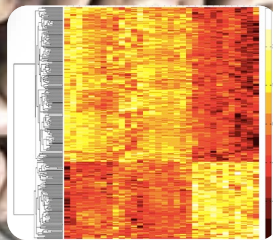
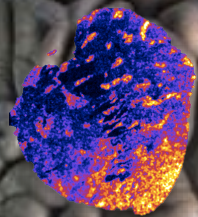
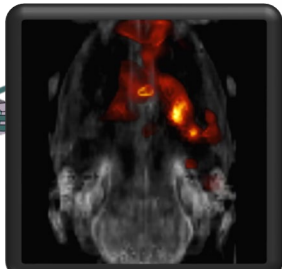


On the Path to Scientific Discoveries Forget the Stats

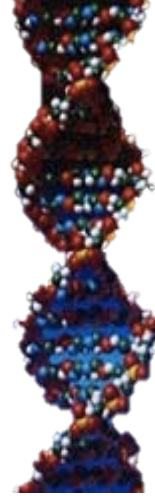


Yasmin Hurd
Ward Coleman Chair of Translational Neuroscience
Director, Addiction Institute, Mount Sinai Behavioral
Health System
Icahn School of Medicine at Mount Sinai
Professor, Depts Psychiatry, Neuroscience and
Pharmacological Sciences

Environmental factors



Genetics



Drug use

Behavioral traits/
Psychiatric comorbidity



Addiction risk

The Stats and Rules

Statistics in science is critical — rigor, experimental design, interpretation of data, etc.

Ignore statistics when pursuing a STEM path to be successful

Dogmas sets the principles of science

'Rules' can often block scientific inquiry and prevent venturing down certain scientific paths; they produce herd mentality where individuality is penalized



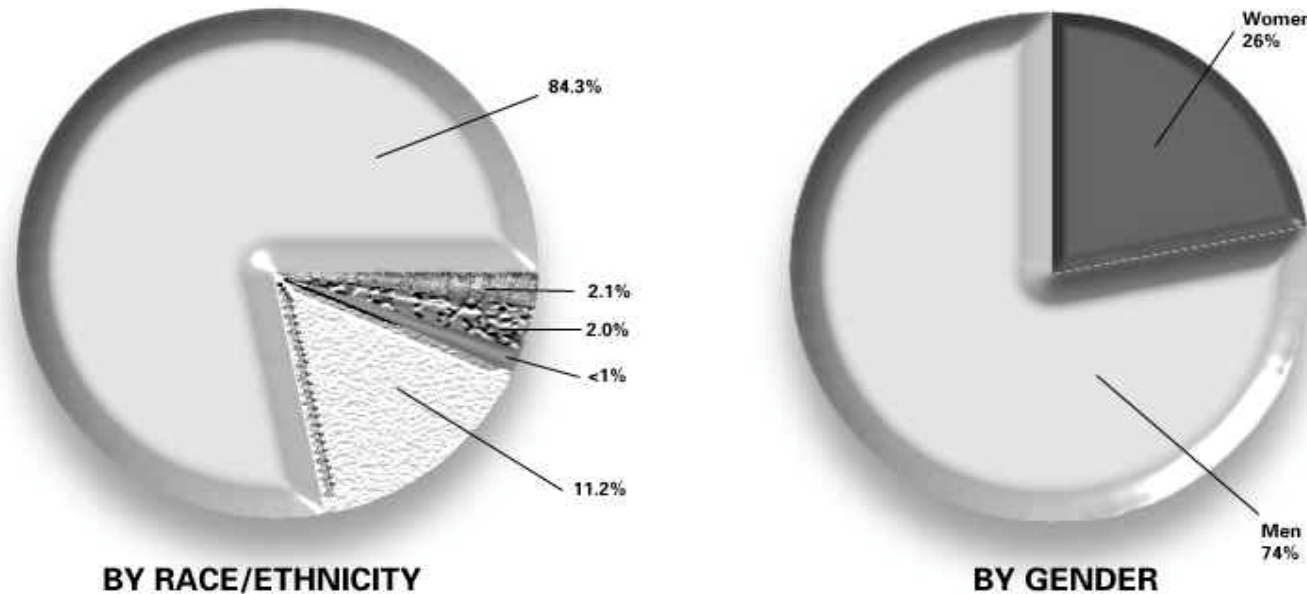
The enemy of science is not religion... . The true enemy is the substitution of thought, reflection, and curiosity with dogma.

Frans De Waal

The Stats: Gender and Race in Academic STEM Careers



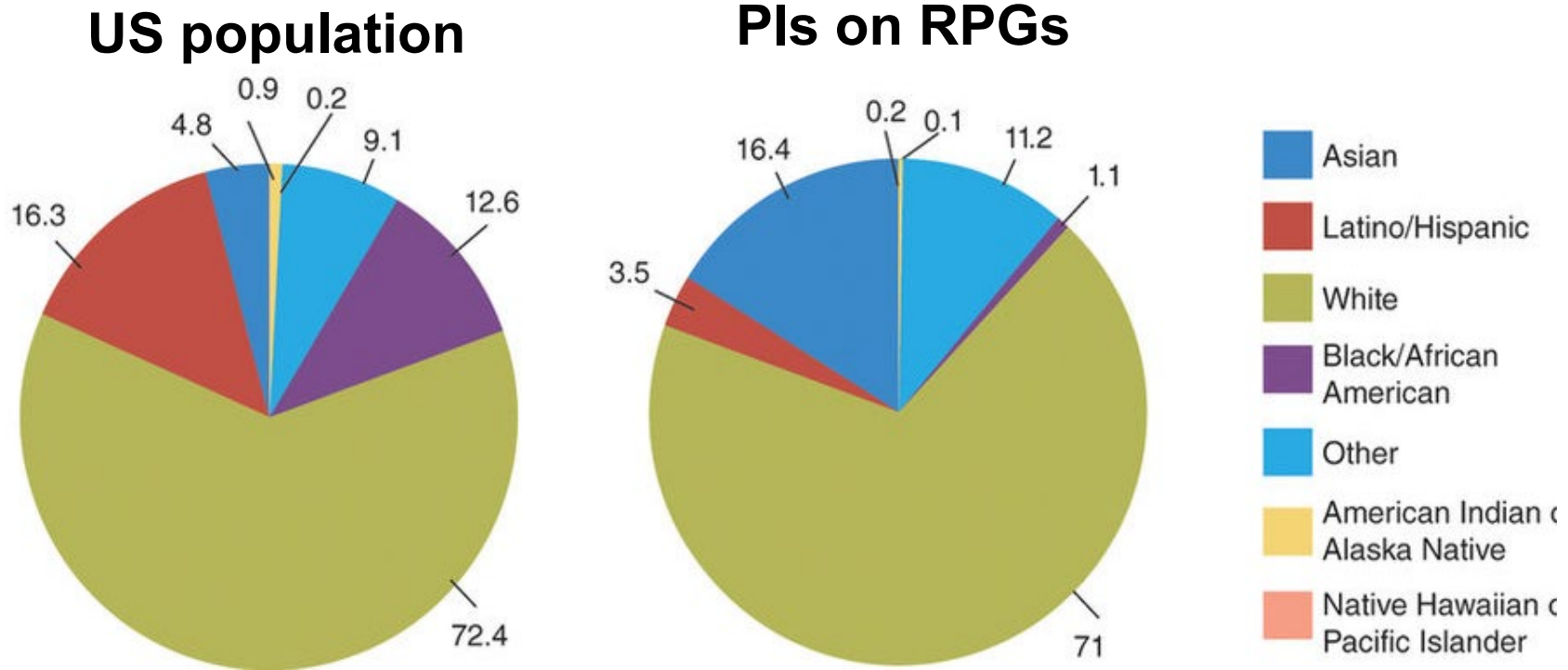
DOCTORAL SCIENTISTS AND ENGINEERS IN THE U.S. LABOR FORCE



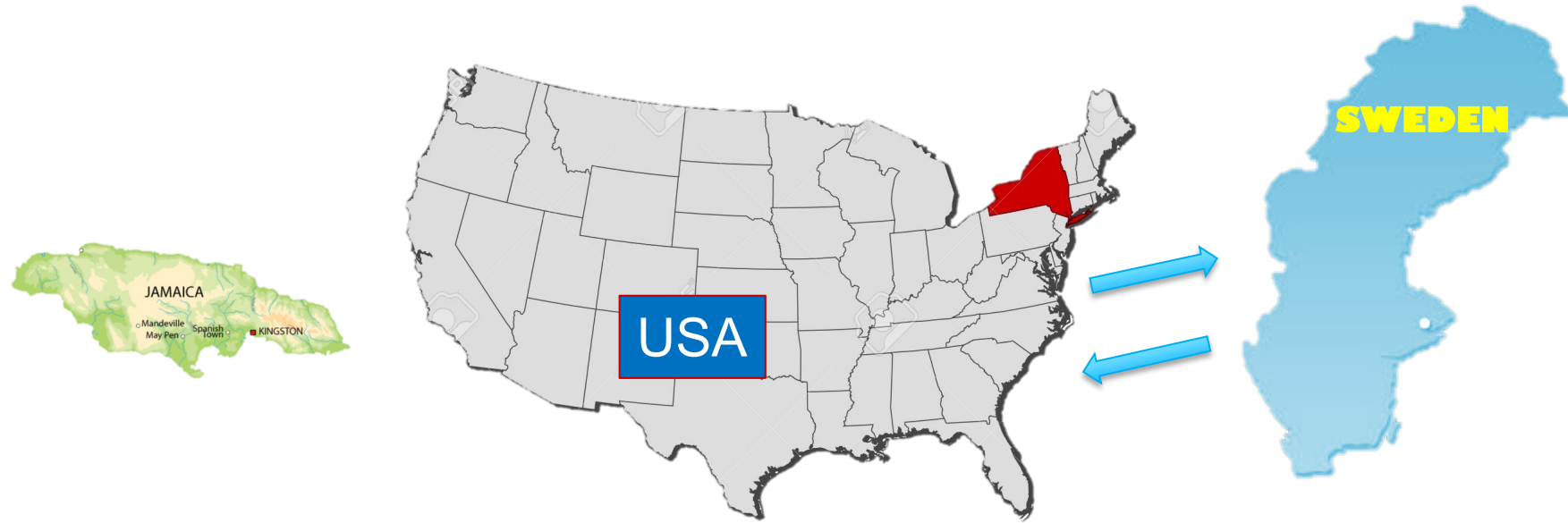
The Scientist: source NSF's "Women, Minorities, and Persons with Disabilities in Science and Engineering: 1996,

The Stats: Race and Ethnicity of NIH PI Grants

Race and ethnicity US population and NIH principal investigators (PIs) of research project grants (RPGs)



My Path

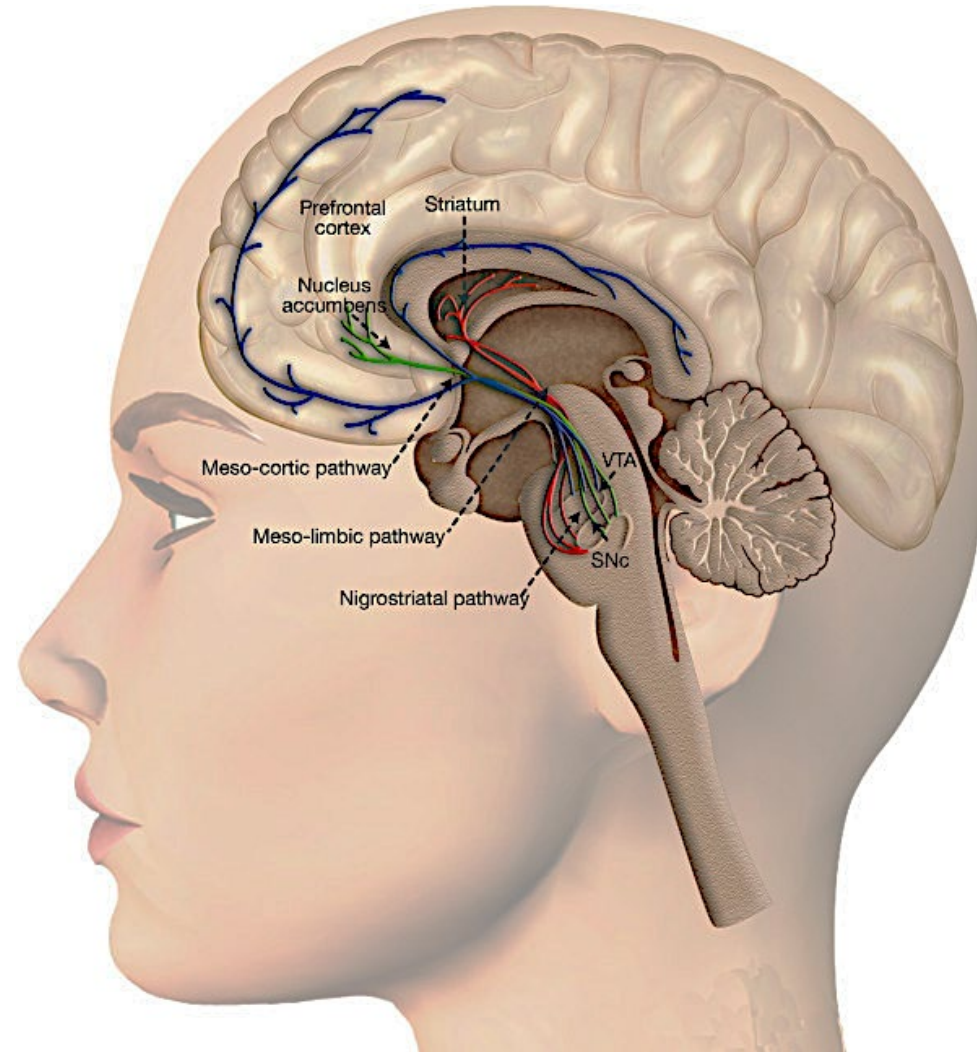
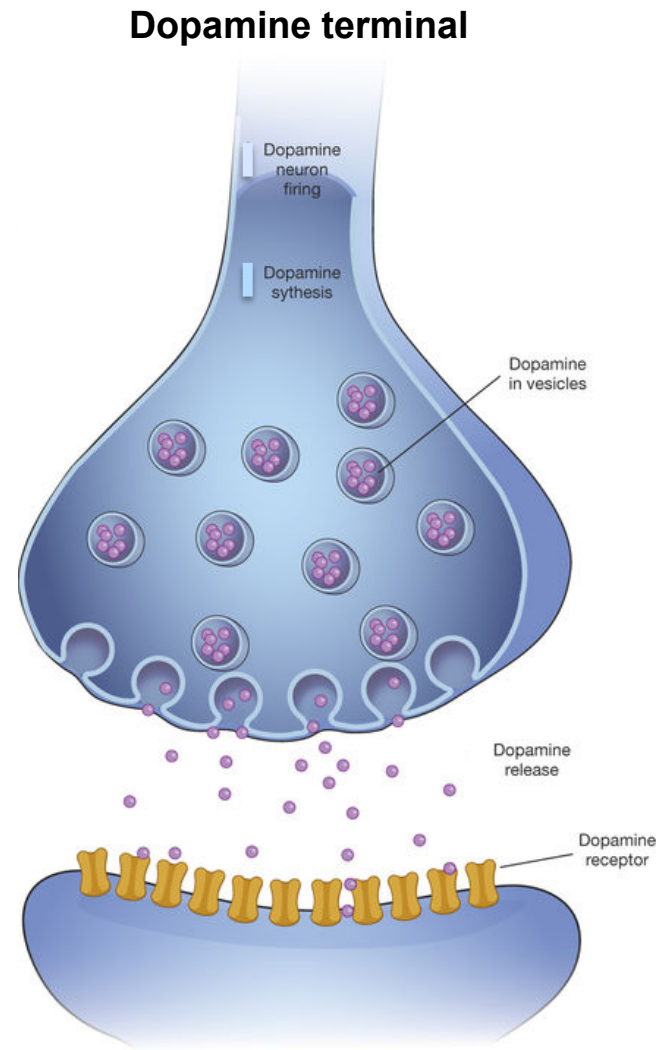


