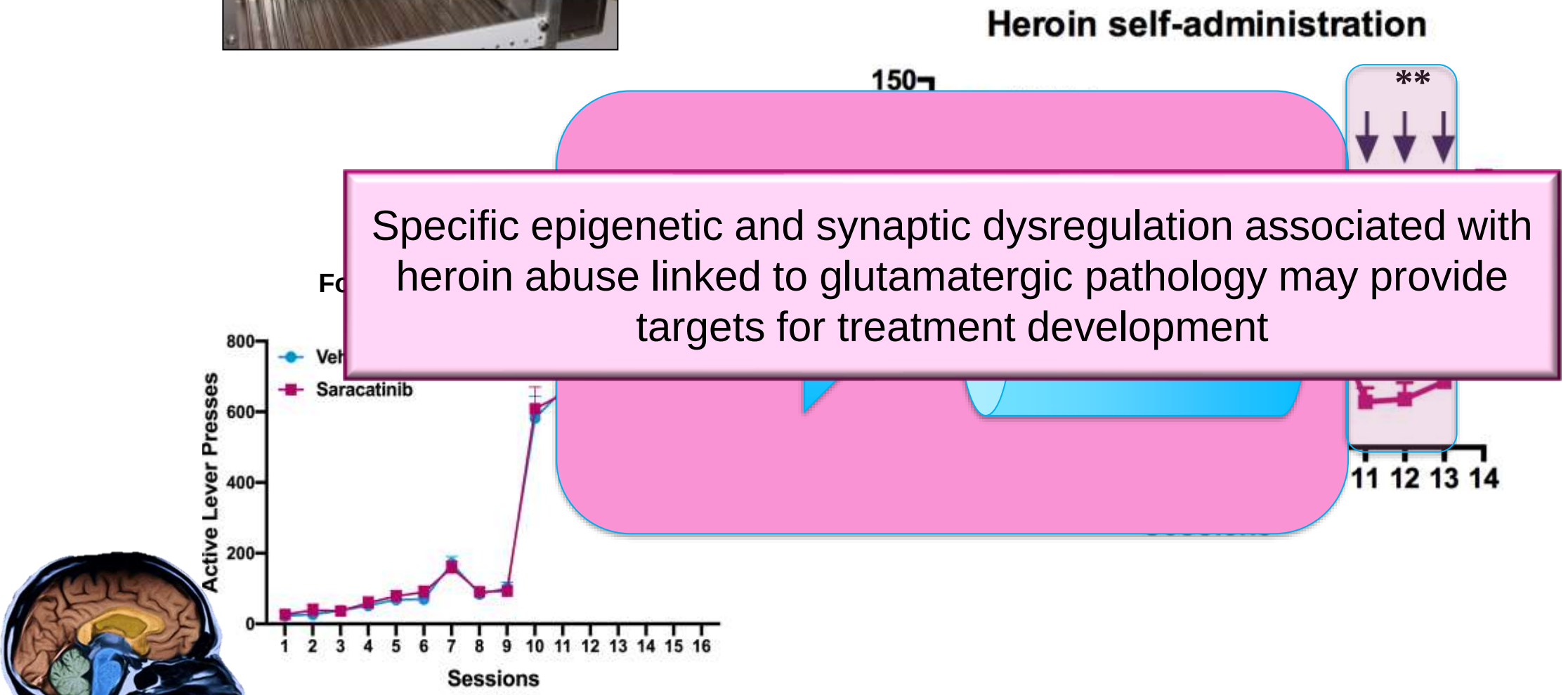


Egervari et al., Nat Communication, 2020

Fyn Medication Development



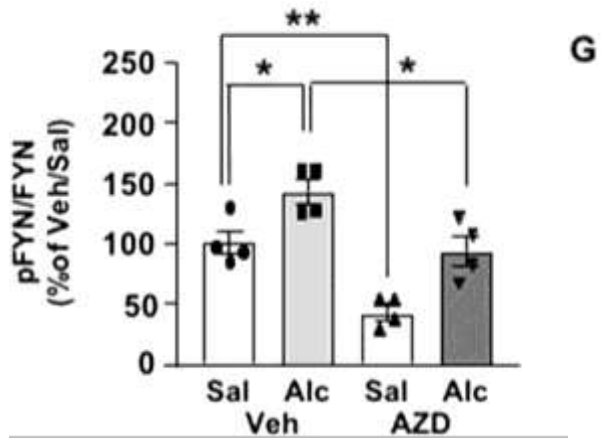
Saracatinib (AZD0530)

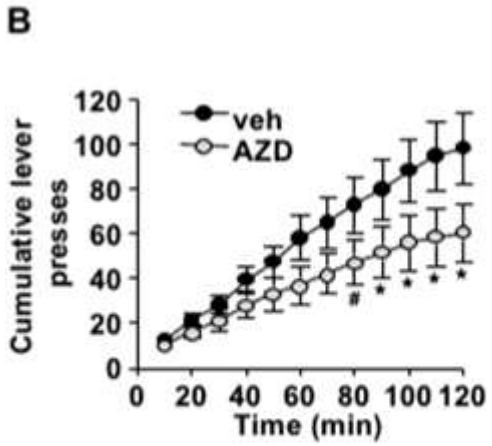


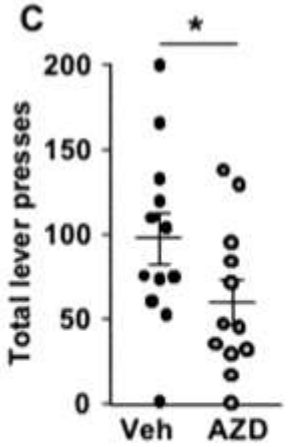
Specific epigenetic and synaptic dysregulation associated with heroin abuse linked to glutamatergic pathology may provide targets for treatment development

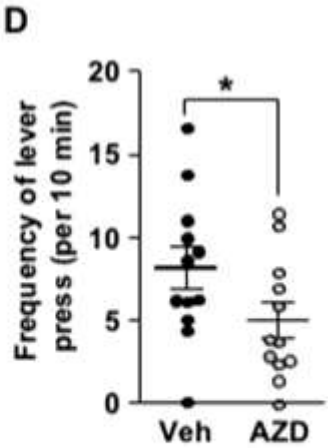
Egervari et al., Nature Commun. 2020

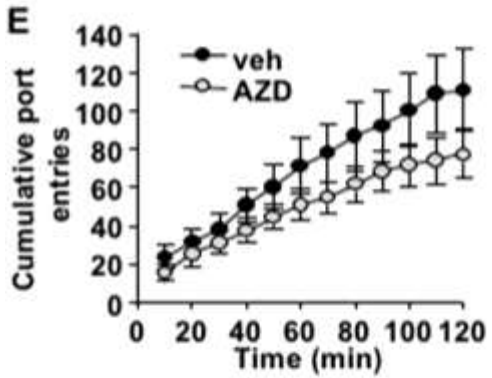
AZD0530 Reduces Alcohol Self-Administration and Seeking Behavior

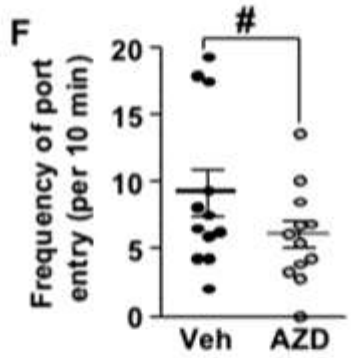


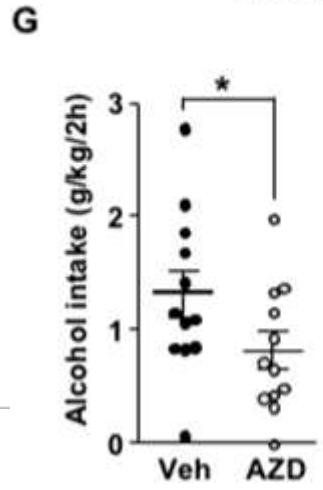


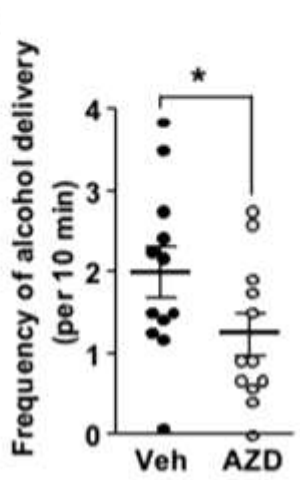












Morisot et al., Addict Biol, 1227-1234, 2019

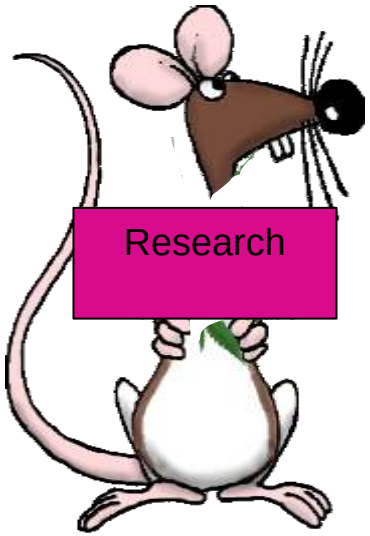
Treatment Development - Part III

Human molecular studies

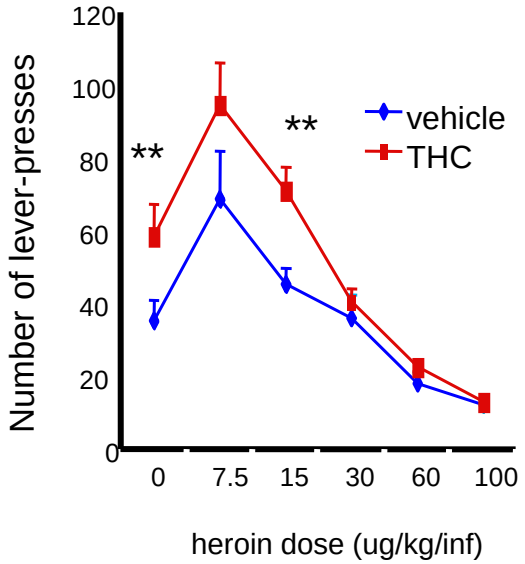
Preclinical Animal Models

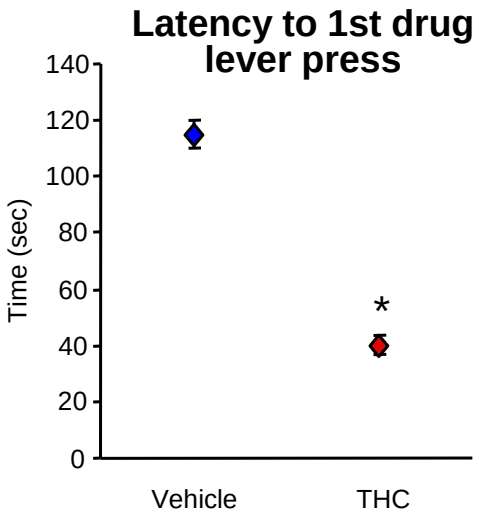
Neurobiological targets

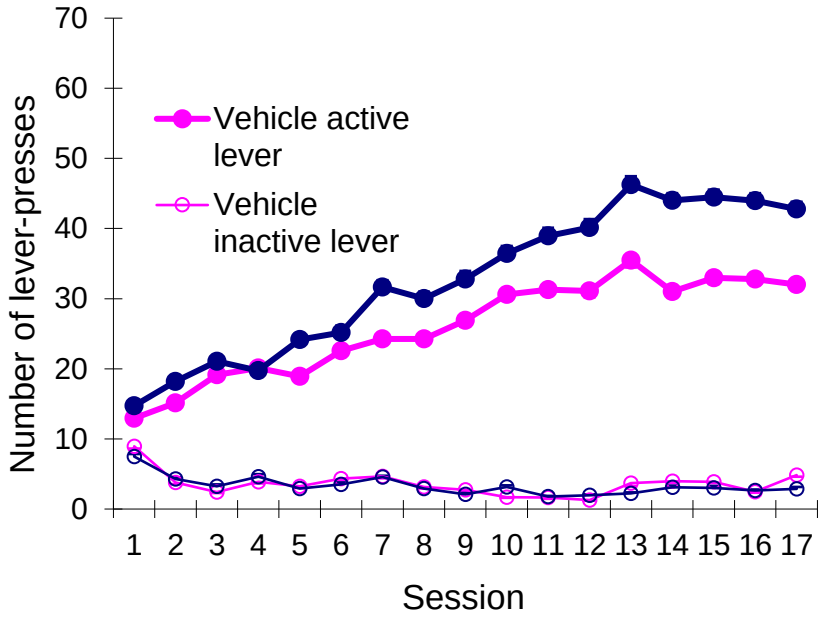
Clinical Studies



Developmental THC Exposure Increases Heroin Self-Administration in Adulthood





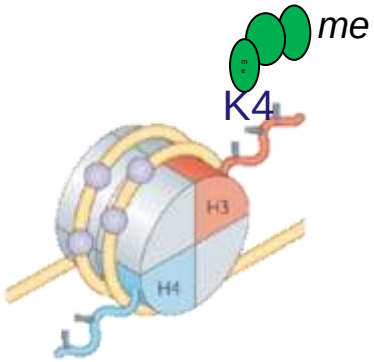


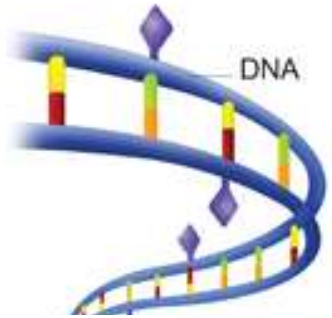
Epigenetic Mechanisms

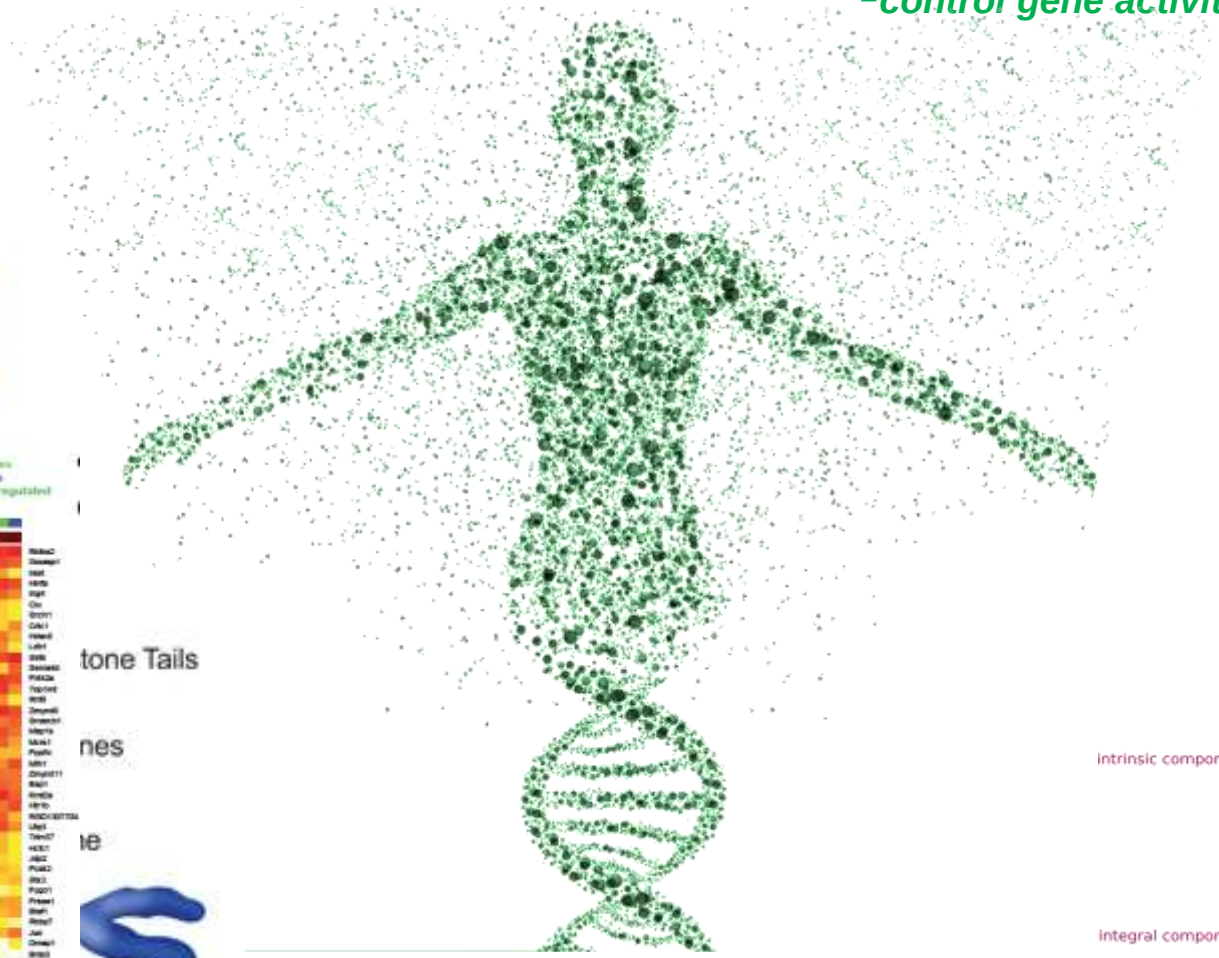
Prenatal and Adolescent THC exposures induce protracted alteration of epigenetic modifications