Being different is challenging, but being (and thinking) outside the box can advance your science

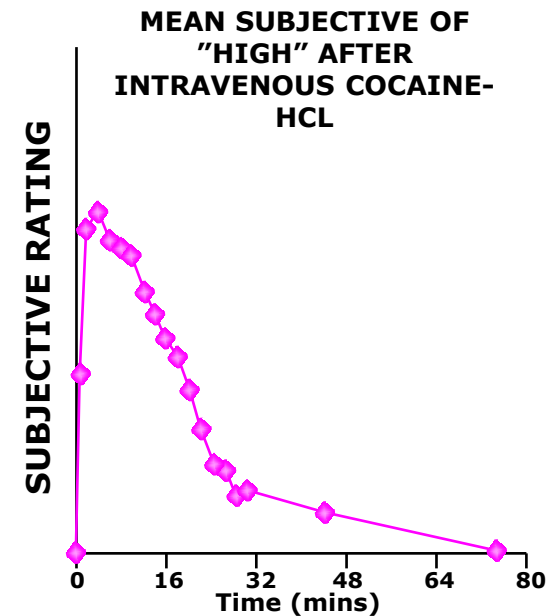
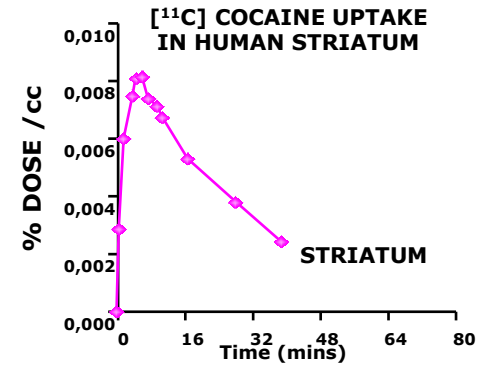
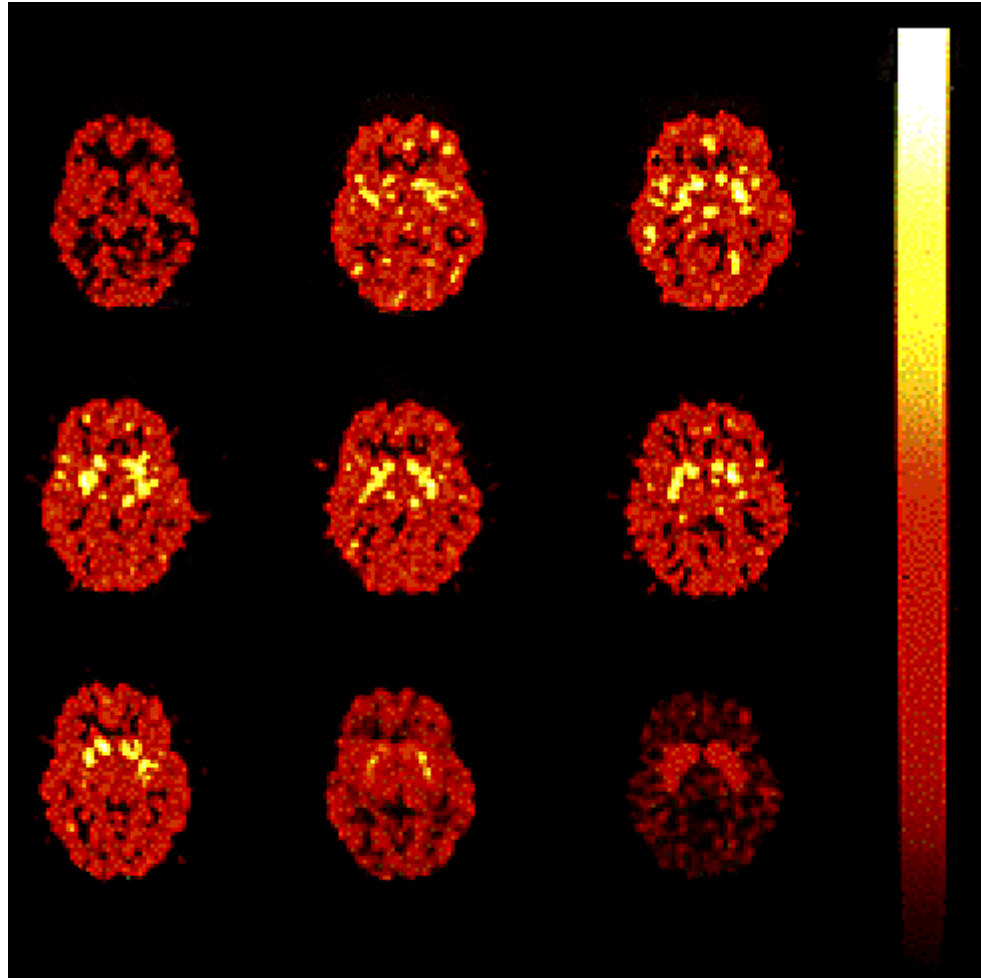


- **Visibility**
 - Fine to be different since I was supposed to be different
 - Be comfortable in your own skin
- **Oblivious to the rules**
 - I did not put myself in a box [*because I did not know the cultural rules*]
- **Ignore negative biases**
 - Focused on my research rather than to listen to the negative outside noise that would not bring success
- **Focus on the biases that work in your favor:** “You are American and therefore must be the **best**”
 - live up to **positive expectations** rather than struggling to push off the heavy weight of the negatives

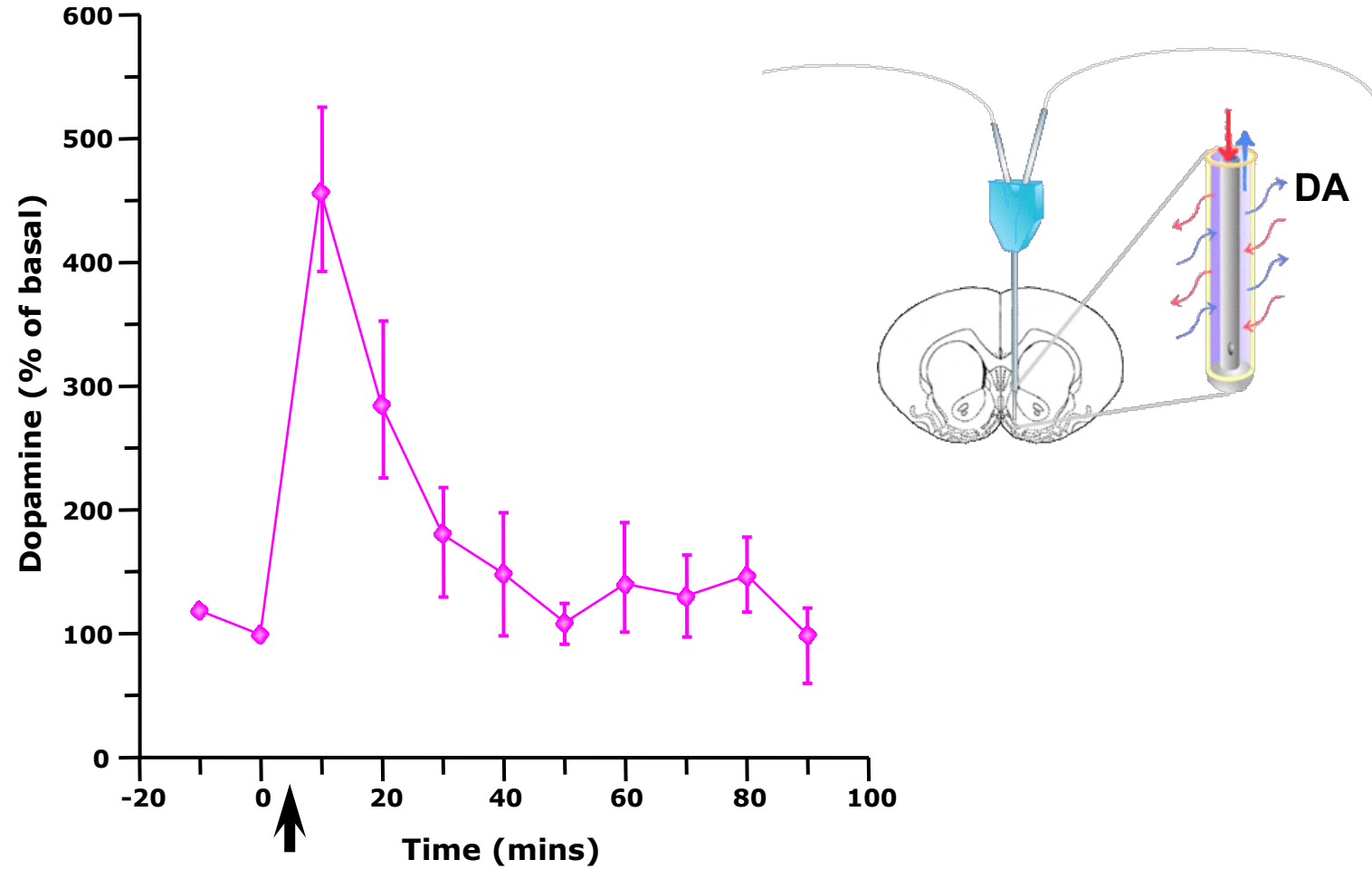
Dopamine



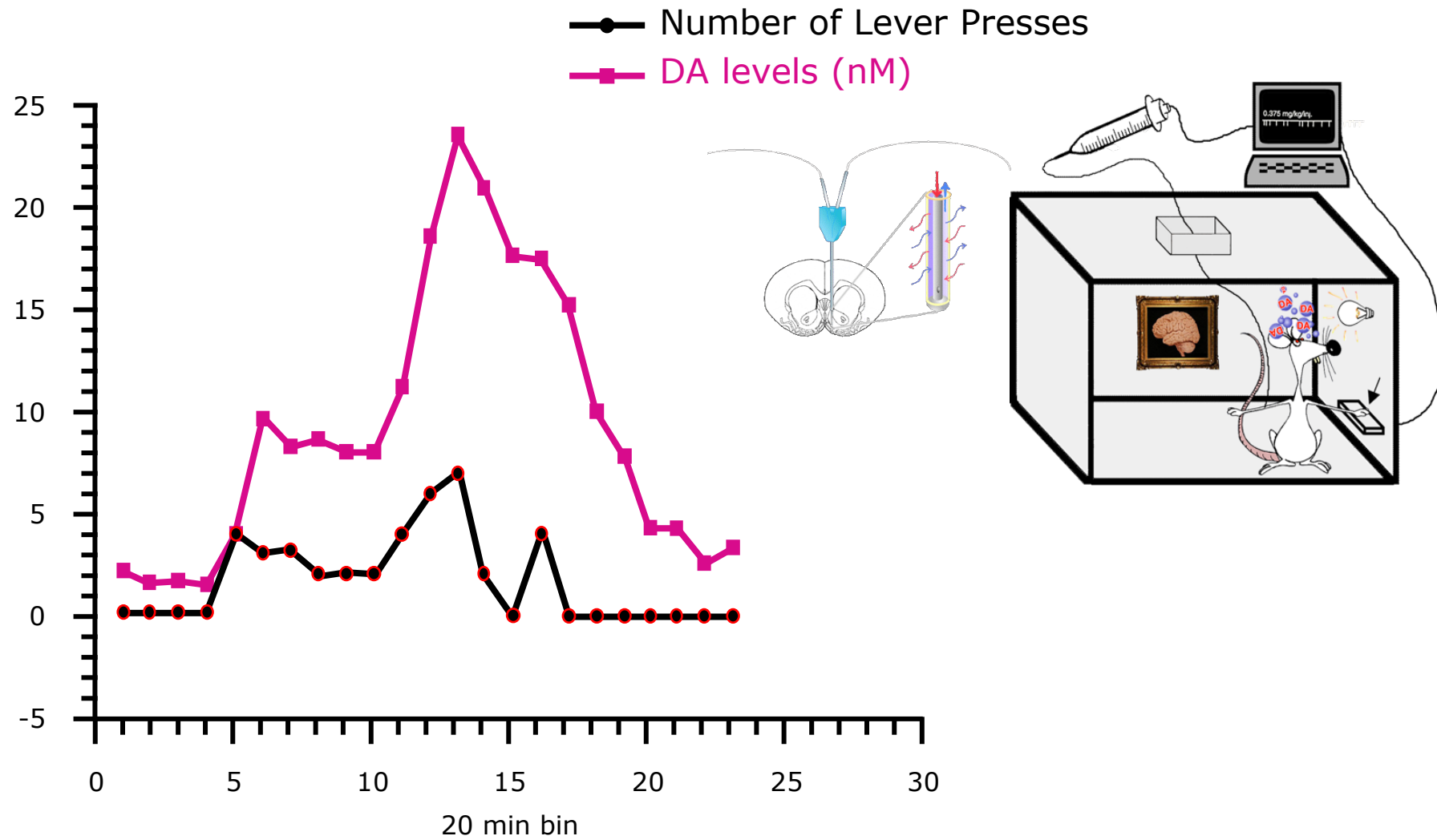
^{11}C Cocaine in the Human Brain



Cocaine Effects on *In Vivo* Dopamine Striatal Levels: In vivo Microdialysis

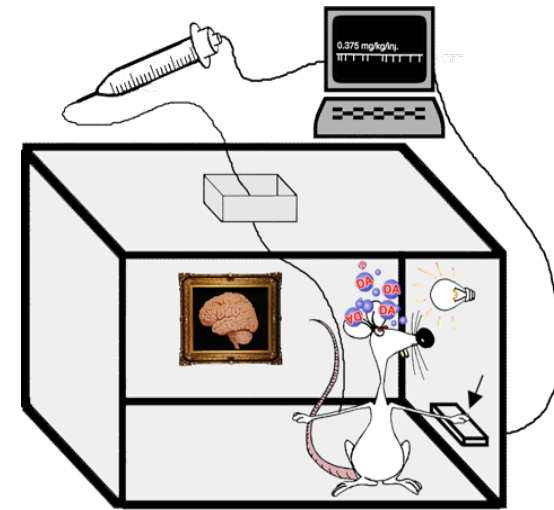
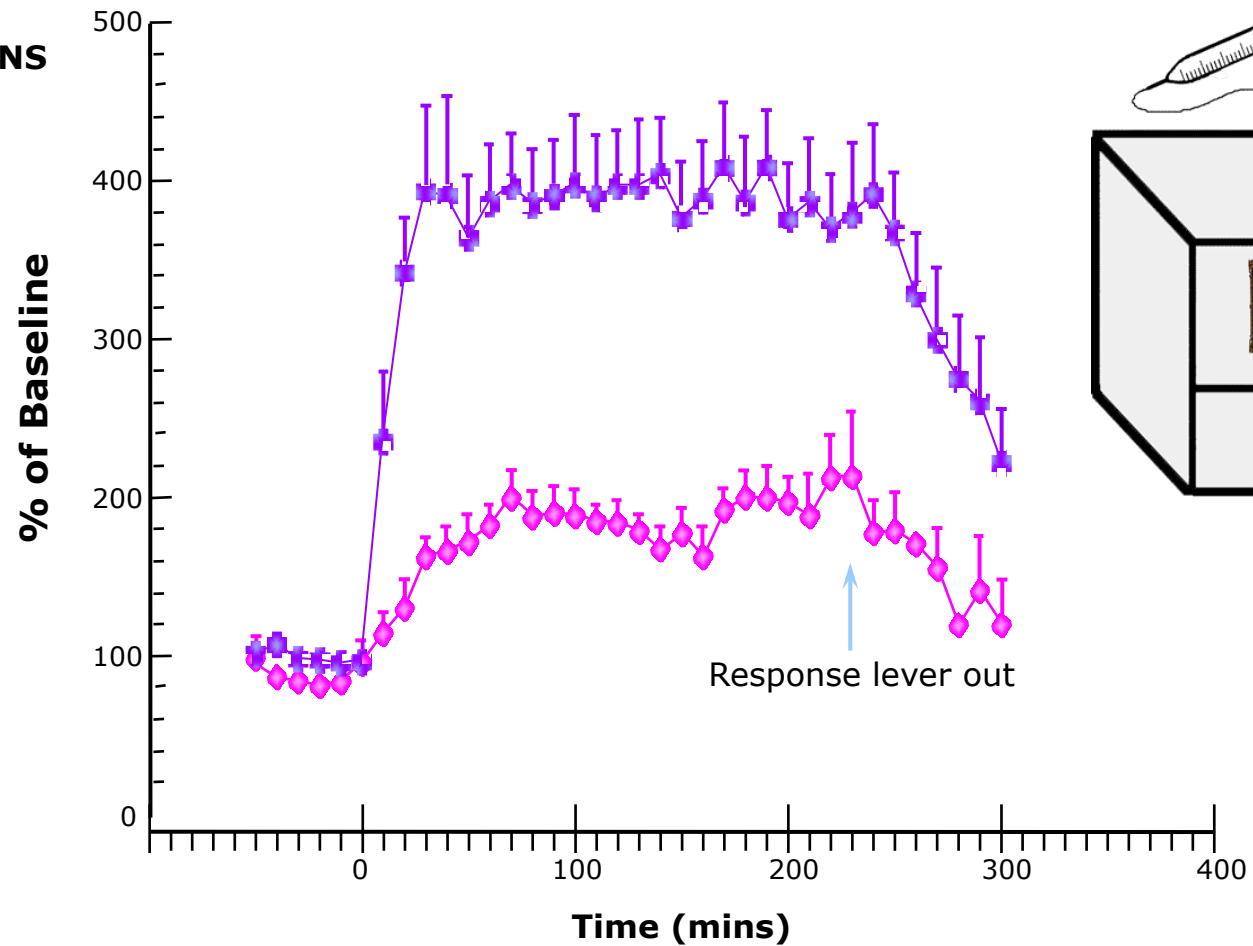


Cocaine Self-administration: *In Vivo* Microdialysis

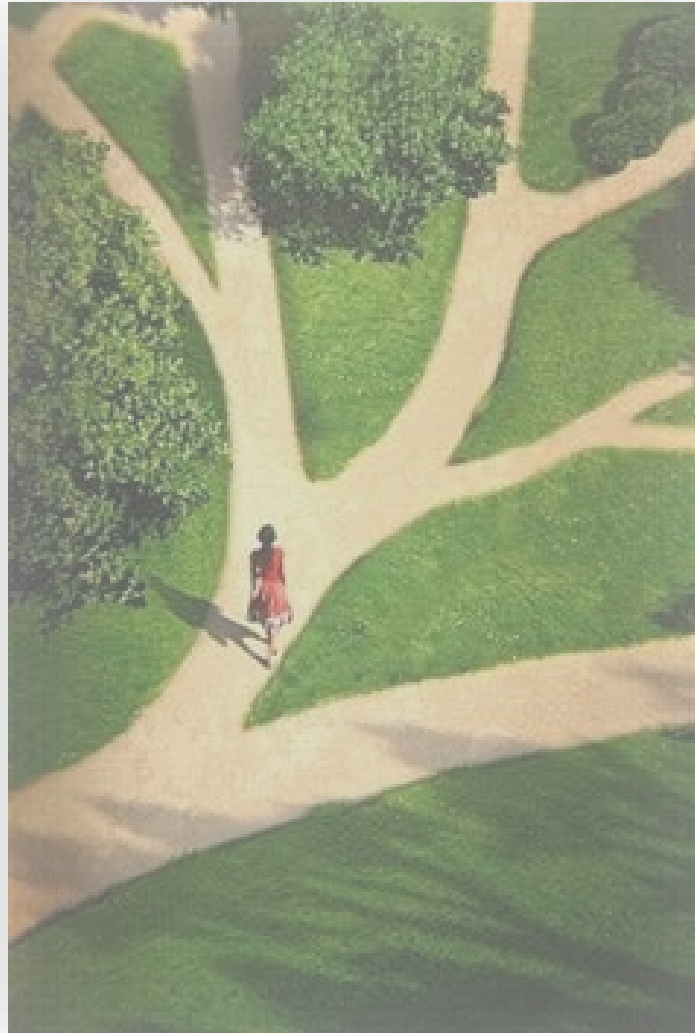


In Vivo Dopamine — Maintenance of Stable Levels During Cocaine Self-administration

- ◆ AMYGDALA
- NUCLEUS ACCUMBENS



Post-doctoral Training and First Independent Steps



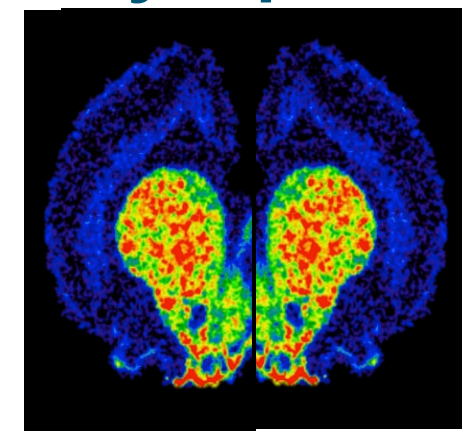
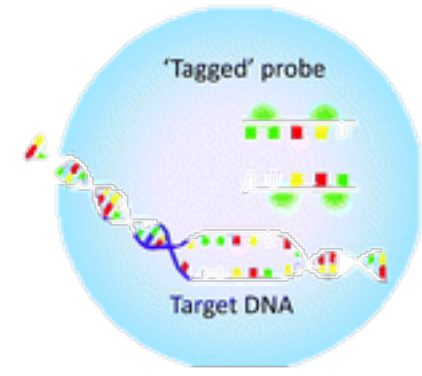
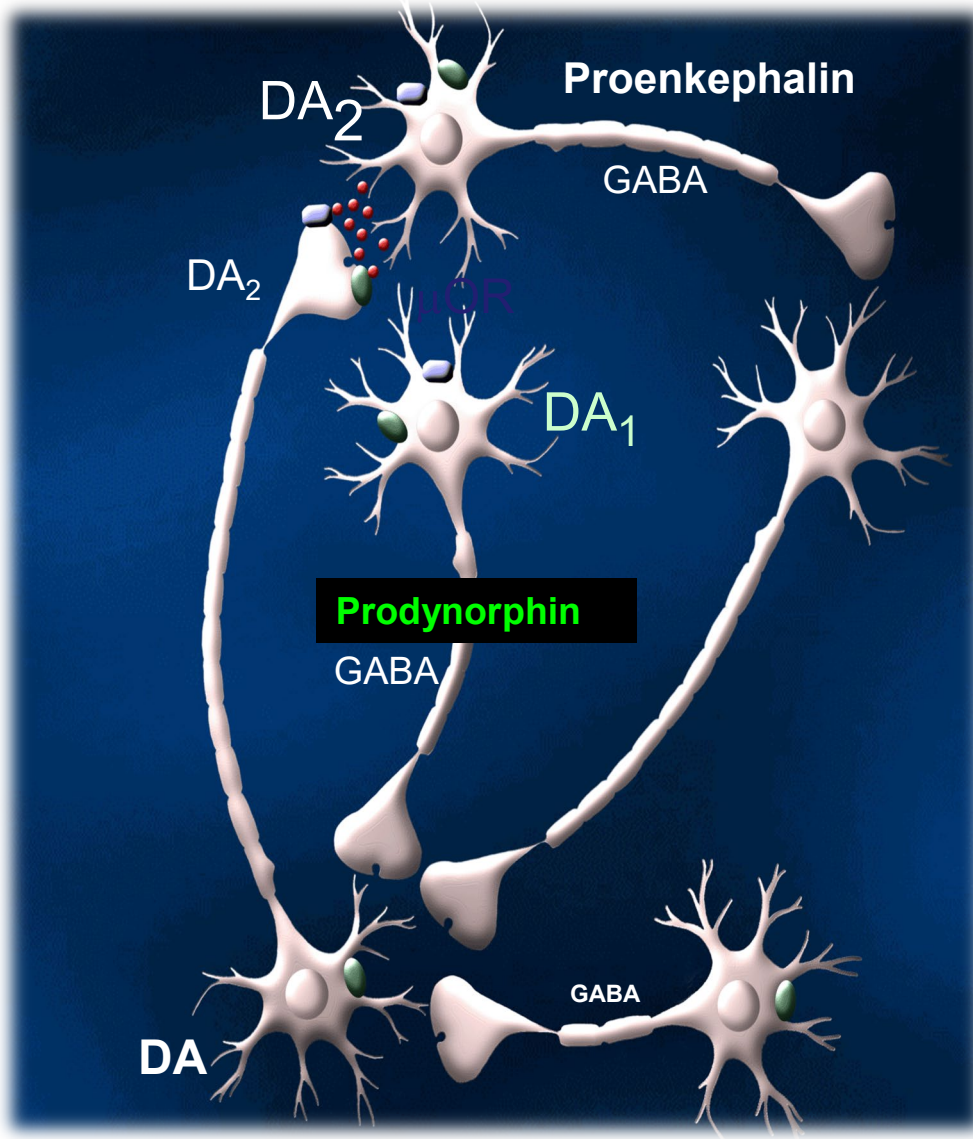
- ▶ Apply (for everything)
- ▶ Publications are the currency
- ▶ Do not underestimate yourself
- ▶ Have something to offer
- ▶ Add to your Toolbox
- ▶ A time to be novel



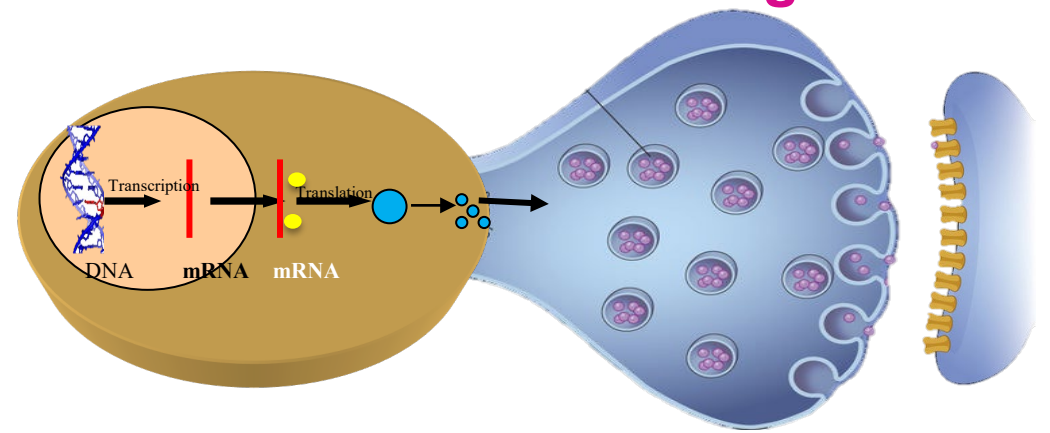
**Postdoctoral Research
Associate (PRAT) Fellow**



Mesolimbic Dopamine System and Post-Synaptic Striatal Neurons

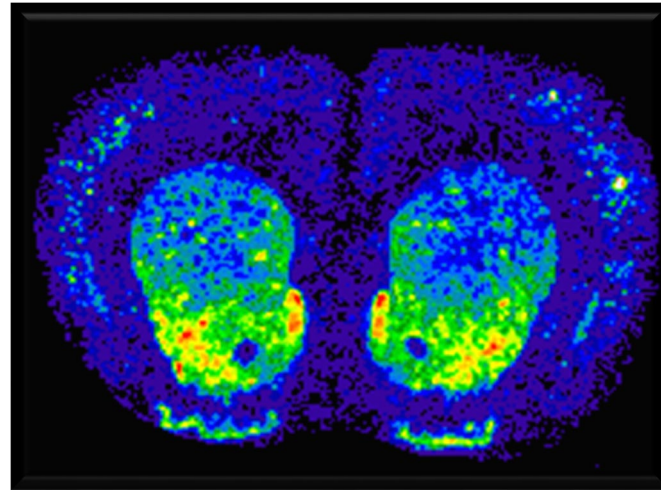


Molecular Knowledge

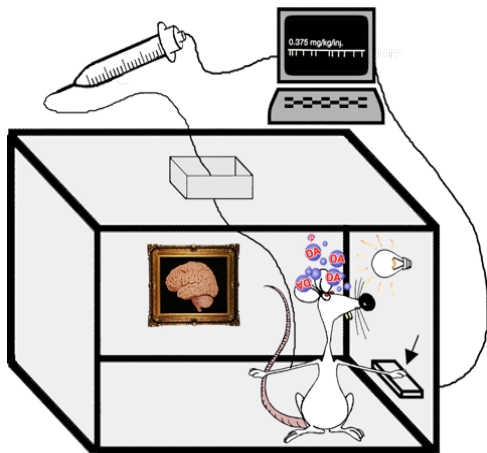
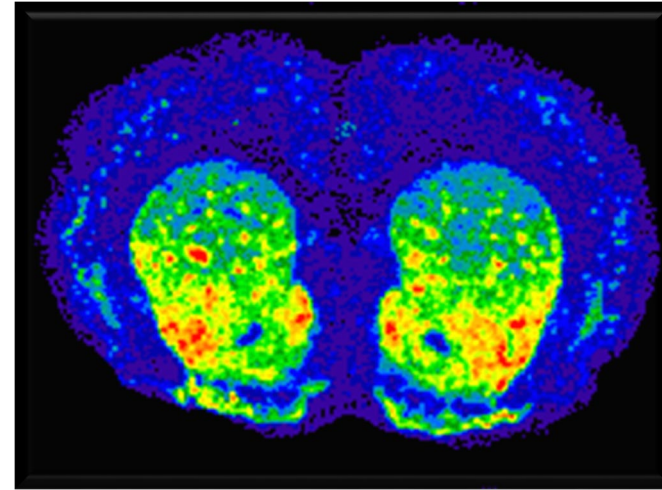