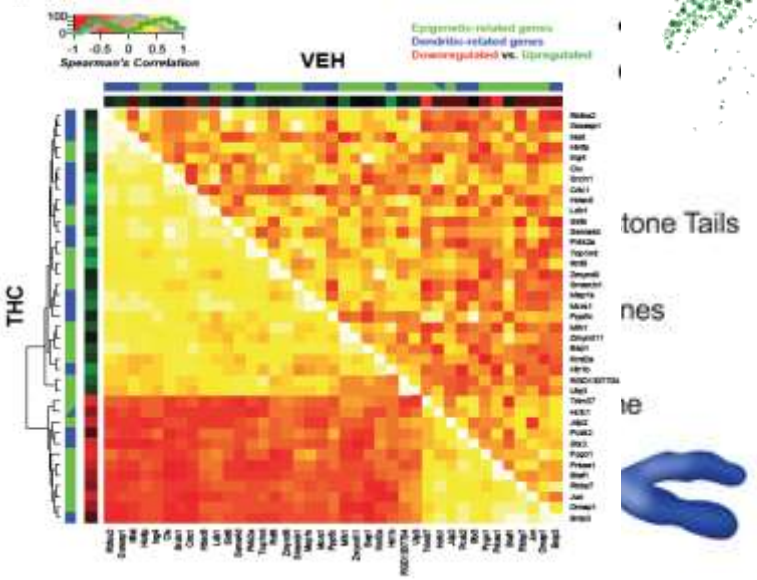
Environment

-control gene activity

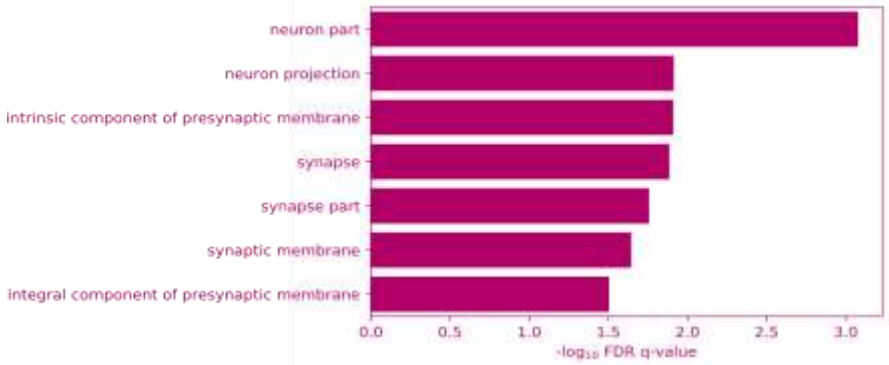




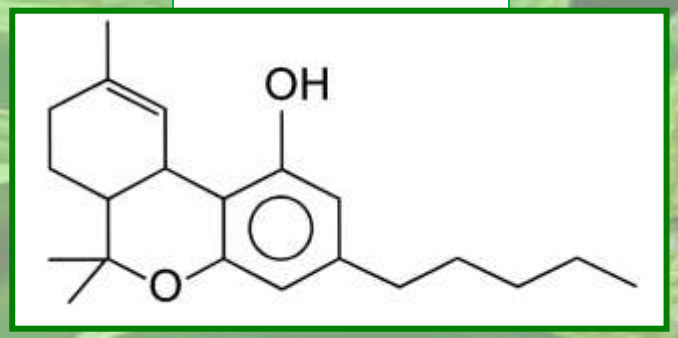




Synaptic Plasticity

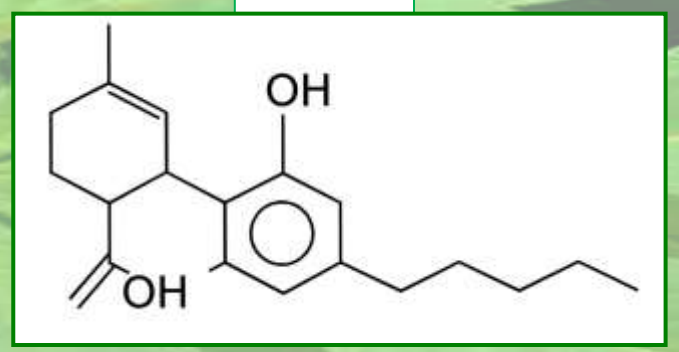


Δ^9-THC



Δ^9-tetrahydrocannabinol

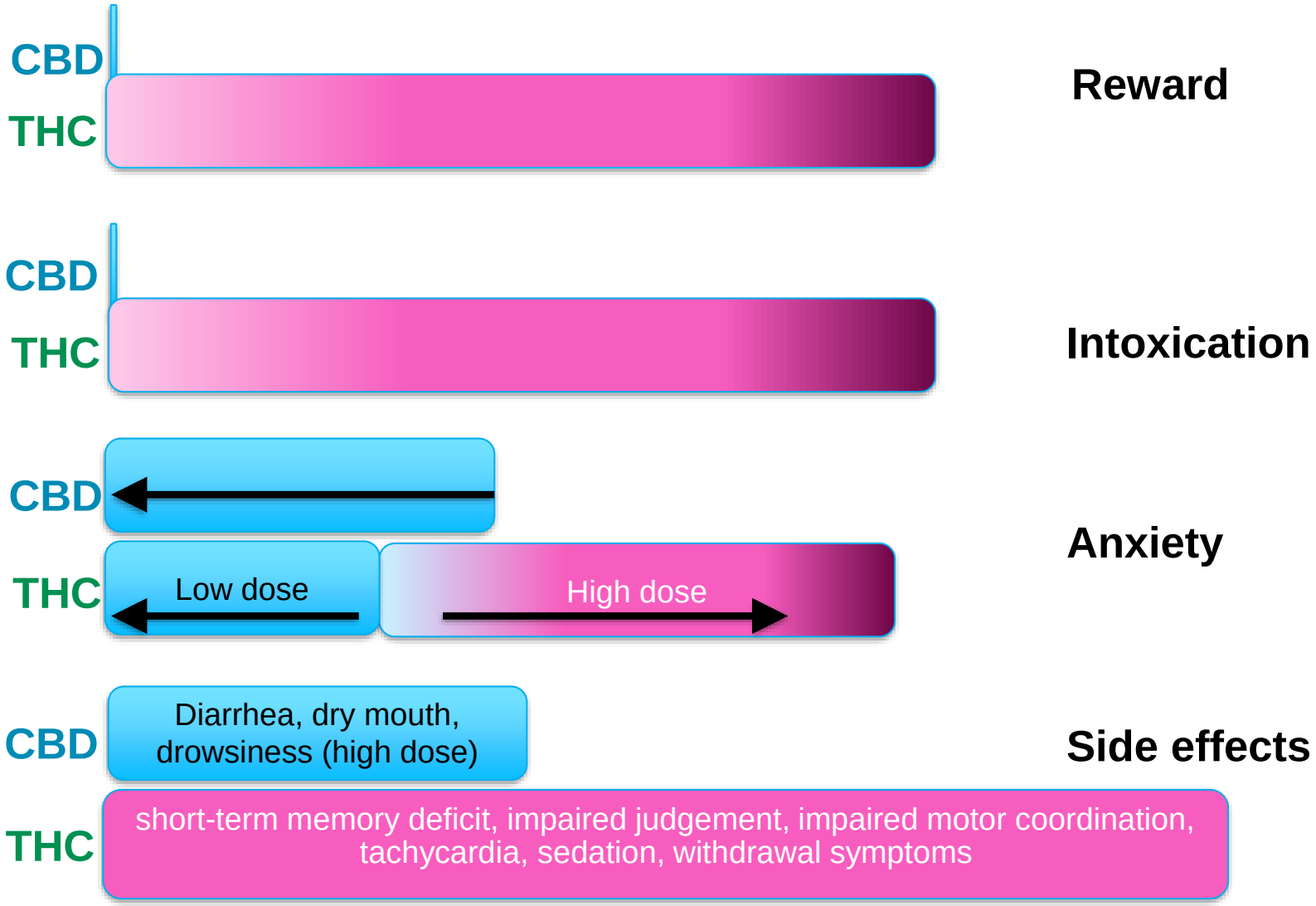
CBD



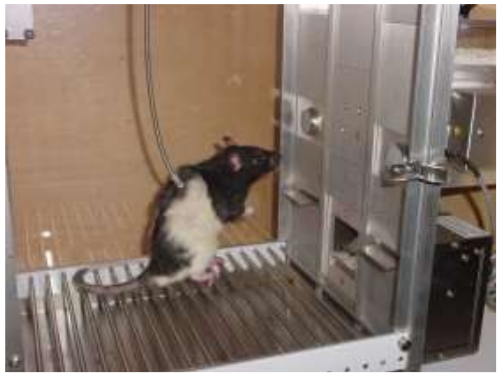
Cannabidiol

Cannabis contains over 500 chemicals including >140 cannabinoids which have a greater or lesser degree of psycho-pharmaco-activity

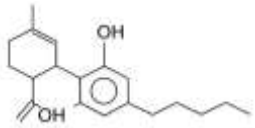
THC and CBD: Cannabinoids with Different Actions



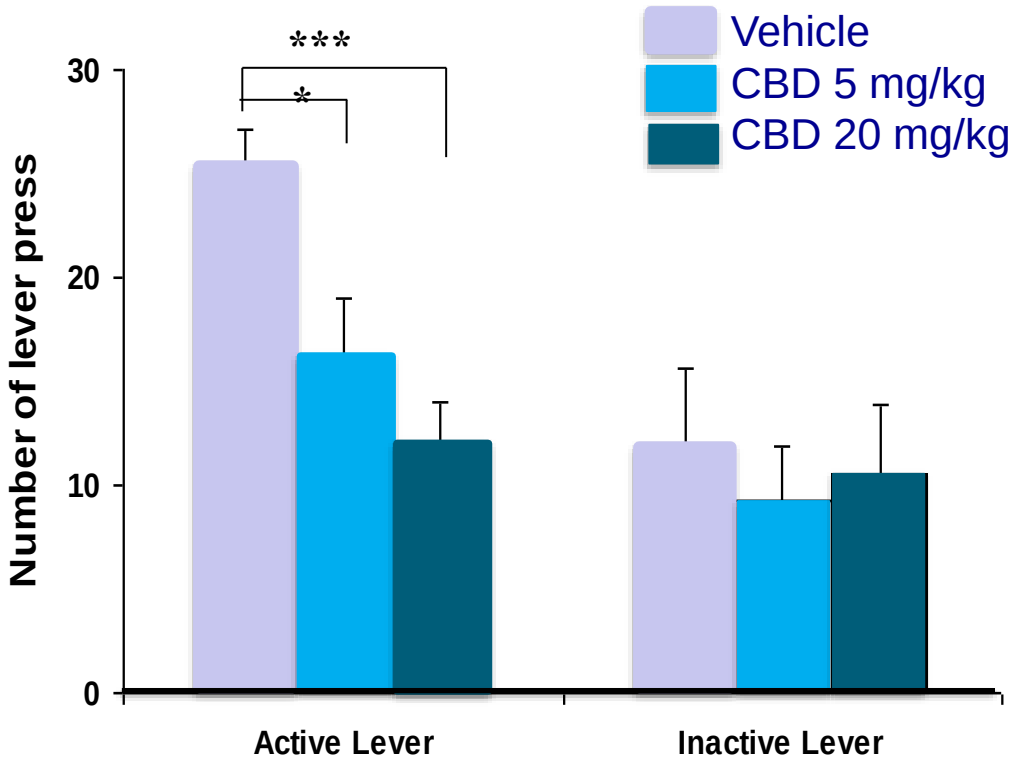
CBD Reduces Cue-induced Reinstatement of Heroin-Seeking Behavior



Cannabidiol



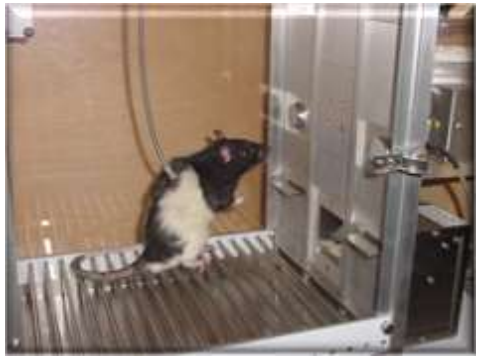
24hr prior to heroin reinstatement session



CBD

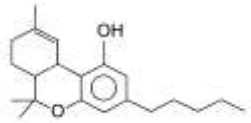
Initial training → Maintenance → Abstinence → Drug seeking

Ren et al, Journal Neuroscience, 2009

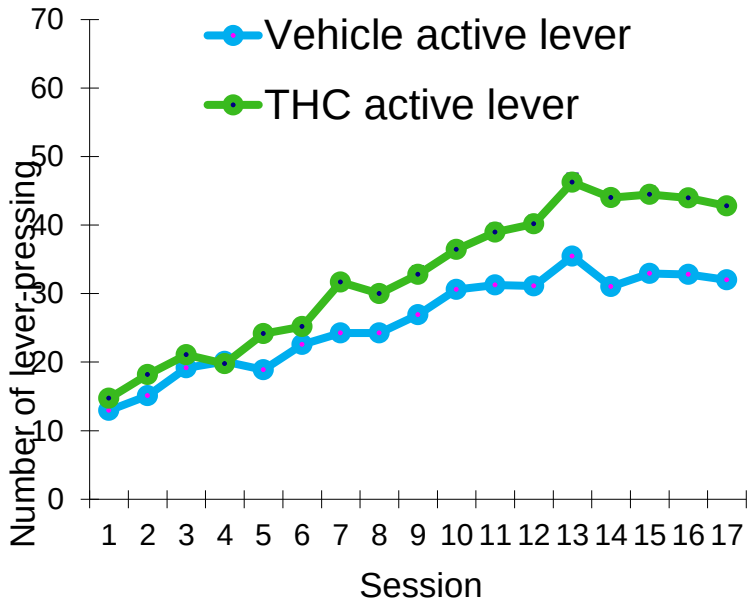


Distinct Effects of THC and CBD On Heroin Vulnerability

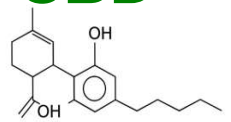
Δ^9-THC



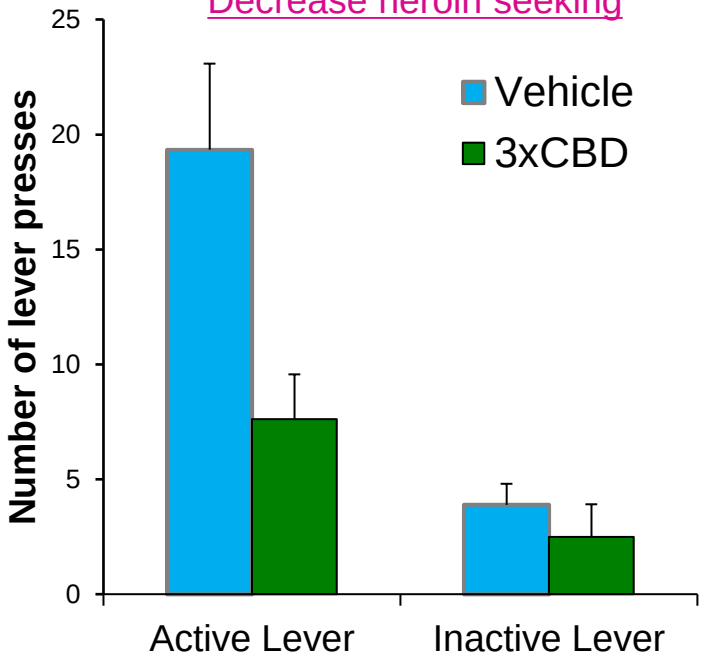
Enhance heroin self-adminstration



CBD

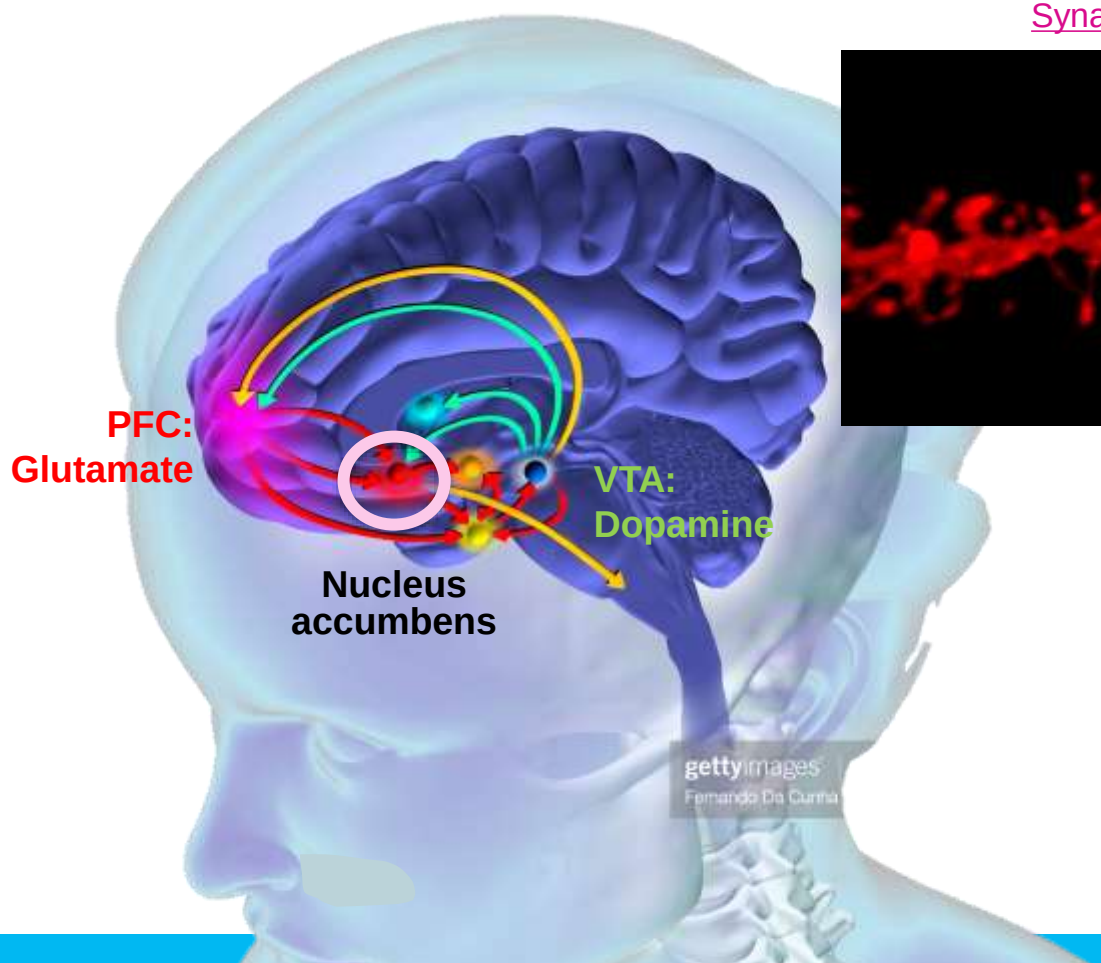


Decrease heroin seeking



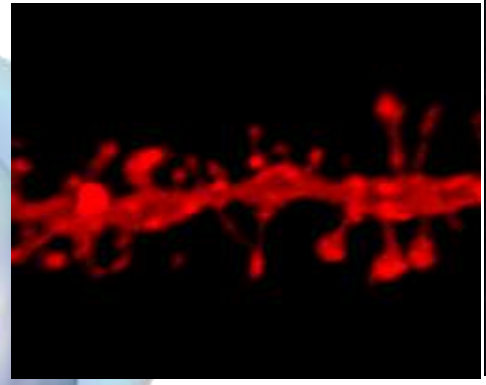
Heroin Abuse is Characterized by Impairments of Glutamatergic Transmission