Prodynorphin mRNA Expression in the Rat Striatum as a Consequence of Cocaine Self-administration

SALINE



COCAINE



Translational Approach

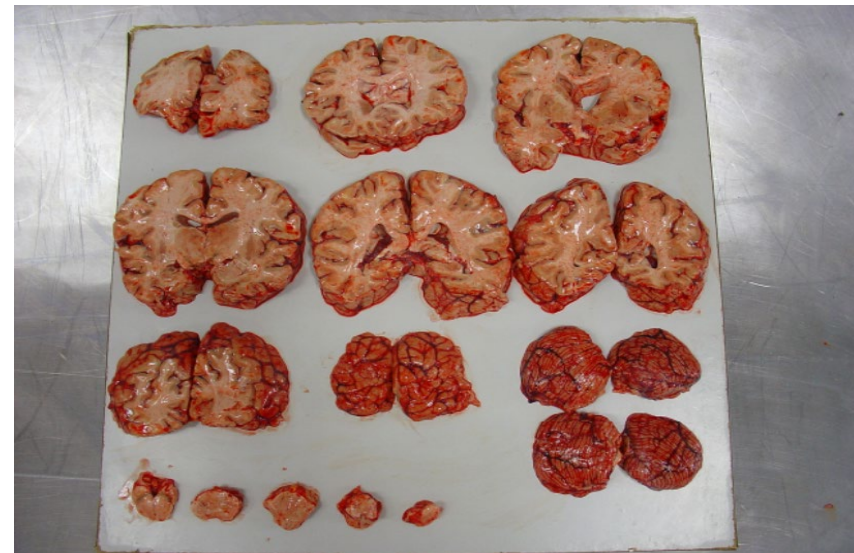
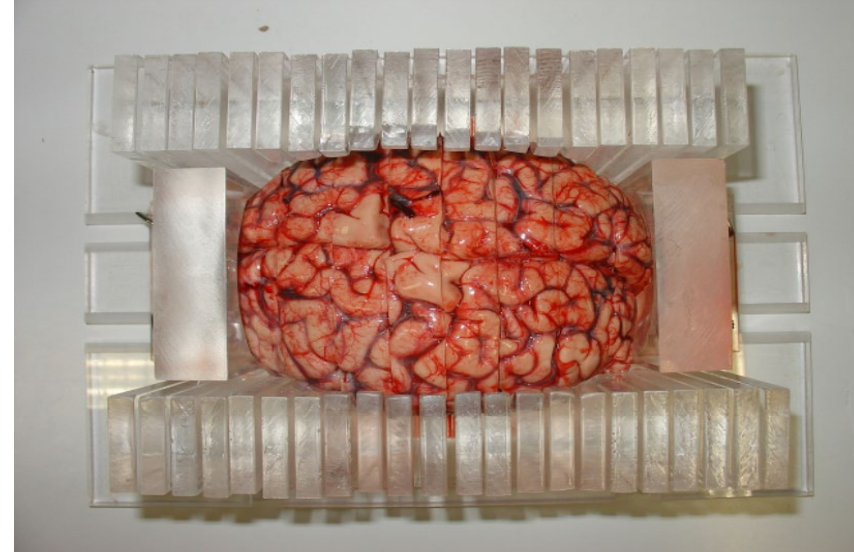
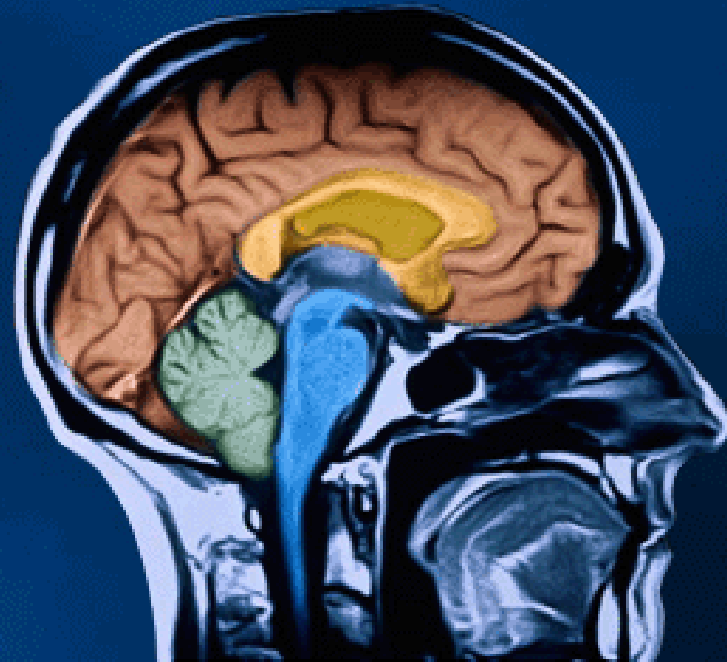
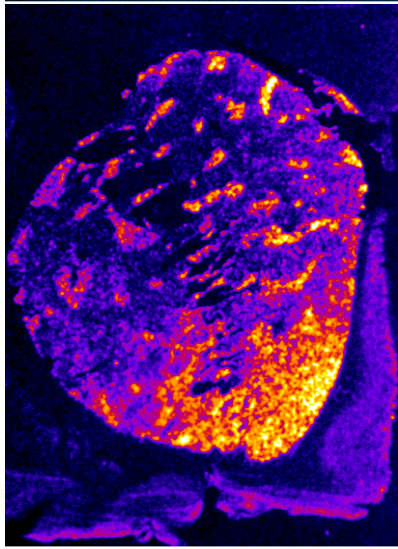
Human Studies



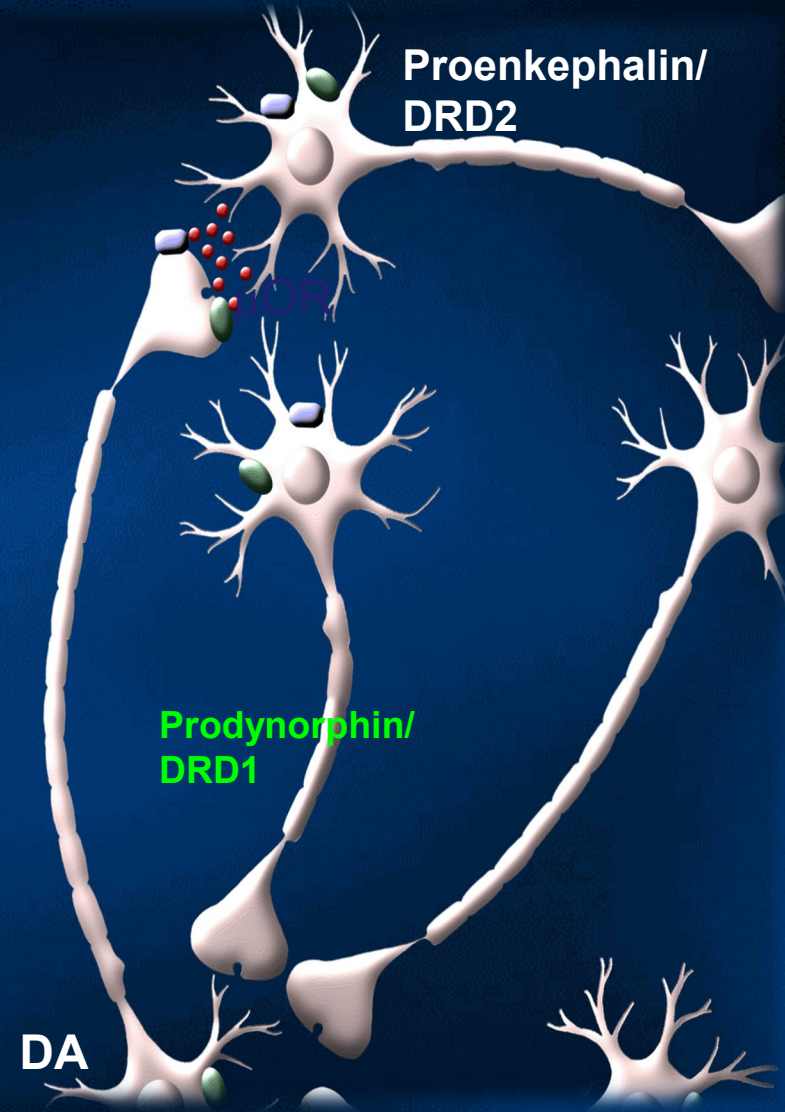
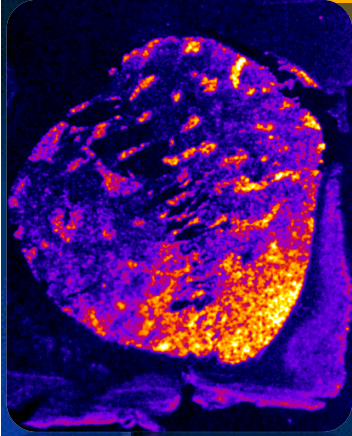
Animal Models



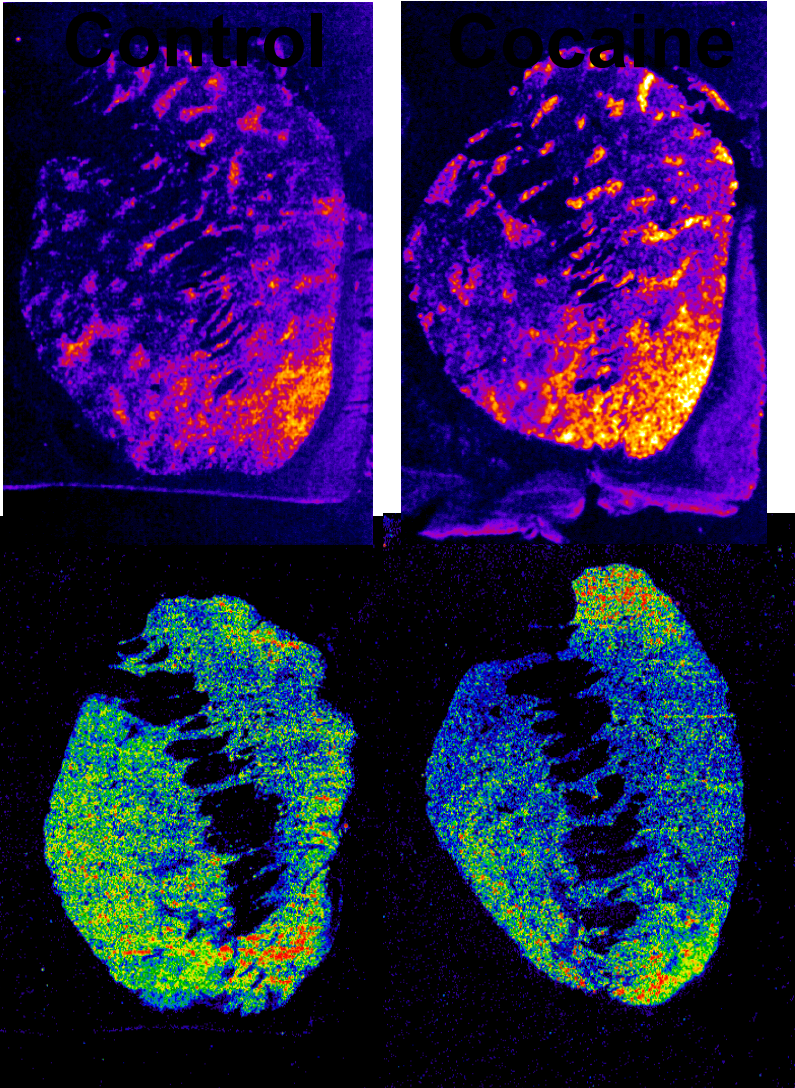
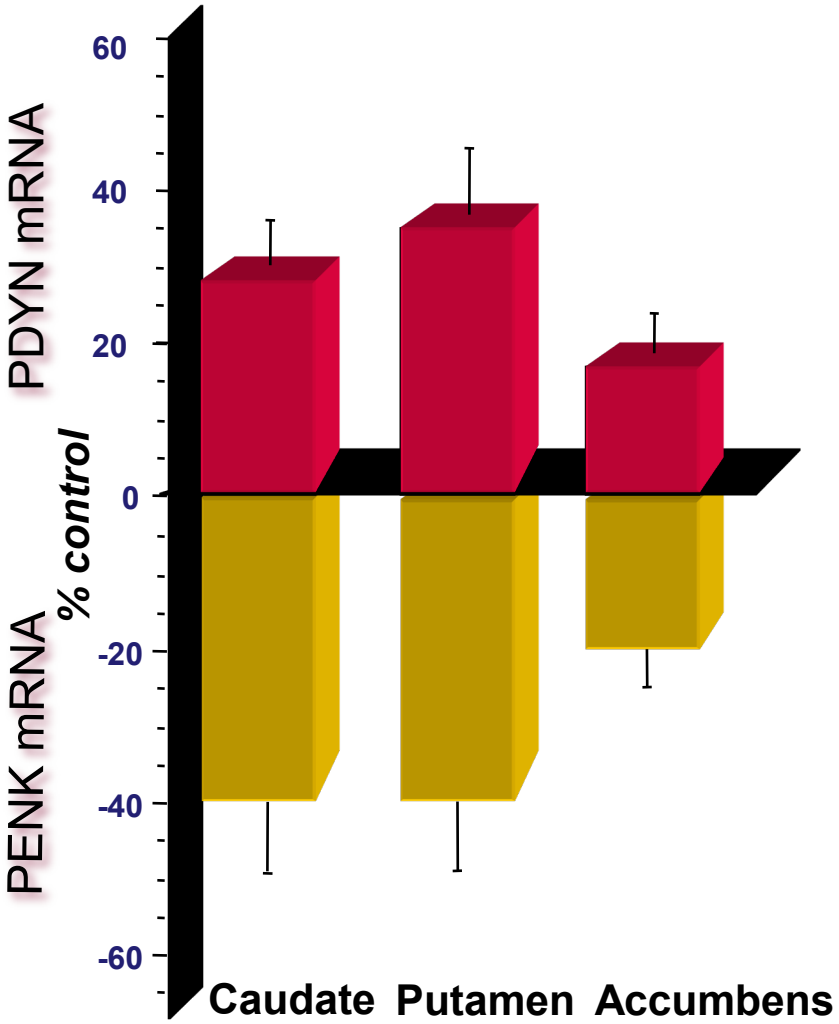
Molecular Insights: Human Brain



Striatum

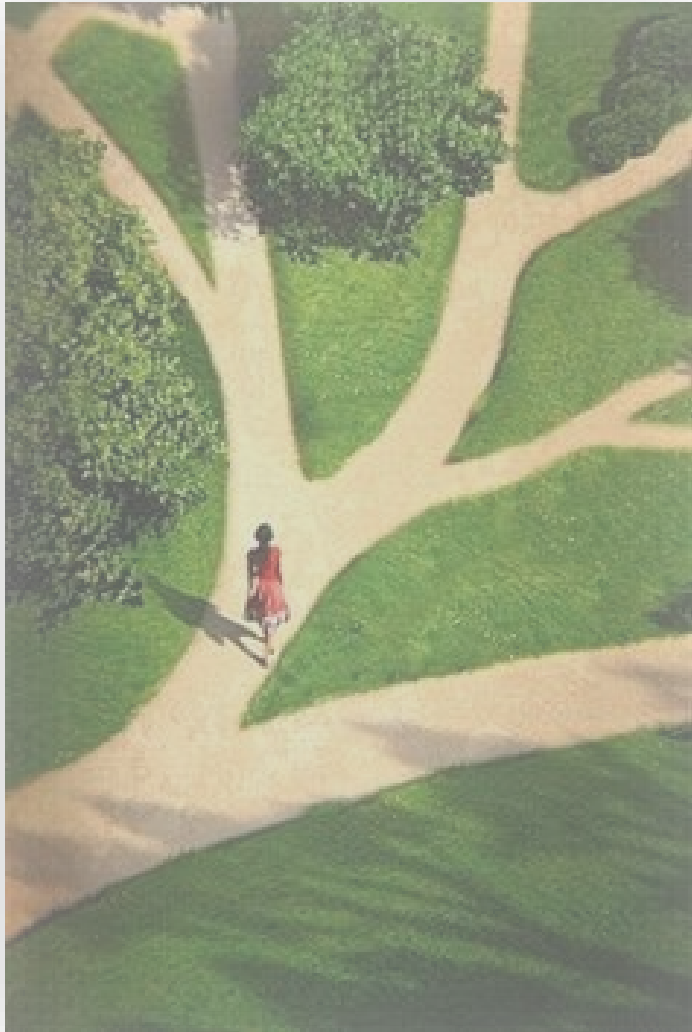


Dysfunction of Striatal Opioid Neuropeptide Gene Expression in Human Cocaine Users





Assistant Professor and Beyond



- **Oblivious to the rules**
 - One of youngest Full Professor; few female professors
- **Challenges can enhance novelty**
 - Foreigner status for NIH grants enhanced translational work
- **Study Section Reviewers and Program Officers can be great mentors**

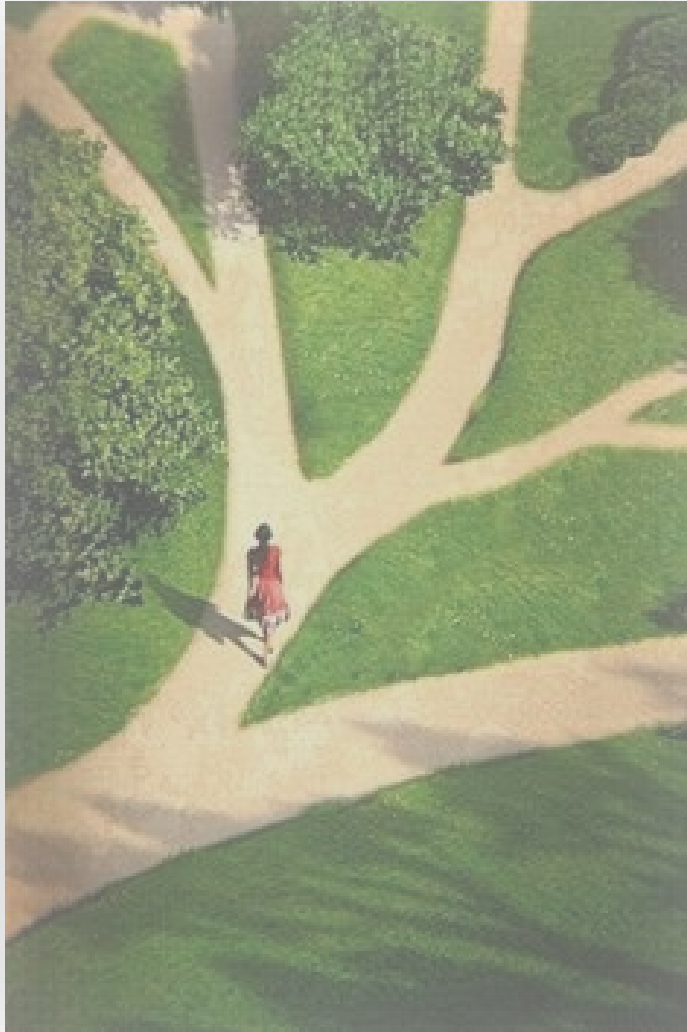


Genetics

**Behavioral
traits/psych
comorbidity**

**Developing
brain**

Environment

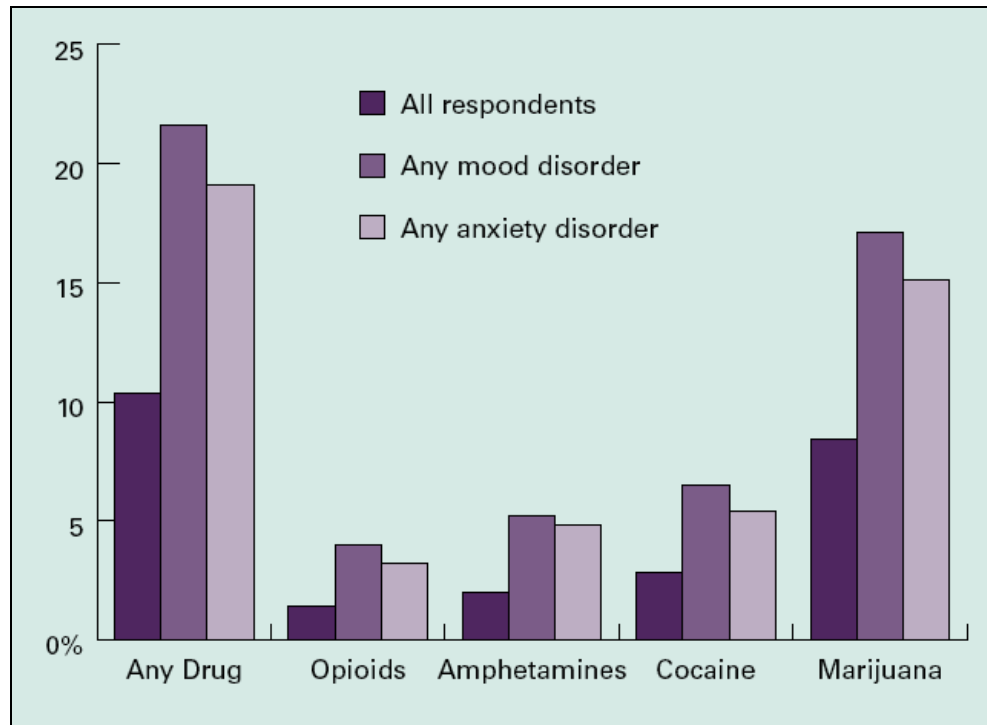


Be scientifically creative....

“Necessity is the mother of invention” or at least the mother of combining different inventions to answer challenging questions

- **Develop a research team with different skillsets**
- **Train junior scientists to prepare for their future**

Drug Addiction and Psychiatric Comorbidity

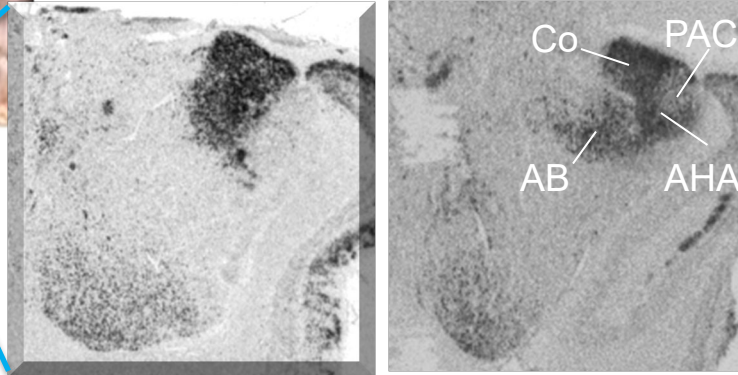


Anxiety and Major depression are the most common disorders comorbid with drug abuse

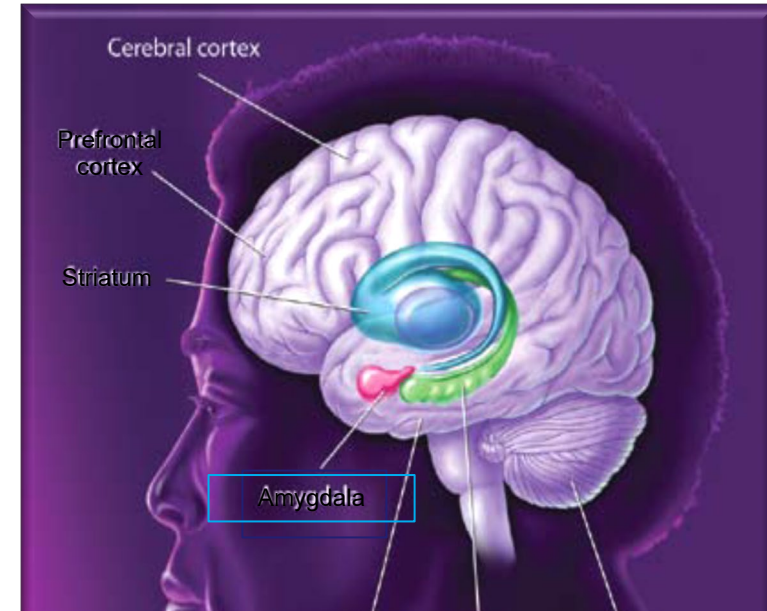
Amygdala Dysfunction in Psychiatric Disorders



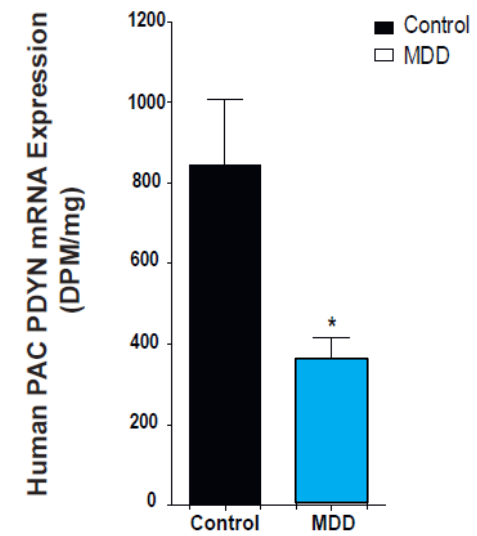
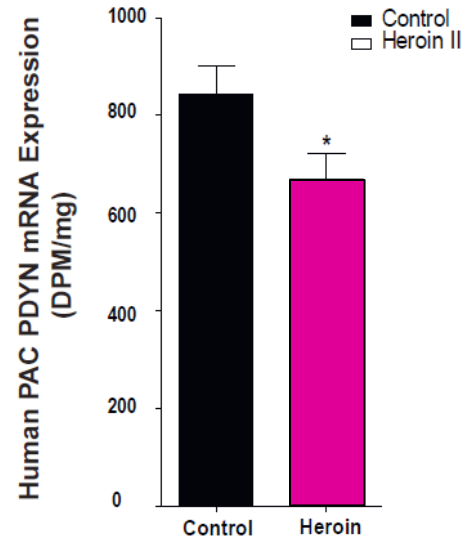
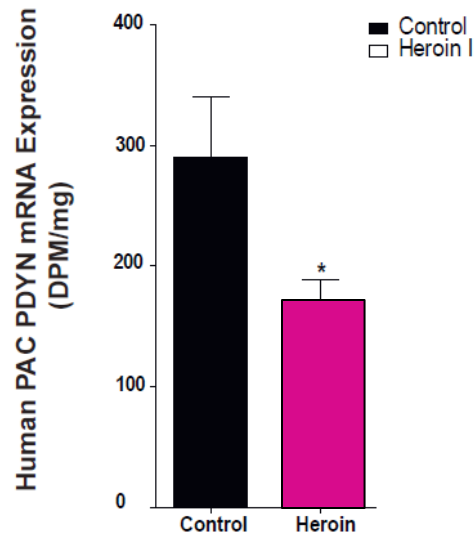
Prodynorphin mRNA Expression



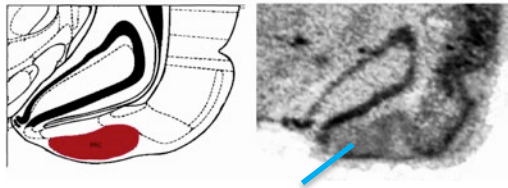
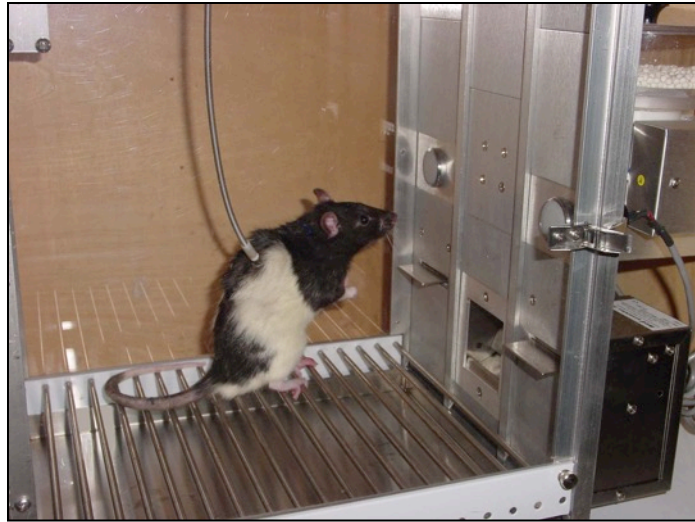
AHA = amygdalohippocampal area
 AB = accessory basal nucleus
 Co = cortical nuclei



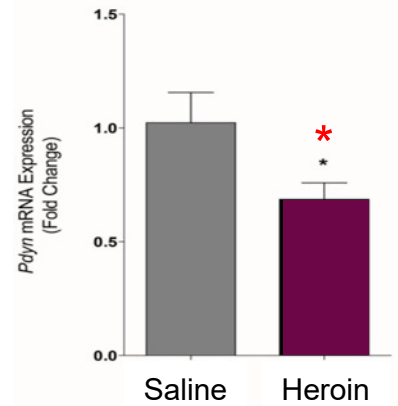
Anderson et al., *J. Clinical Investigation*, 2013



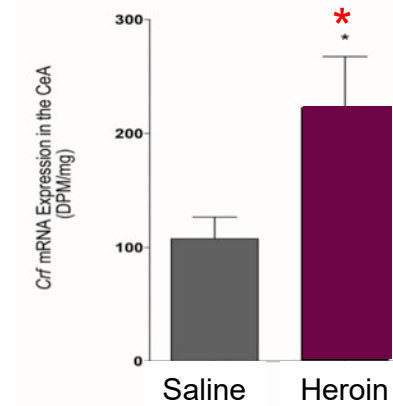
Prodynorphin mRNA in the Rat PAC is Reduced Following Heroin Self-Administration during the Acute Stress Withdrawal Period