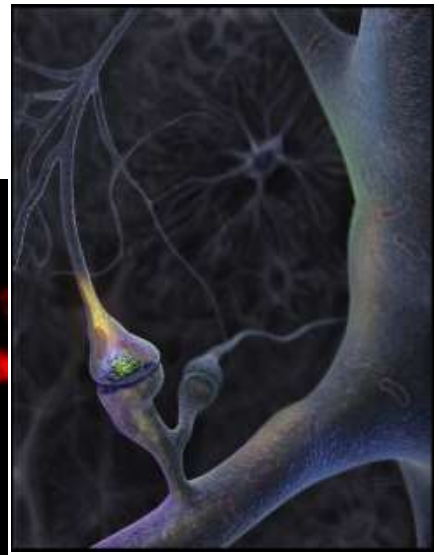
Dopamine – reward
Glutamate – excitatory neurotransmission; modulate reward system; drug seeking



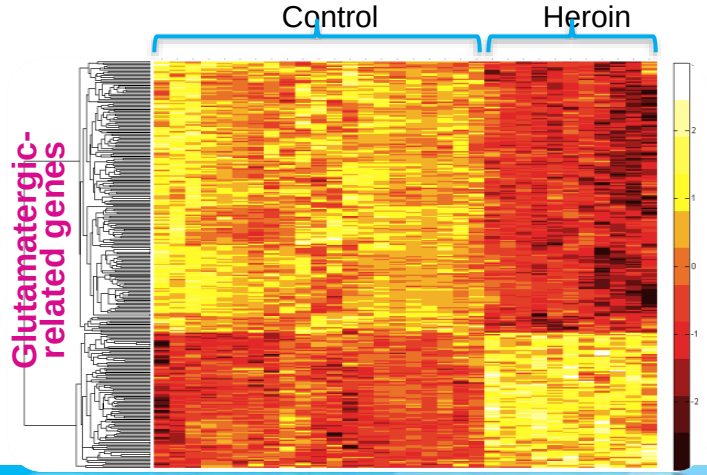
Nucleus accumbens

Synaptic plasticity

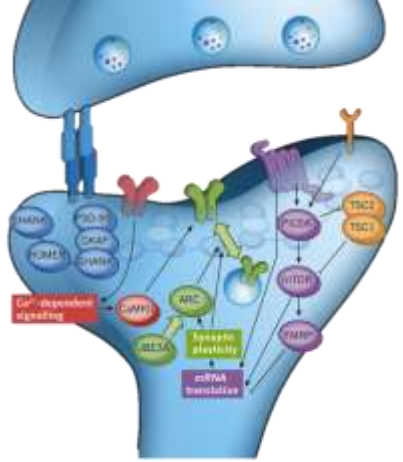


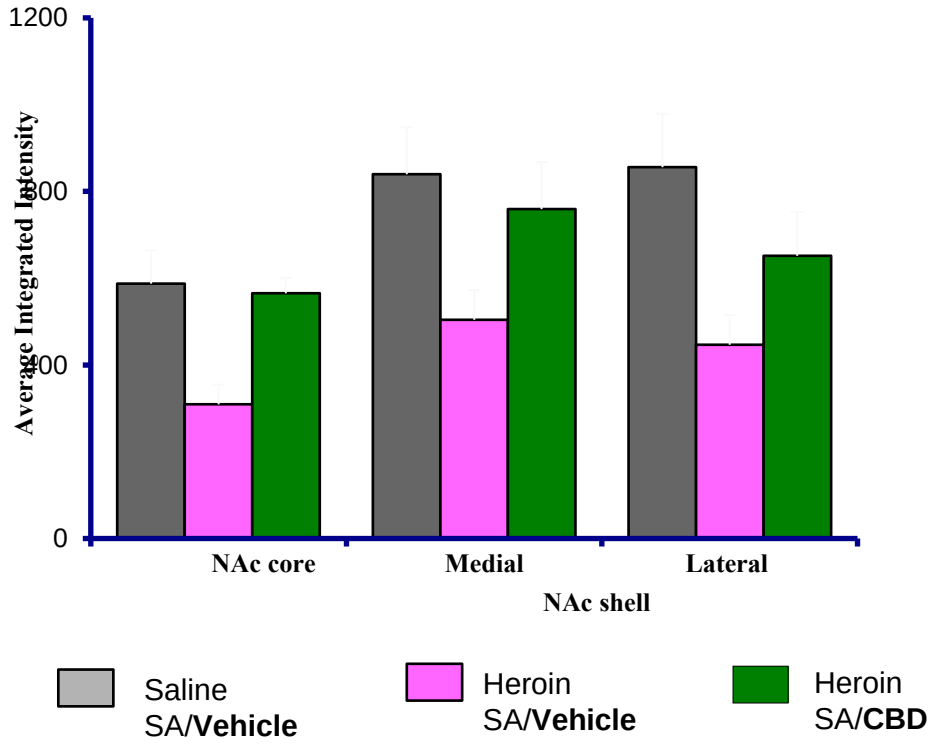


Gene transcription



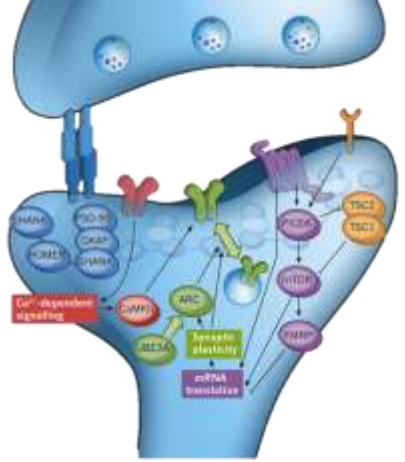
CBD Normalizes Heroin-Induced Alteration of AMPA Glutamate Receptor

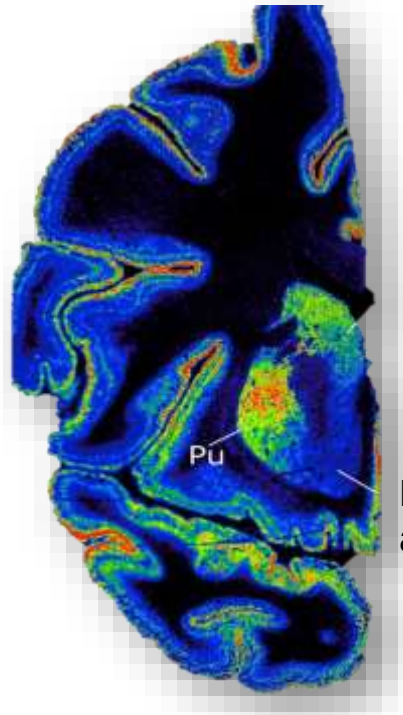




Ren et al, Journal Neuroscience, 2009

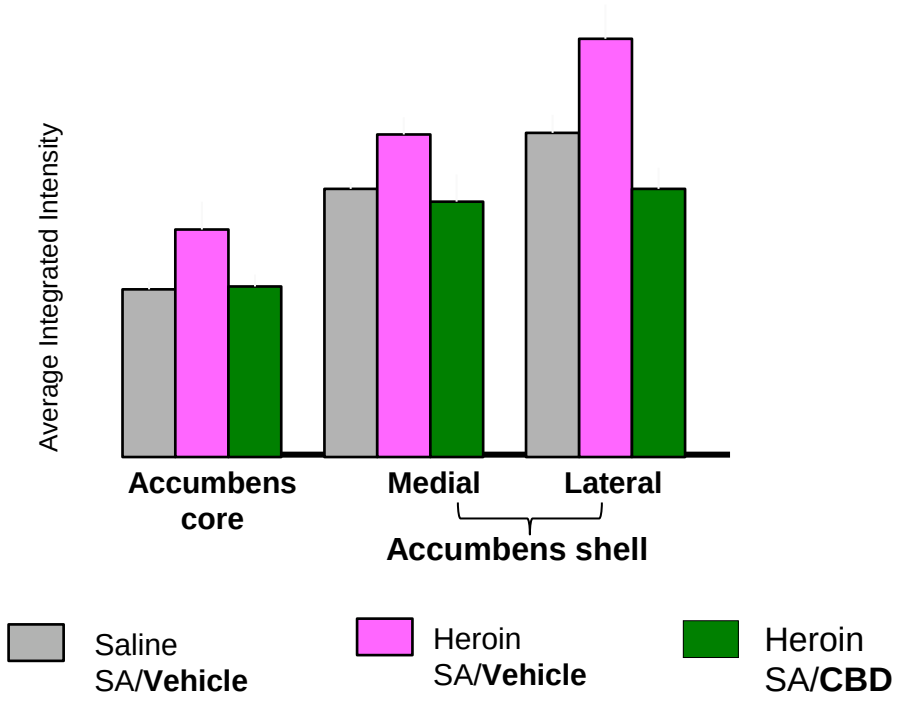
CBD Normalizes Heroin-Induced Alteration of the Cannabinoid CB1 Receptor





Nucleus accumbens

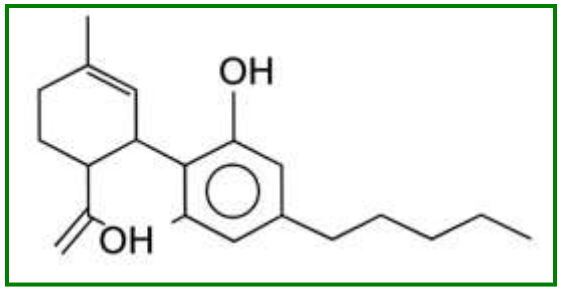
Ren et al, Journal Neuroscience, 2009



CBD promotes dendritic remodeling indirectly through CB_1 and/or CB_2 receptors and increases synaptic protein expression:
Fogaça et al., Neuropharmacology, 135:22-33, 2018.