Pdyn mRNA in PAC



Crf mRNA in CeA



24 hours after self-administration session

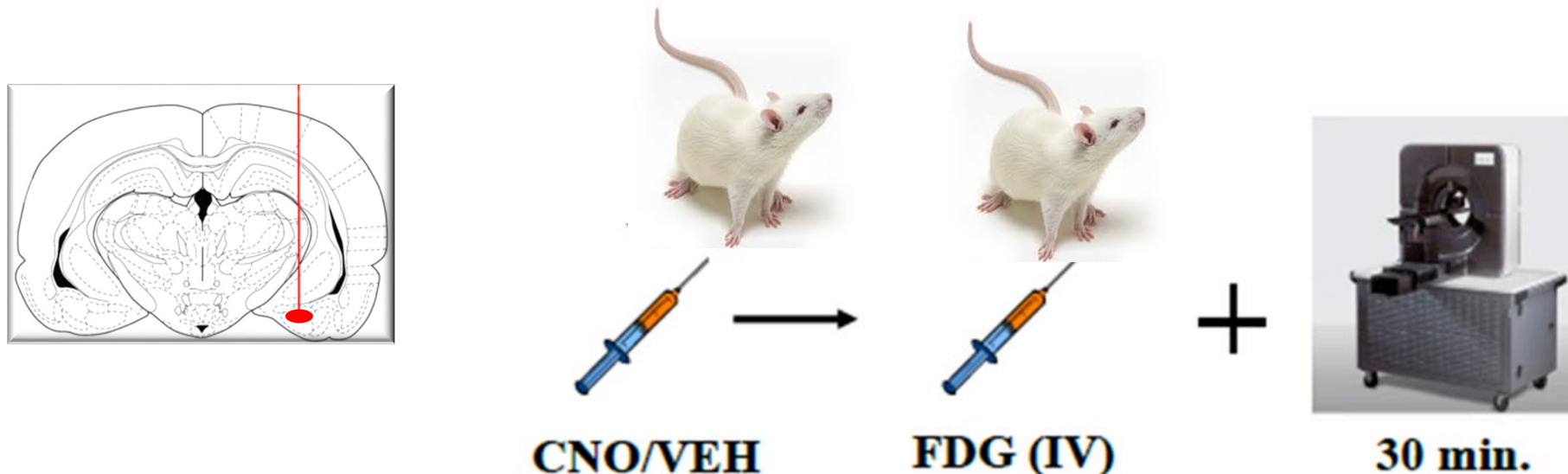
DREADD-Assisted Metabolic Mapping (DREAMM)

Map behavior to neurochemistry

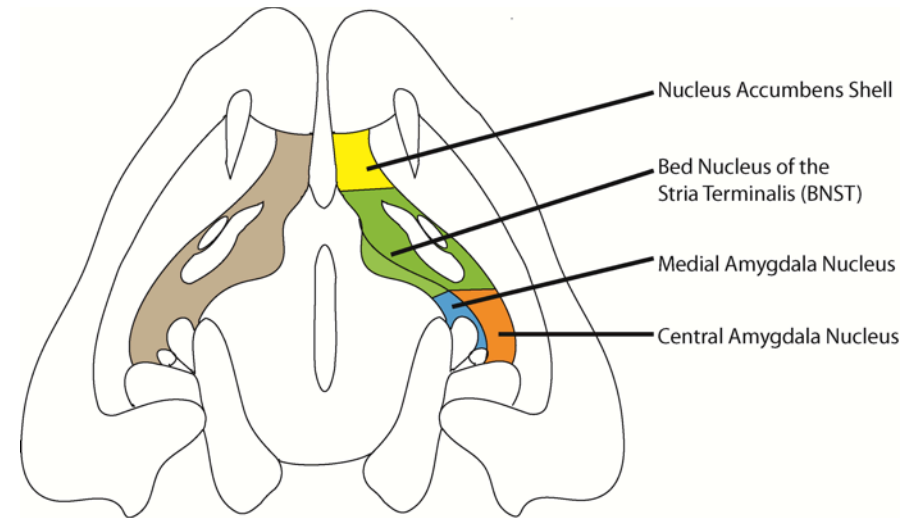
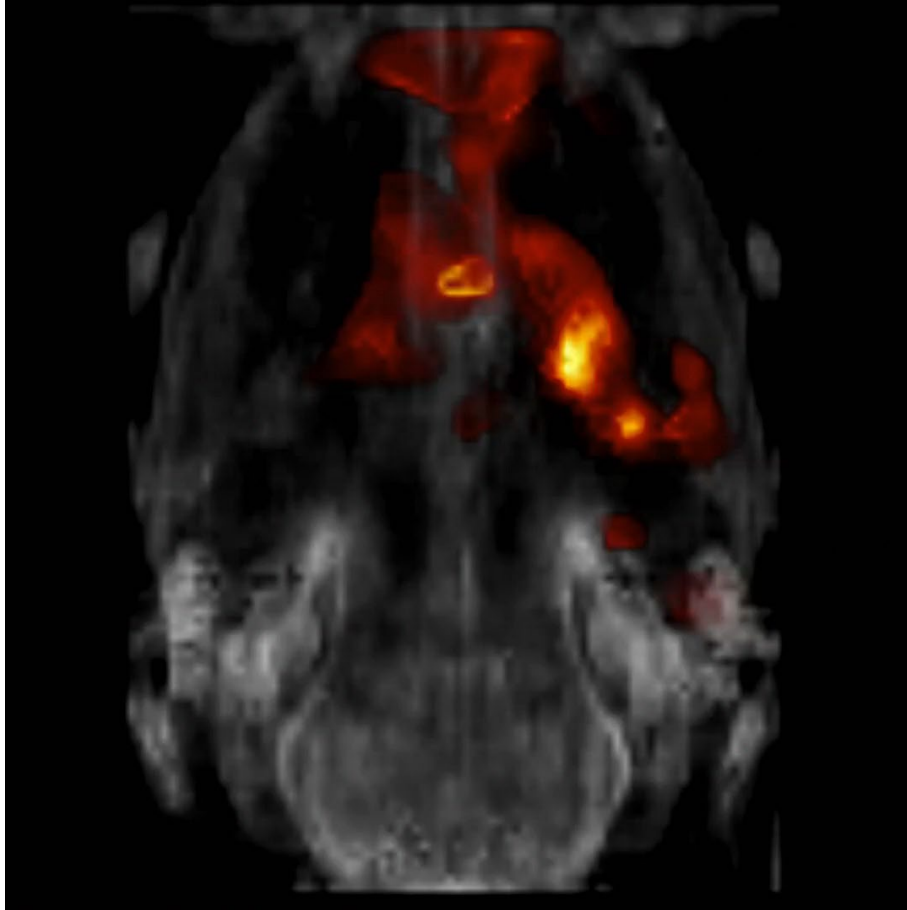
Manipulate neurochemistry & behavior



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

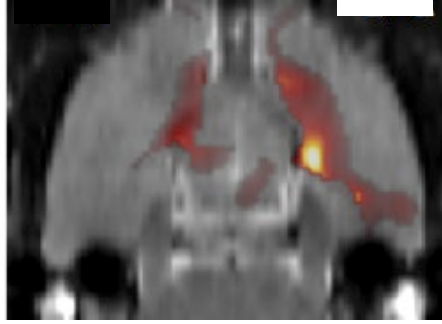


Chemogenetic inhibition of Prodynorphin Neurons in the PAC Activates the Extended Amygdala

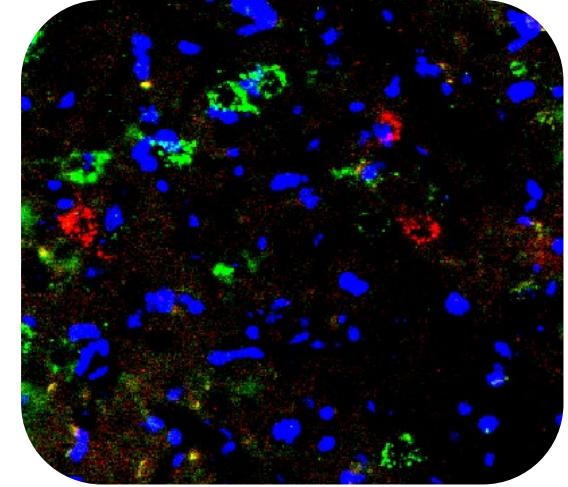


Central amygdala, bed nucleus stria terminalis and nucleus accumbens shell (L. Heimer & G. Alheid 1991)

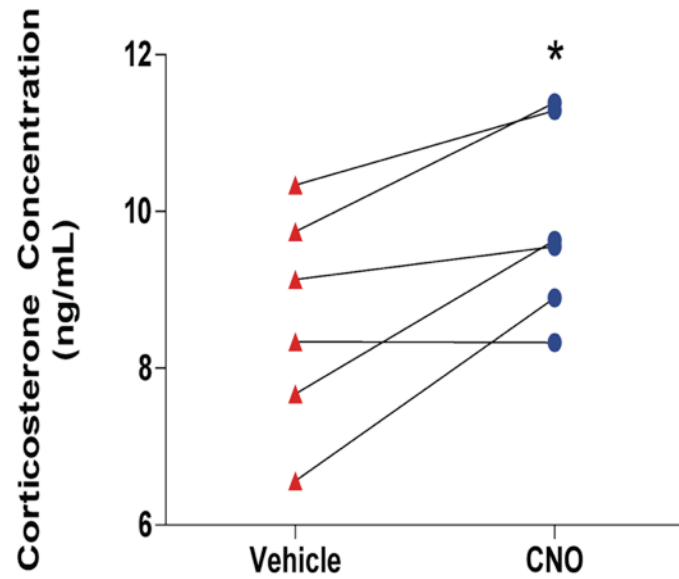
- ▣ Roles:
 - Adaptive motivational behaviors
 - Maladaptive response to fear, anxiety and stress
- ▣ Dysregulation of the extended amygdala has been implicated in psychiatric disorders



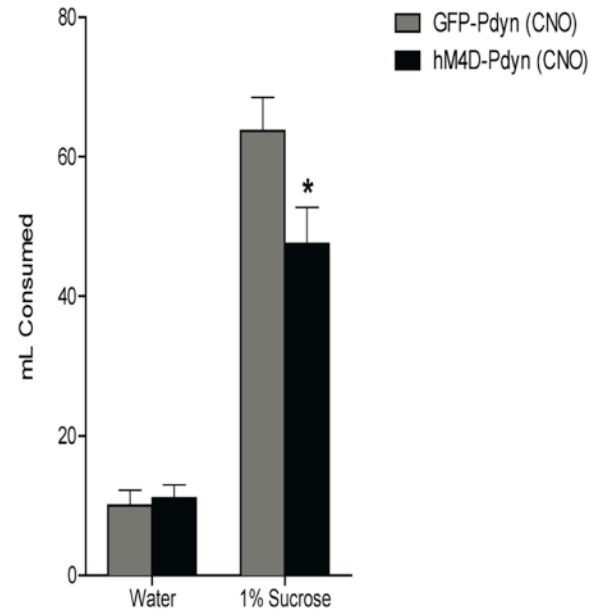
Inhibition of Prodynorphin PAC Neurons Enhance Physiological and Behavioral Measures of Stress and Negative Affect



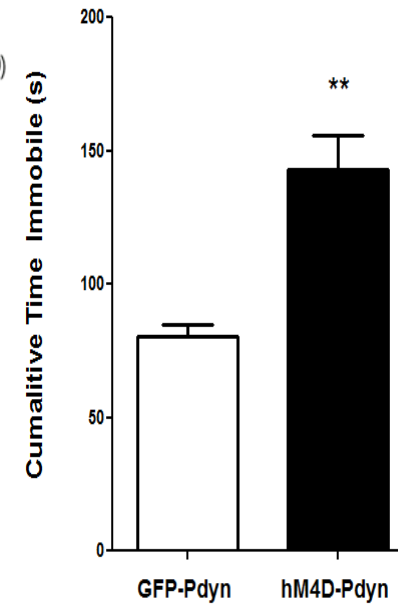
Increased Corticosterone levels



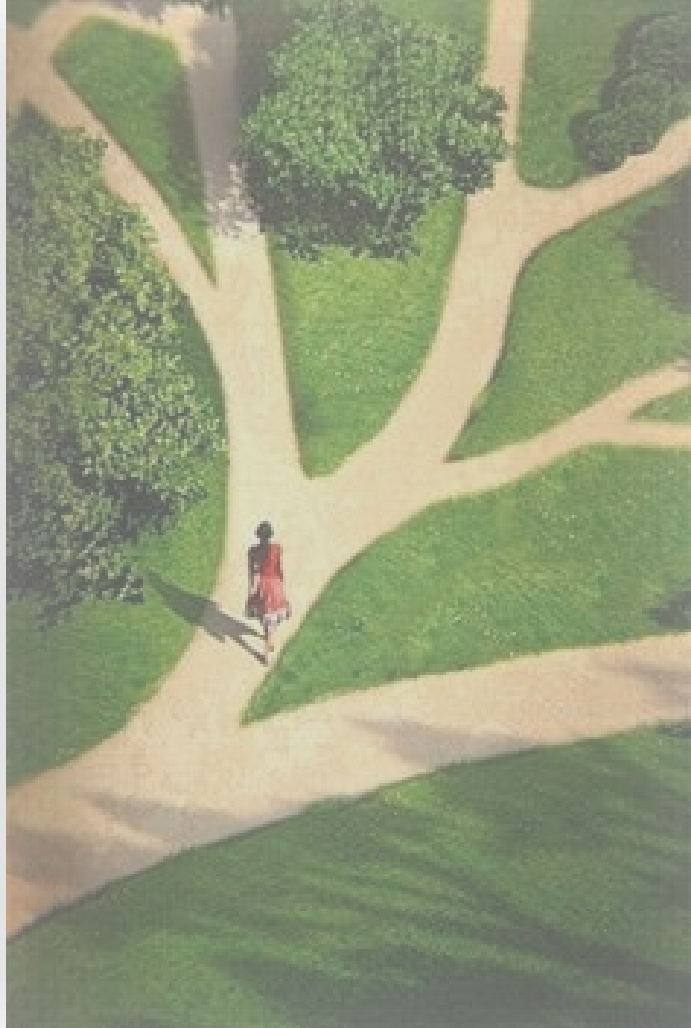
Anhedonia: Attenuated sucrose preference



Depression-like behavior: Forced Swim Enhanced Immobility



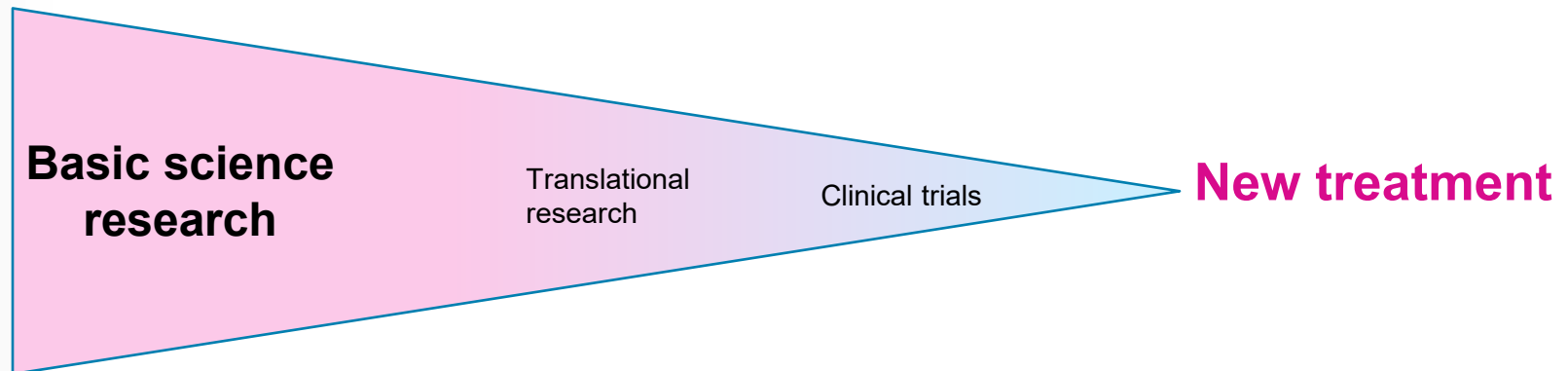
➤ Research with direct impact on the human condition and treatment potential

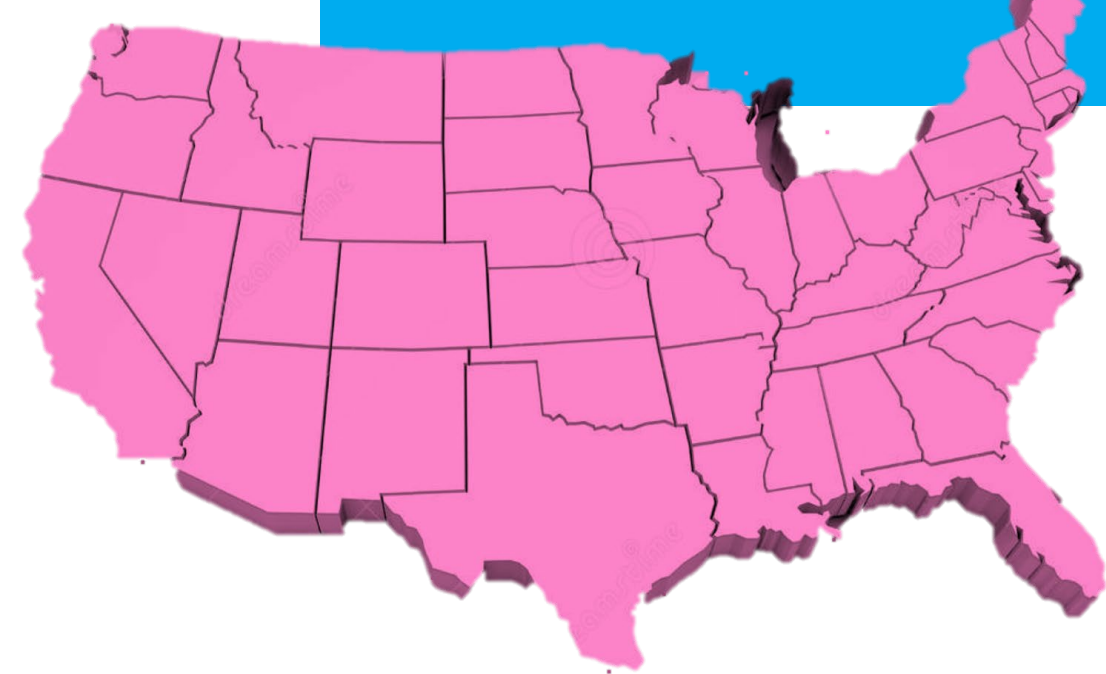


The stats does not favor translation of basic science research

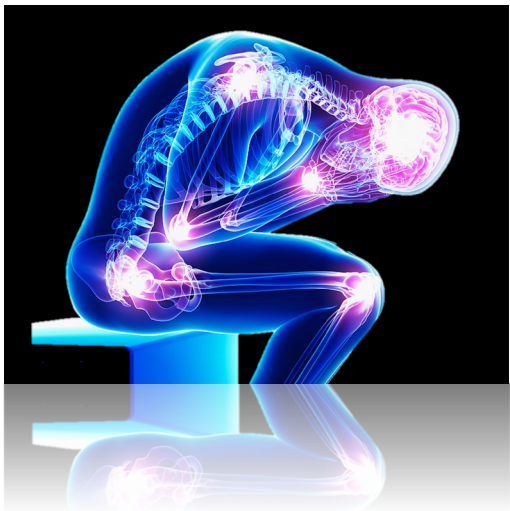
~3.9% of publications produced by basic research awards are translational

Moving new drug candidates from preclinical research into human studies and becoming an approved drug is only approximately 0.1%.



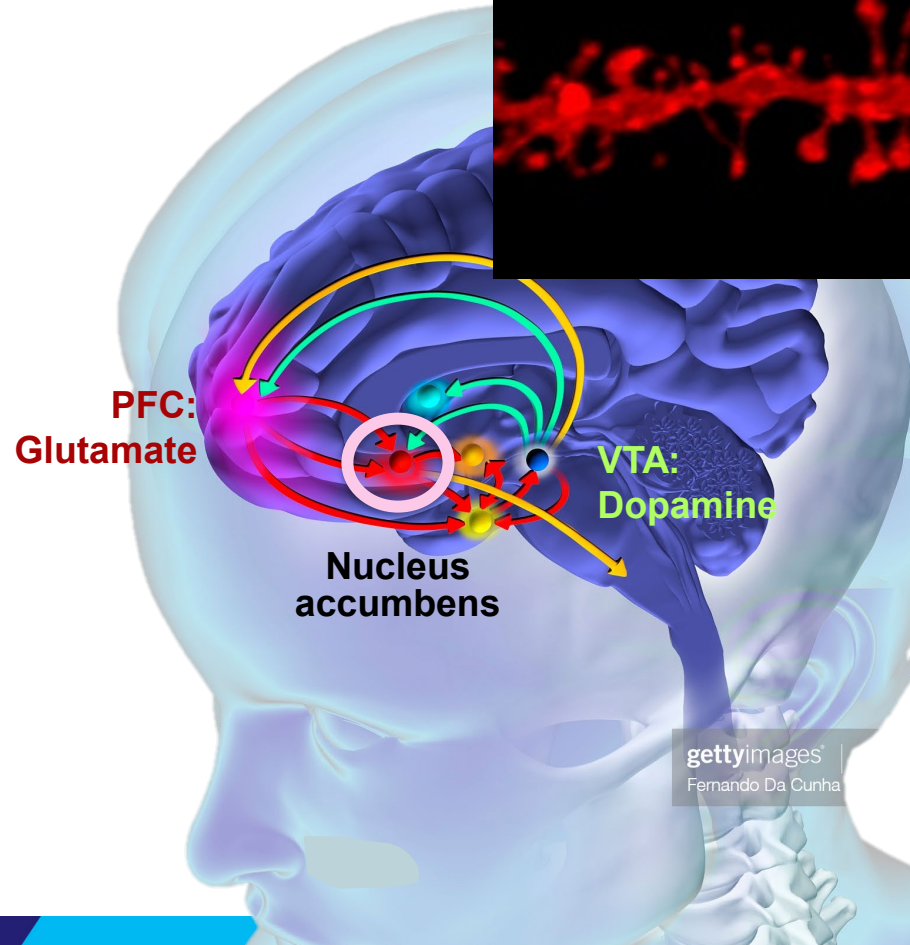
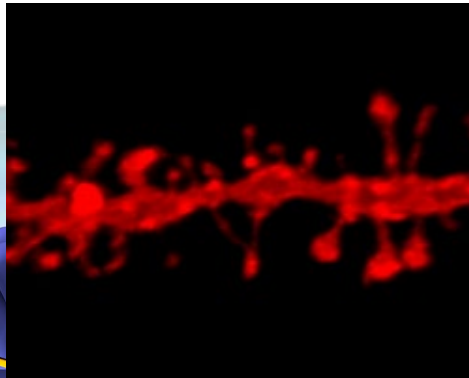


- ▶ **Nationally, ~130 people a day die from opioid overdose**
- ▶ **5-6 deaths by the time this panel is over**
- ▶ **Four in five new heroin users started out misusing opioid prescription painkillers**
- ▶ **Over 200 million opioid painkiller prescriptions annually, approximating the entire adult population in the USA**
- ▶ **Opioid abuse cost 3 times more to treat than other medical disorders**
- ▶ **Every 15 mins a baby is born with Neonatal Abstinence Syndrome**

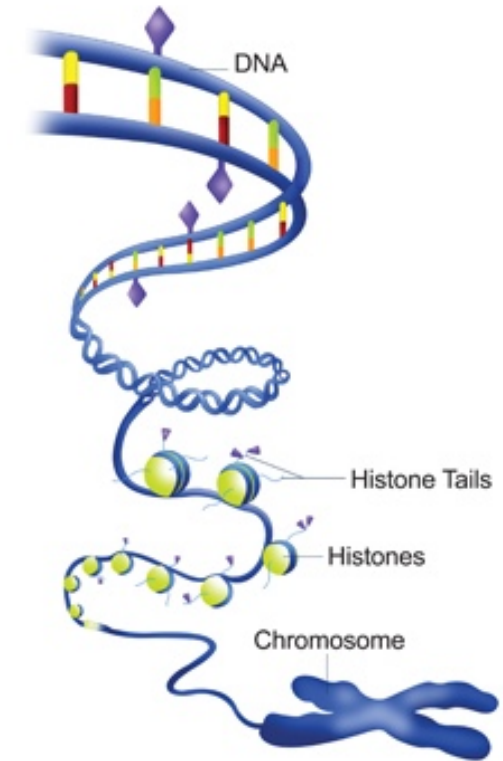
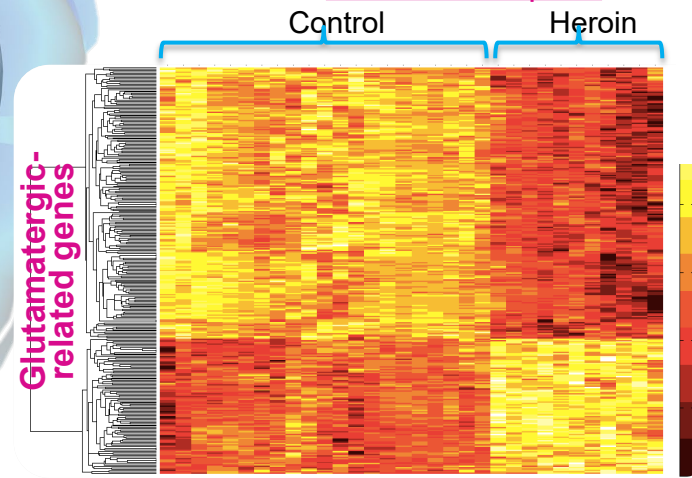


Molecular Neurobiology of Opioid Abuse

Synaptic plasticity



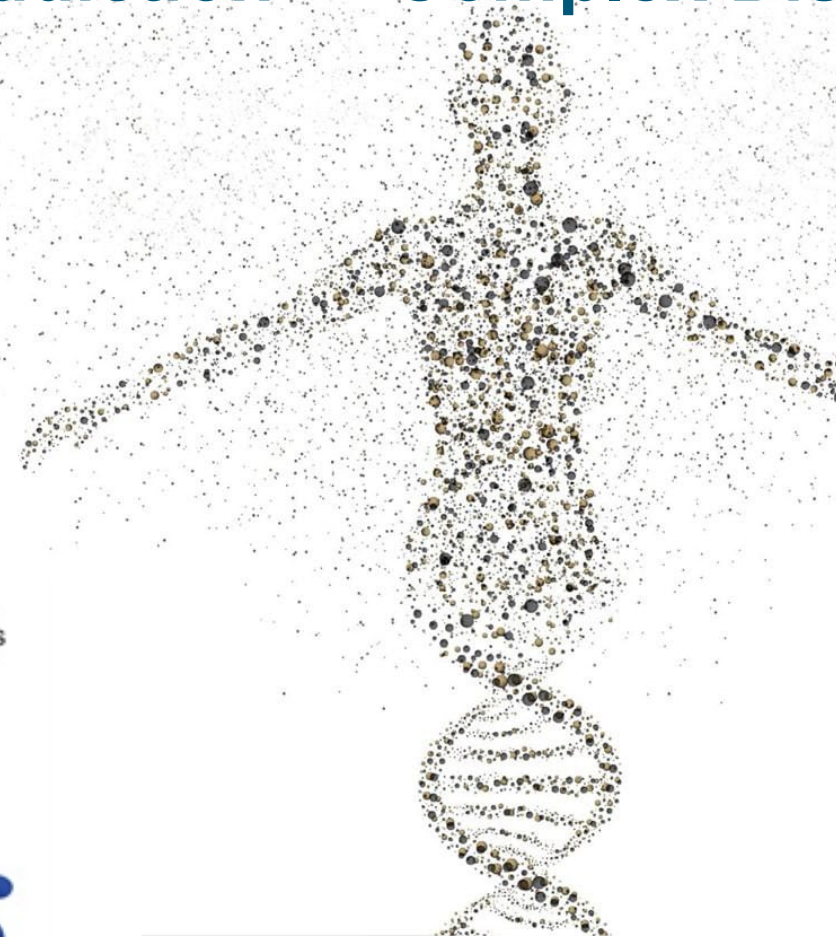
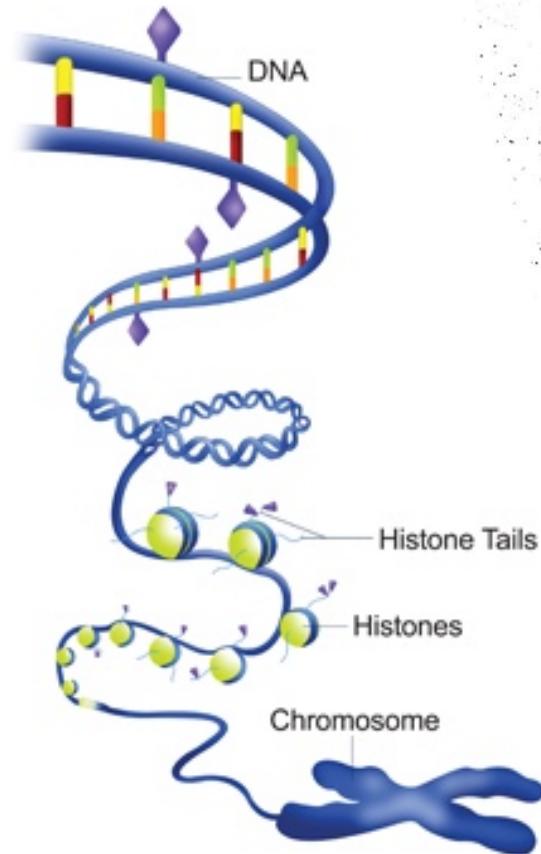
Gene transcription