Cannabidiol as Potential Treatment Intervention for Opioid Relapse: Double-Blinded Placebo Control Study

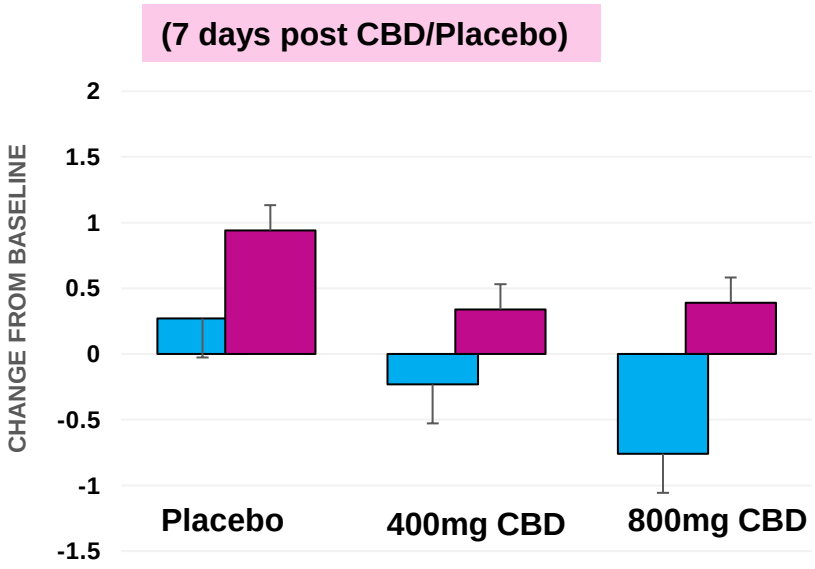
Double-blind, Randomized, Placebo-Controlled: Participants with Opioid Use Disorder



Prescreen tests	Session 1	Session 2	Session 3	Session 4
	Day 1	Day 2	Day 3	Day 10
	•CBD/Pl •Cue tests	•Cue tests •CBD/Pl	•CBD/Pl •Cognitive tests	•Cue tests

Cue-Induced Effects: Craving

VAS-C

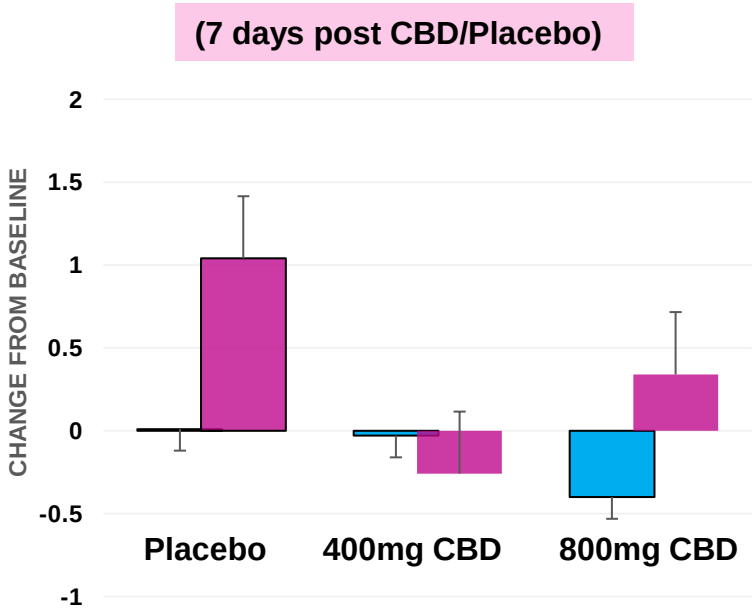


VAS, Visual analog scale

Hurd et al., Am J Psychiatry, 2019

Cue-Induced Effects: Anxiety

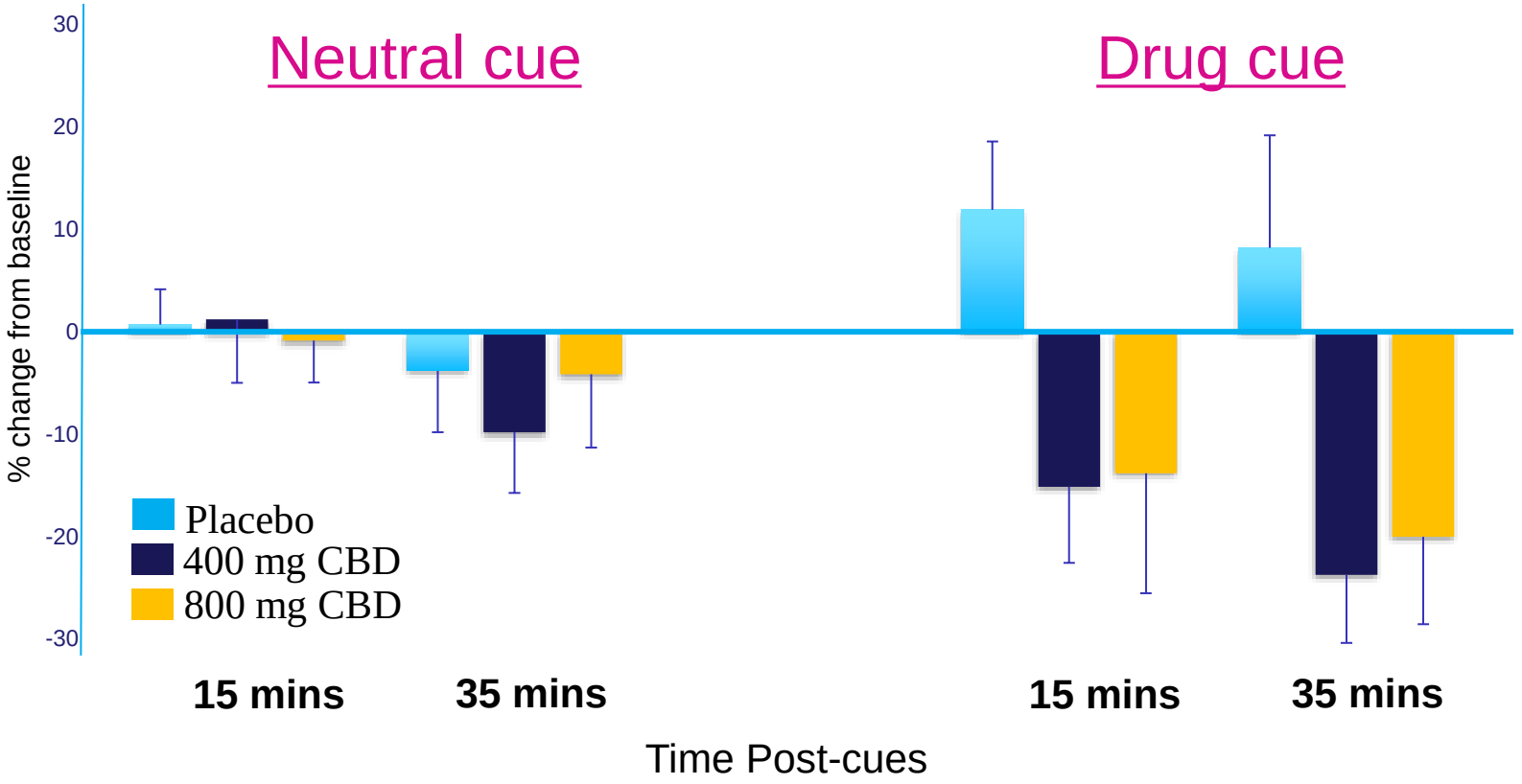
VAS-A



VAS, Visual analog scale

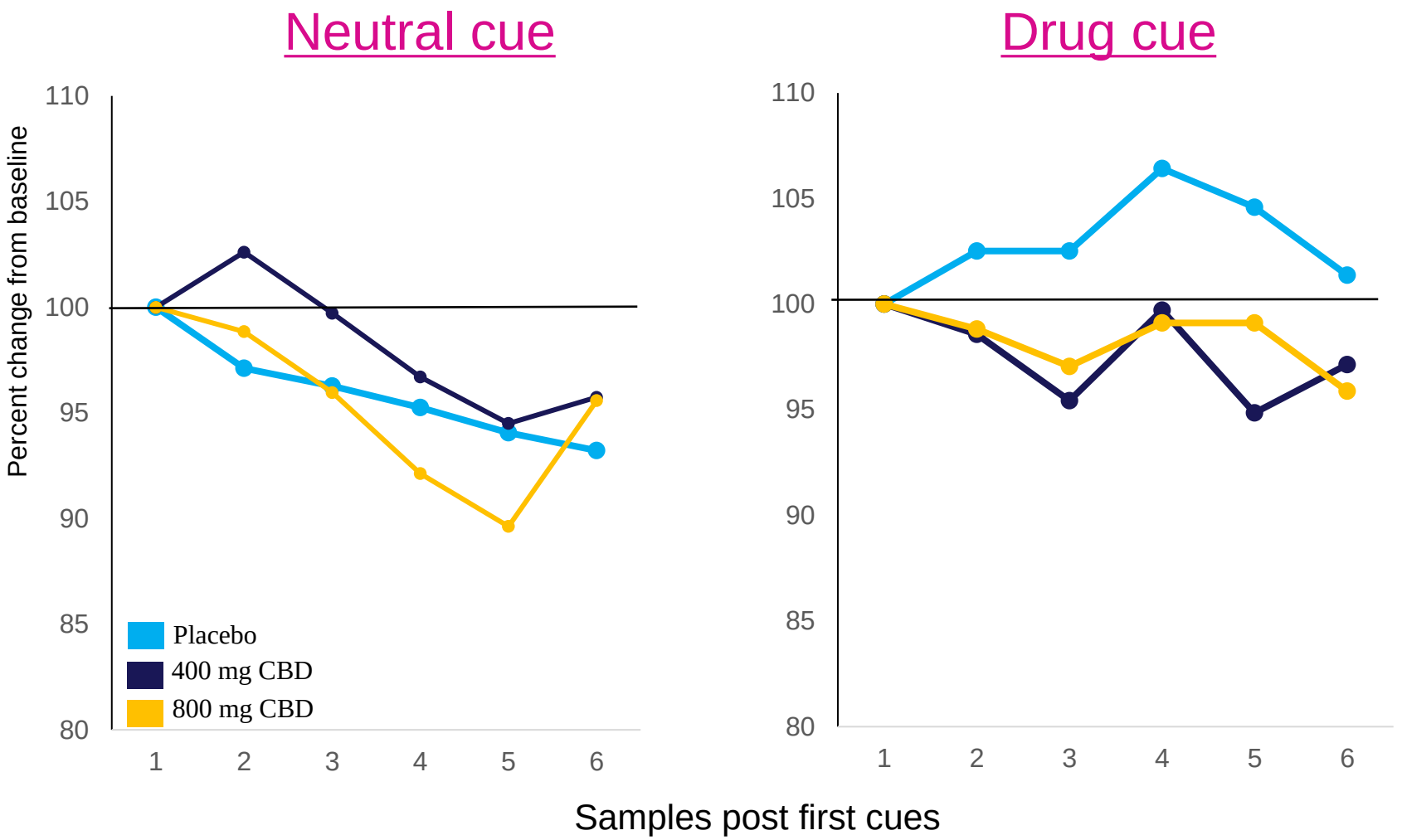
Hurd et al., Am J Psychiatry, 2019

Cannabidiol Reduces Cue-induced Physiological Measures of Stress – Cortisol Levels



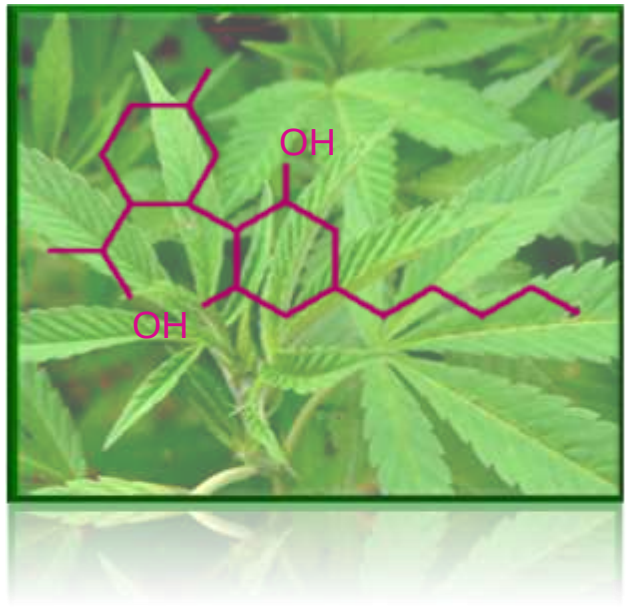
Hurd et al., Am J Psychiatry, 2019

Cannabidiol Reduces Cue-induced Physiological Measures of Stress – Heart rate



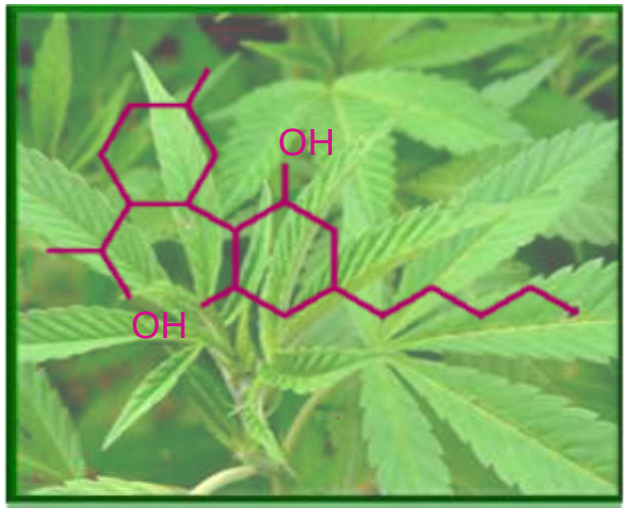
Hurd et al., Am J Psychiatry, 2019

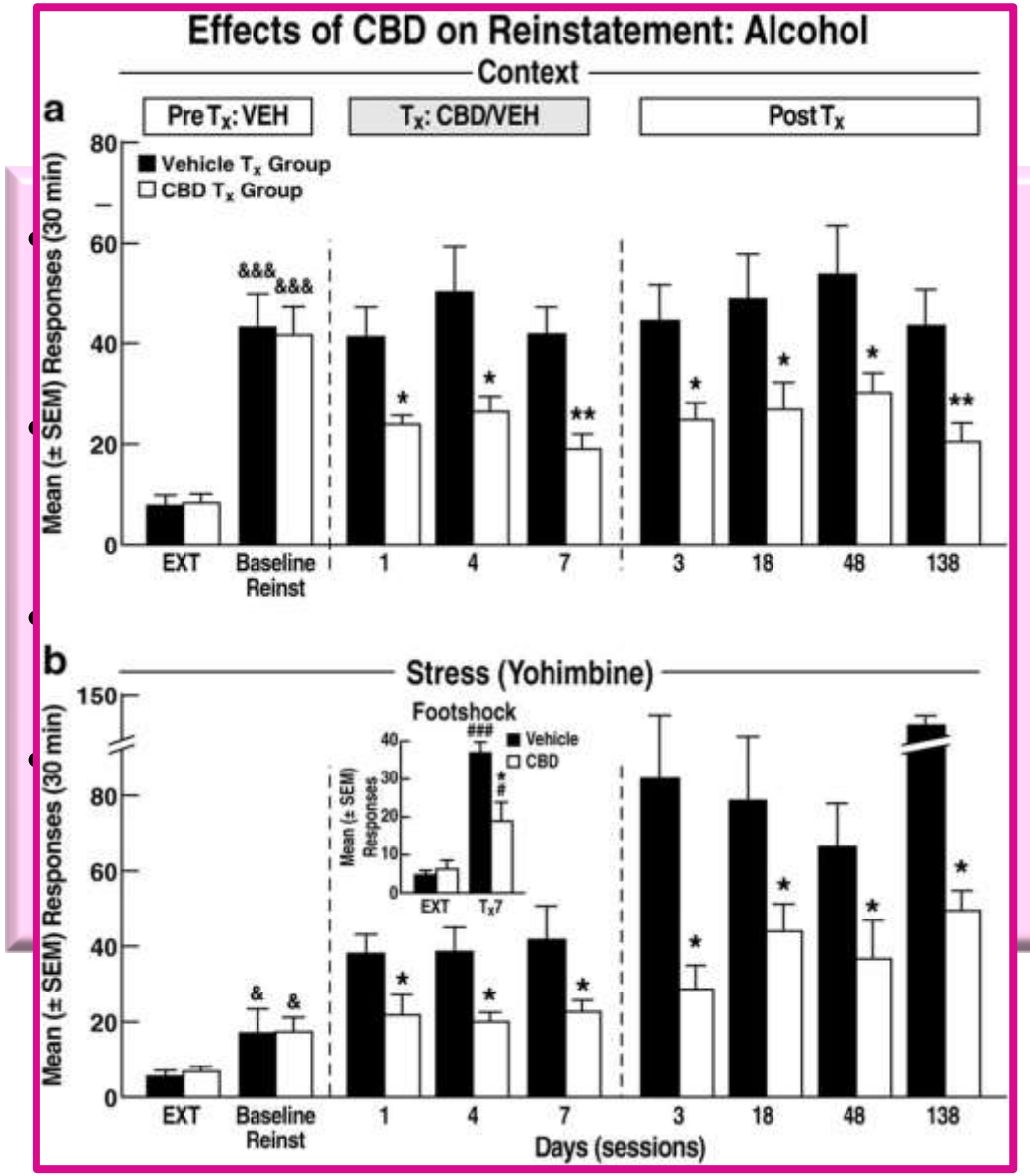
Medical Cannabidiol?



- **Cannabidiol holds promise for opioid use disorder treatment — *craving and anxiety***
- **Effective dose, treatment regimen….needs to be fully determined**
- **Treatment for specific features of OUD (and other substances)?**
- **Formulations/delivery systems need to be developed**

Medical Cannabidiol?





Gonzalez-Cuevas et al., Neuropsychopharmacology. 43:2036-2045, 2018

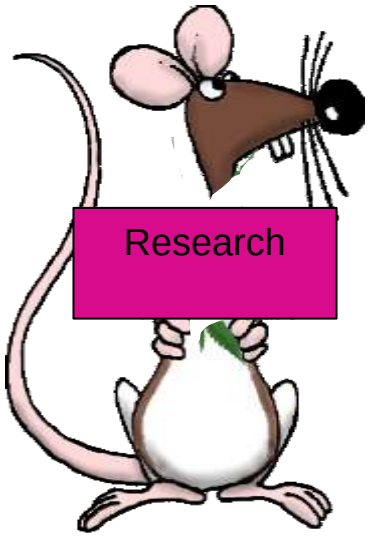
Treatment Development - Part IV

Human molecular studies

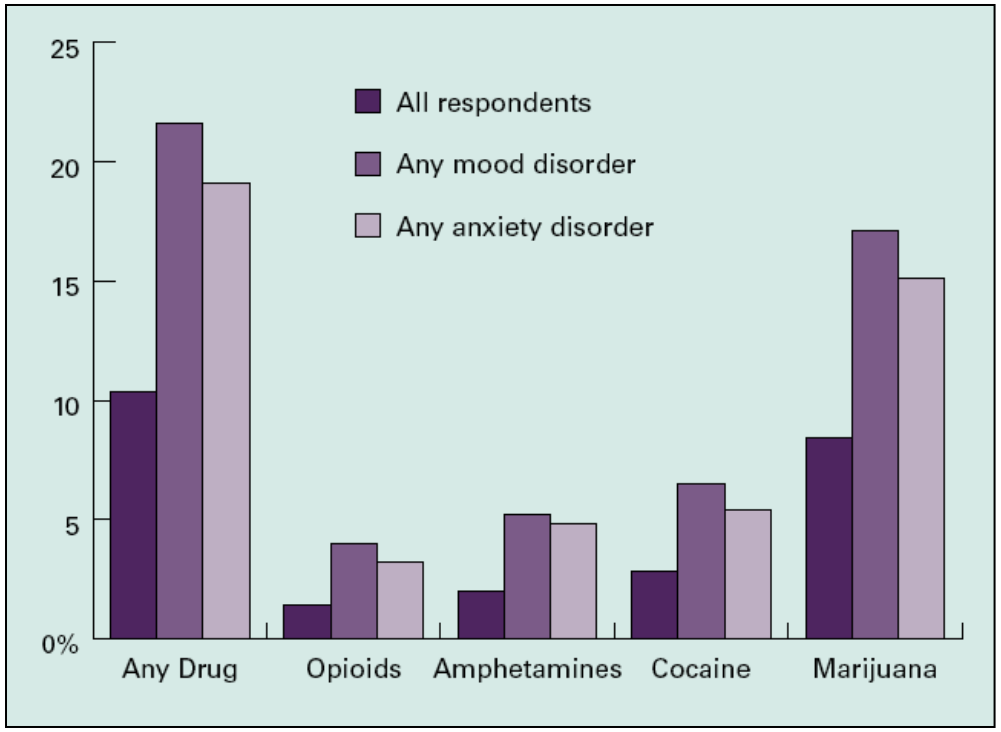
Preclinical Animal Models

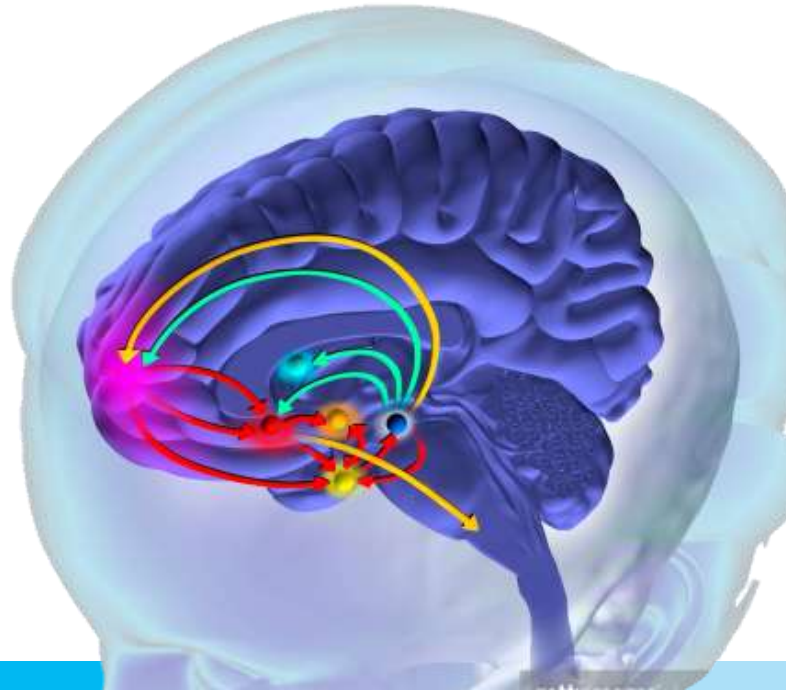
Neurobiological targets

Clinical Studies



Psychiatric Comorbidity with Substance Use Disorders

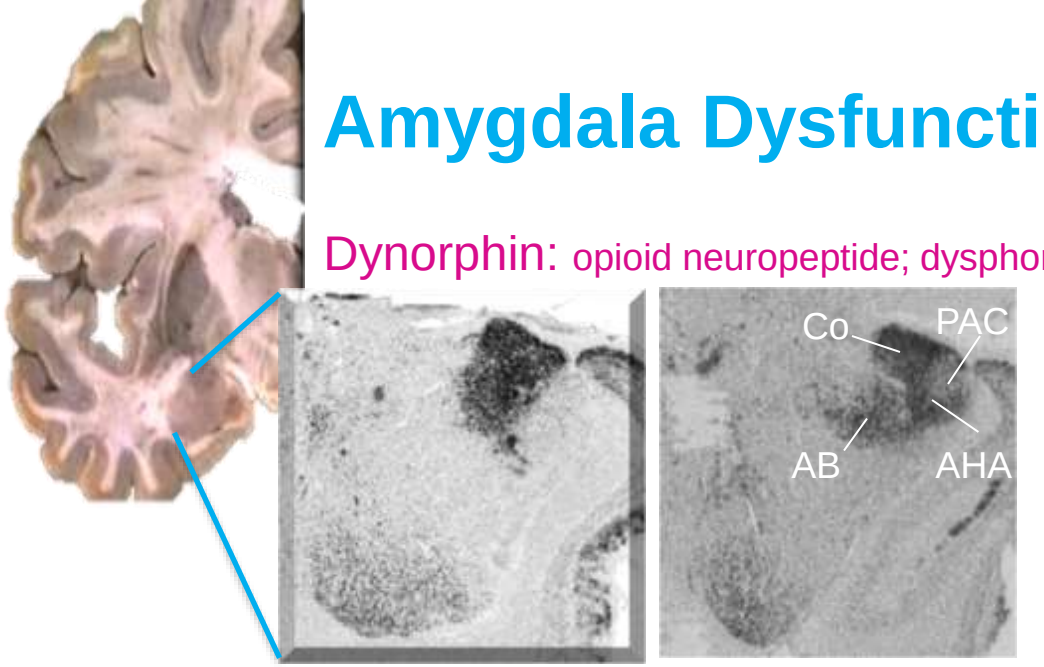




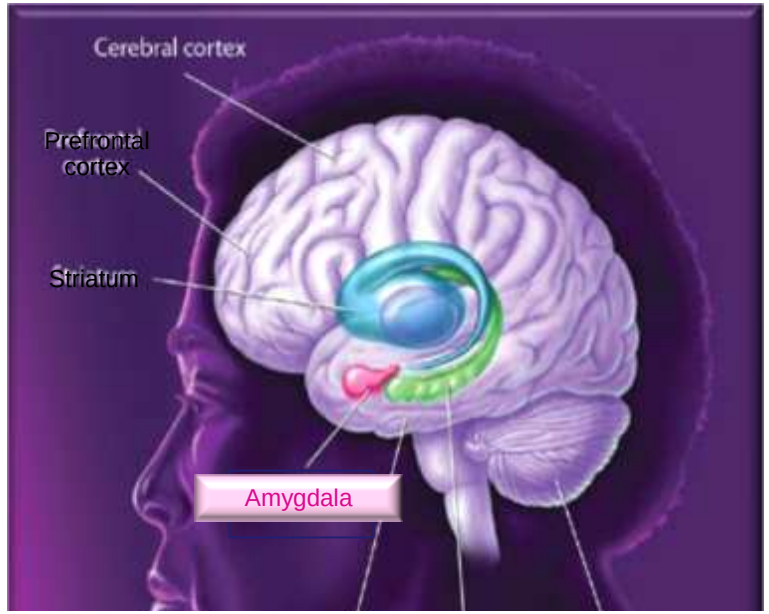
Anxiety and Major depression are the most common disorders comorbid with drug abuse (Conway 2006, NIDA 2010)

Amygdala Dysfunction in Psychiatric Disorders

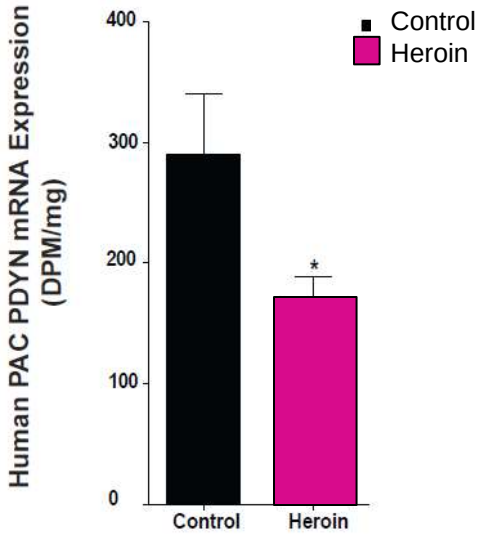
Dynorphin: opioid neuropeptide; dysphoria

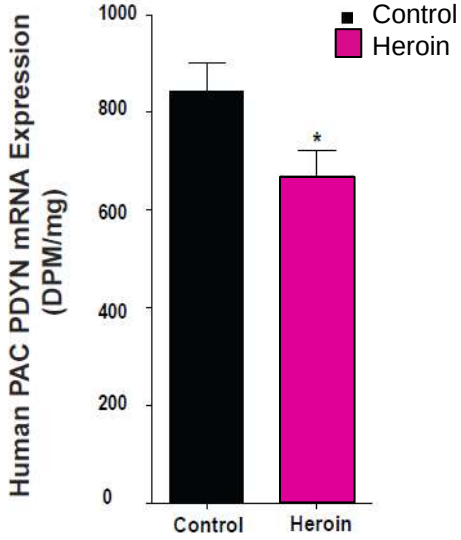


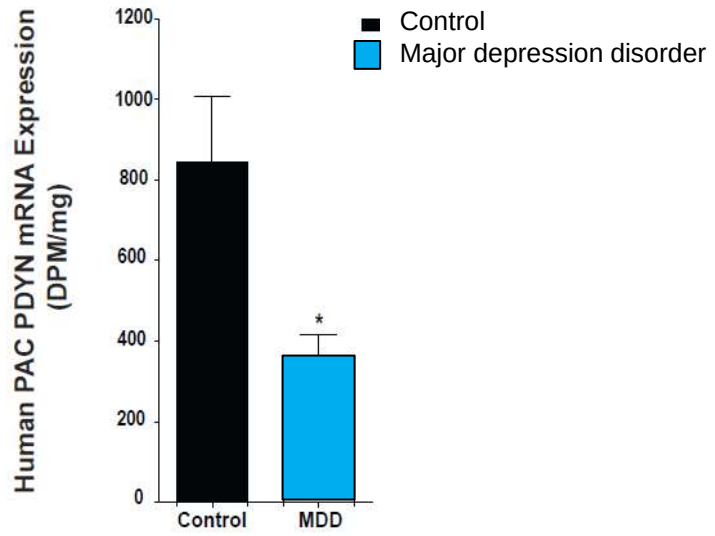
AHA = amygdalohippocampal area
AB = accessory basal nucleus
Co = cortical nuclei
PAC = periamygdaloid cortex



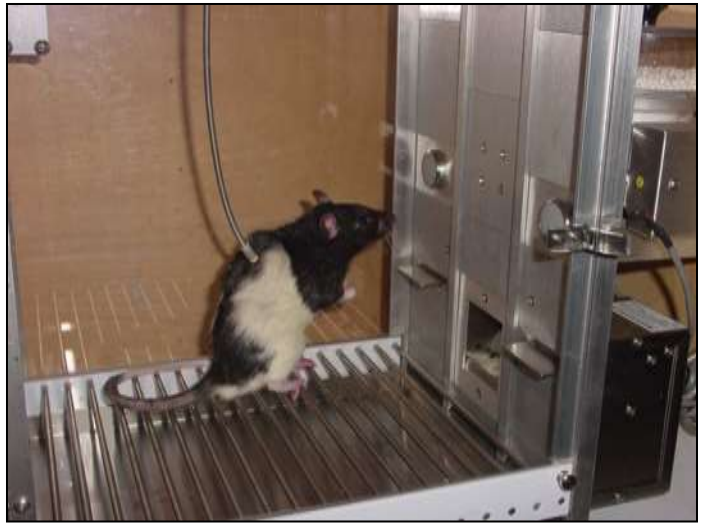
Anderson et al., J. Clinical Investigation, 2013

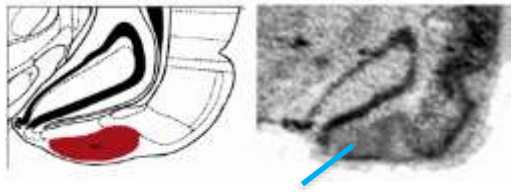






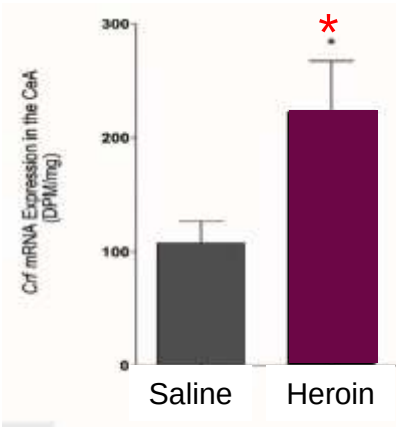
Prodynorphin mRNA in the Rat PAC is Reduced Following Heroin Self-Administration during the Acute Stress Withdrawal Period





Pdyn mRNA in PAC

Crf mRNA in CeA



24 hours after self-administration session

DREADD-Assisted Metabolic Mapping (DREAMM)

Map behavior to neurochemistry

Manipulate neurochemistry & behavior

Behavioral Imaging

(FDG-µPET)

^{18}F-fluorodeoxyglucose

DREAMM

Remote neuronal manipulation

(DREADD)

hM4Di – Gi coupled
CNO – clozapine-N-oxide

DREAMM: Whole-brain functional anatomy of PAC Pdyn-expressing cells

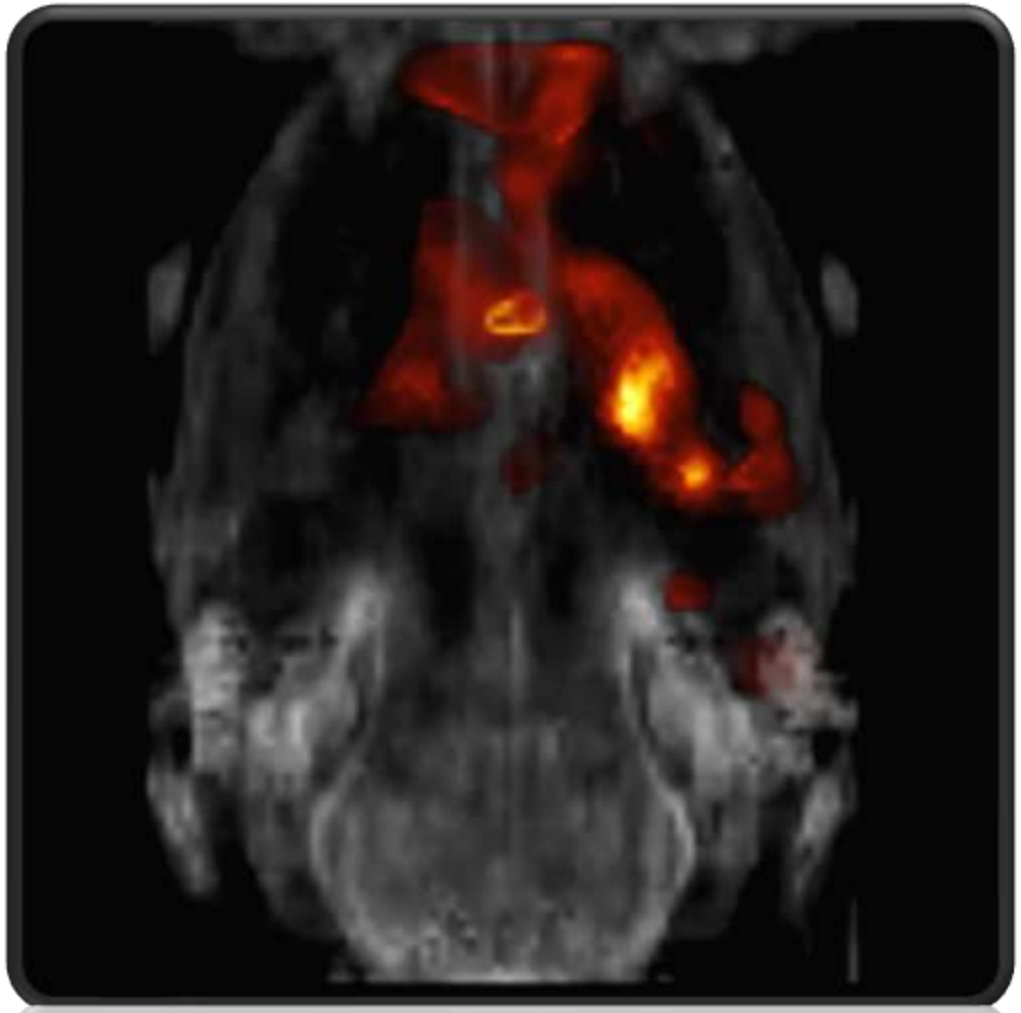
Viral vector

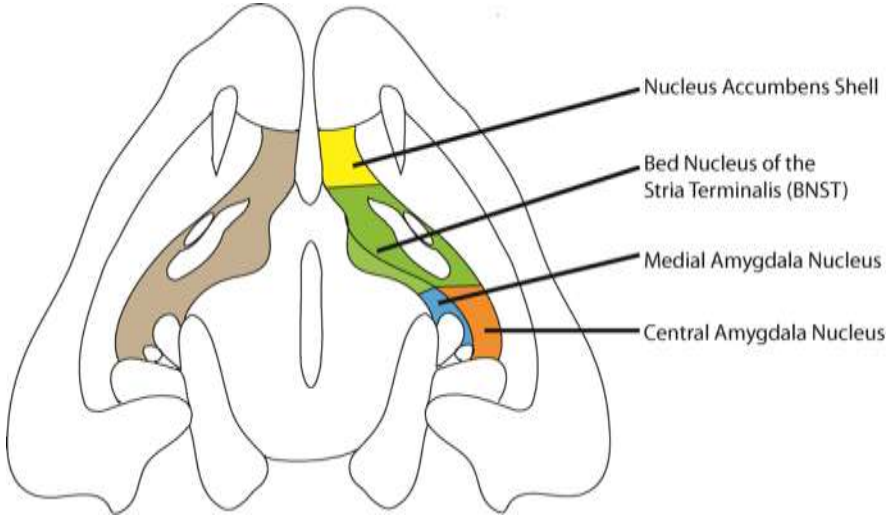
Inert agonist targeting the designer receptor

In vivo imaging

Michaelides et al., J Clinical Investigations, 2013

Chemogenetic inhibition of Prodynorphin Neurons in the PAC Activates the Extended Amygdala



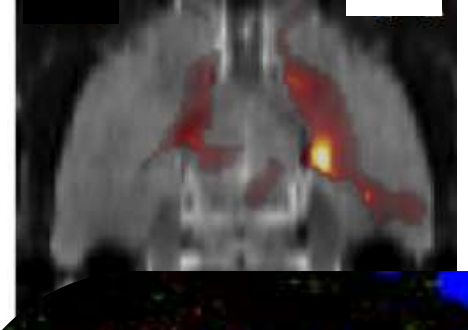


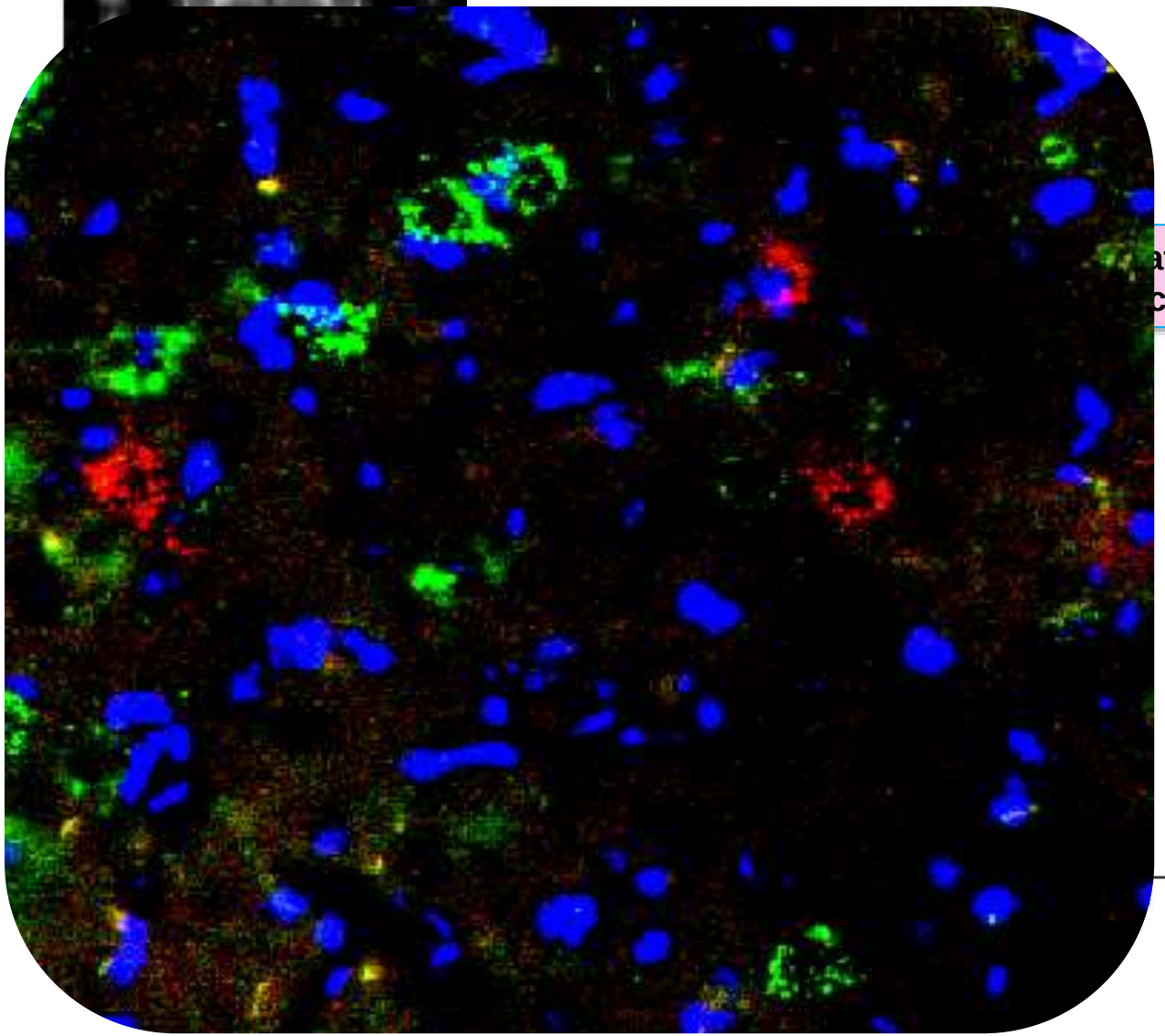
Central amygdala, bed nucleus stria terminalis and nucleus accumbens shell (L. Heimer & G. Alheid 1991)

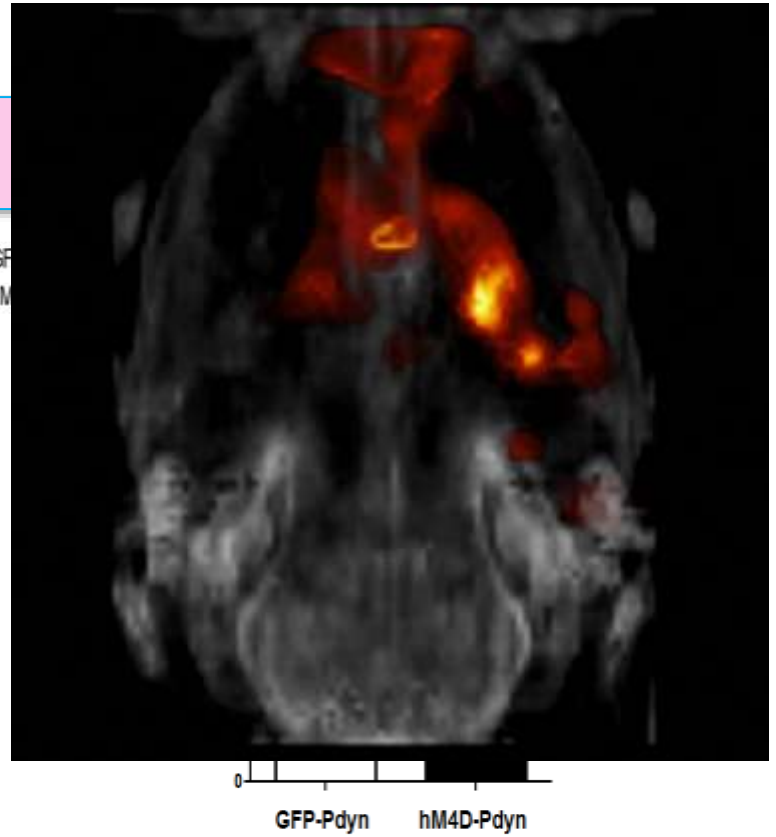
- Roles:
  - Adaptive motivational behaviors
  - Maladaptive response to fear, anxiety and stress
- Dysregulation of the extended amygdala has been implicated in psychiatric disorders

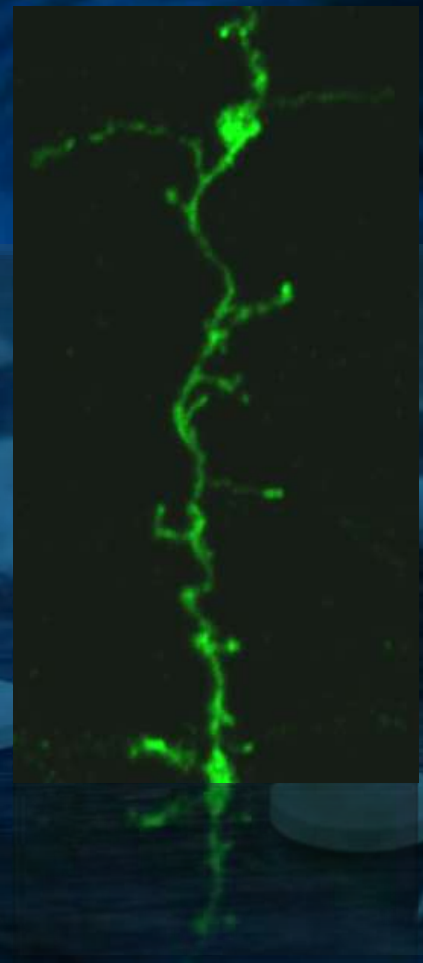
Anderson, Michaelides et al., J Clinical Investigations, 2013

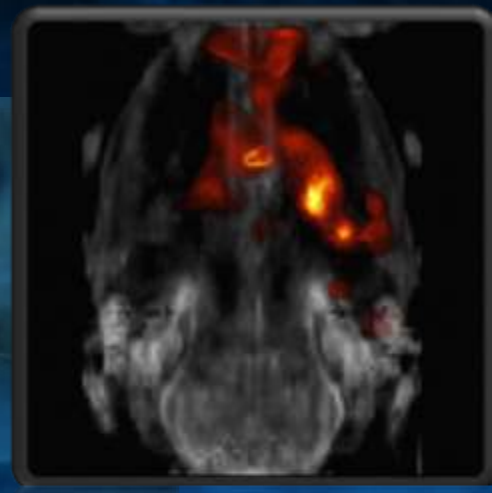
Inhibition of Prodynorphin PAC Neurons Enhance Physiological and Behavioral Measures of Stress and Negative Affect

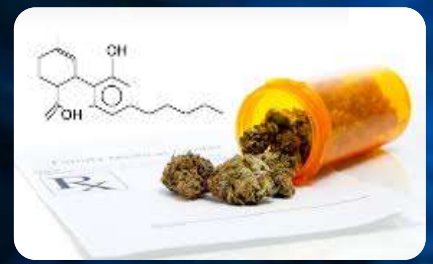








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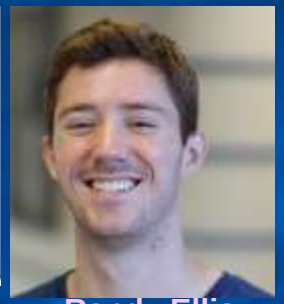
Queens College and Graduate Center, CUNY


Tanni Rahman


Diana Akpoyibo


Randy Ellis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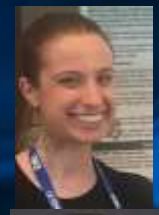
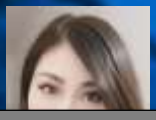
Gabor Egervari

Julia Alishayev
Gary Winkel, Kristina Gurgov, Chris Kudrich

Sharon Spriggs





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Teddy Uzamere


Micah Frier

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Chris Kudrich
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