Epigenetics

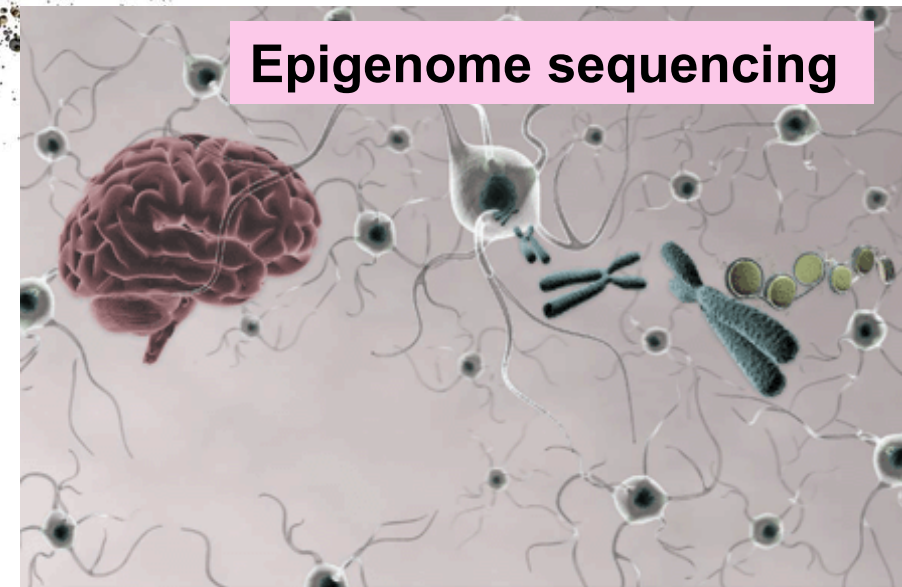
Epi Genetics

Addiction — Complex Disorder



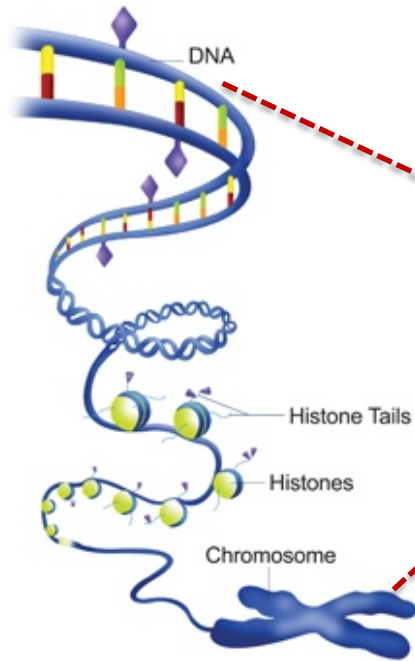
Environment

-control gene activity

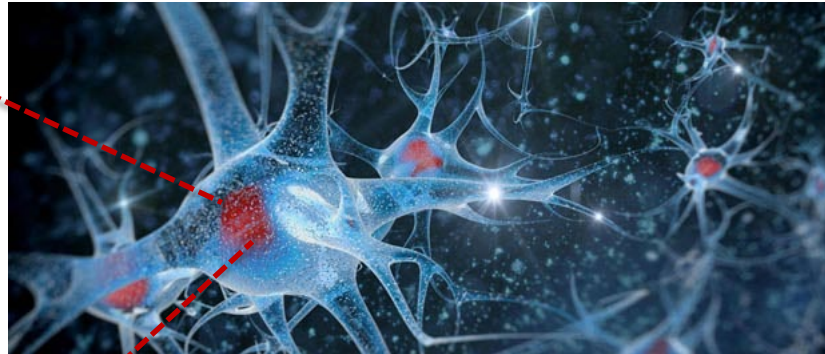


Describes mechanisms by which genes are turned on or off *without* altering the genetic code or DNA sequences

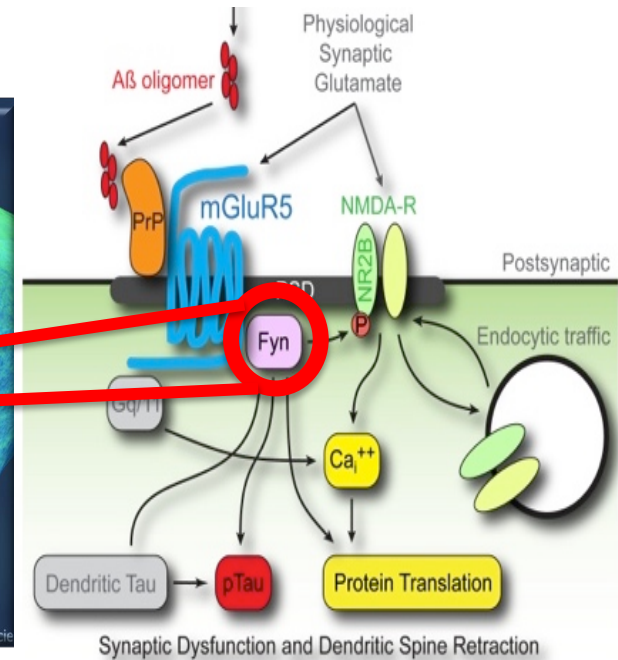
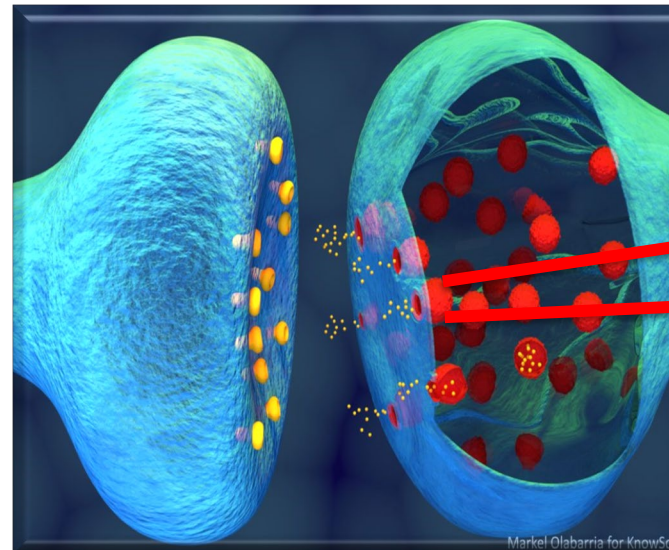
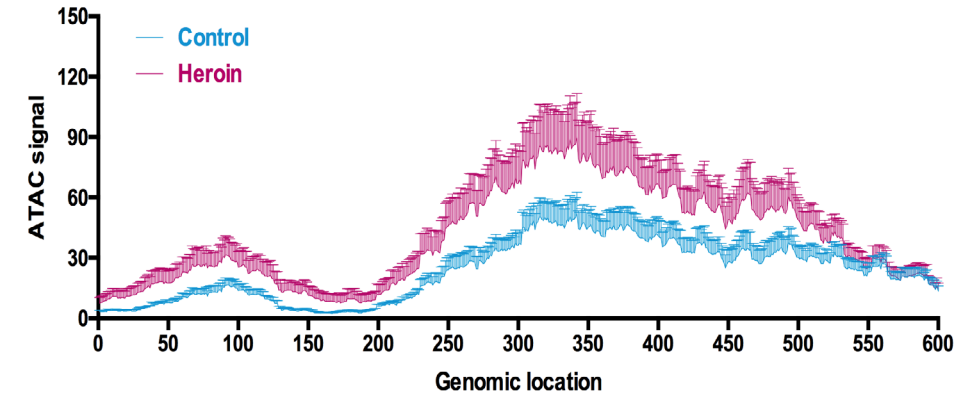
Molecular Neurobiology of Opioid Abuse



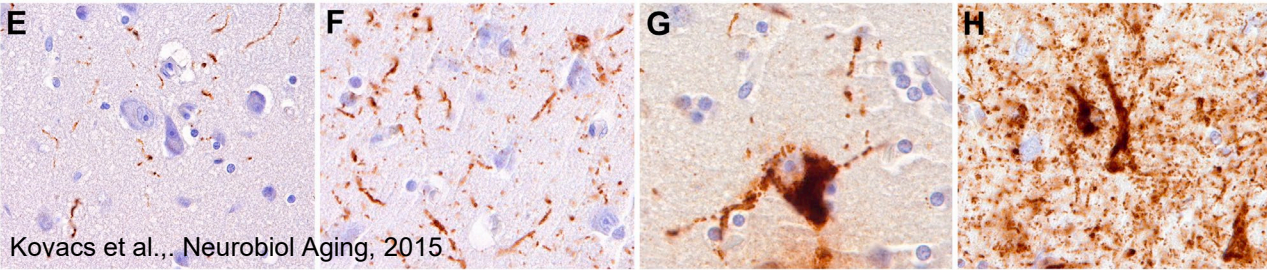
Epigenome



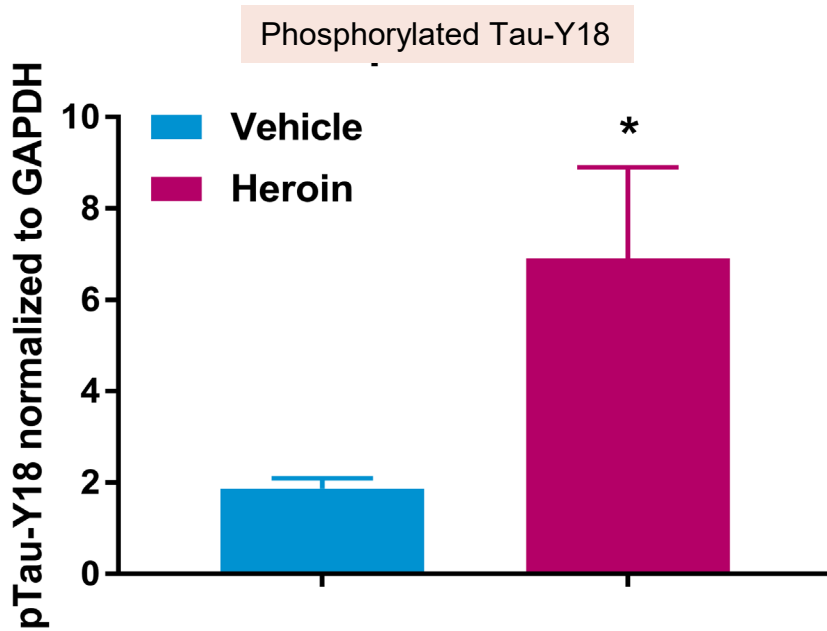
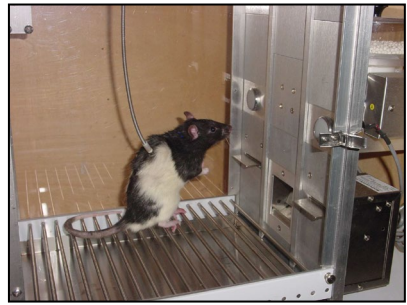
Most significant epigenomic change relate to the *FYN* gene



Increased phosphorylated-Tau in the brains of heroin users

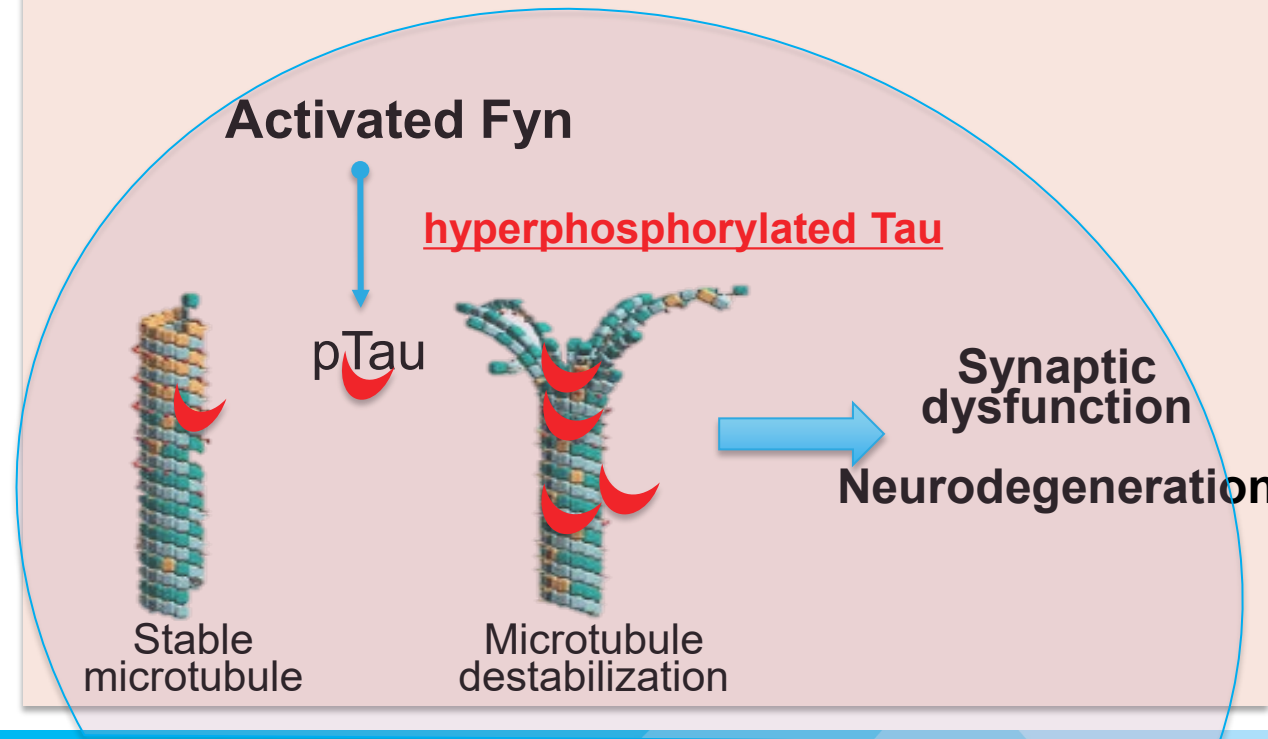
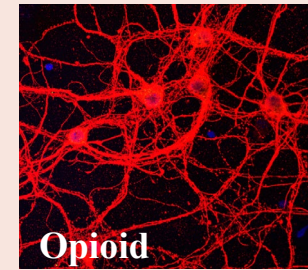
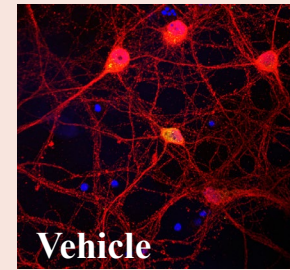


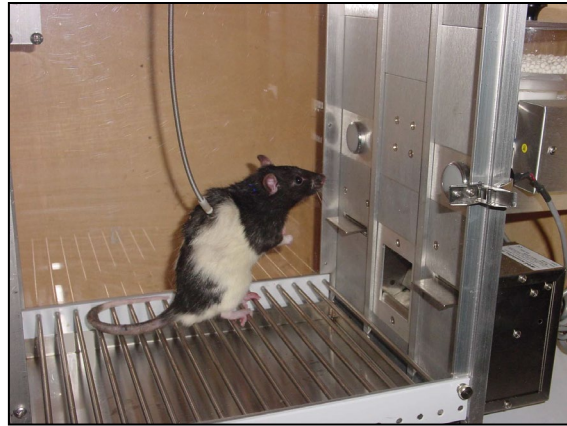
Kovacs et al., Neurobiol Aging, 2015



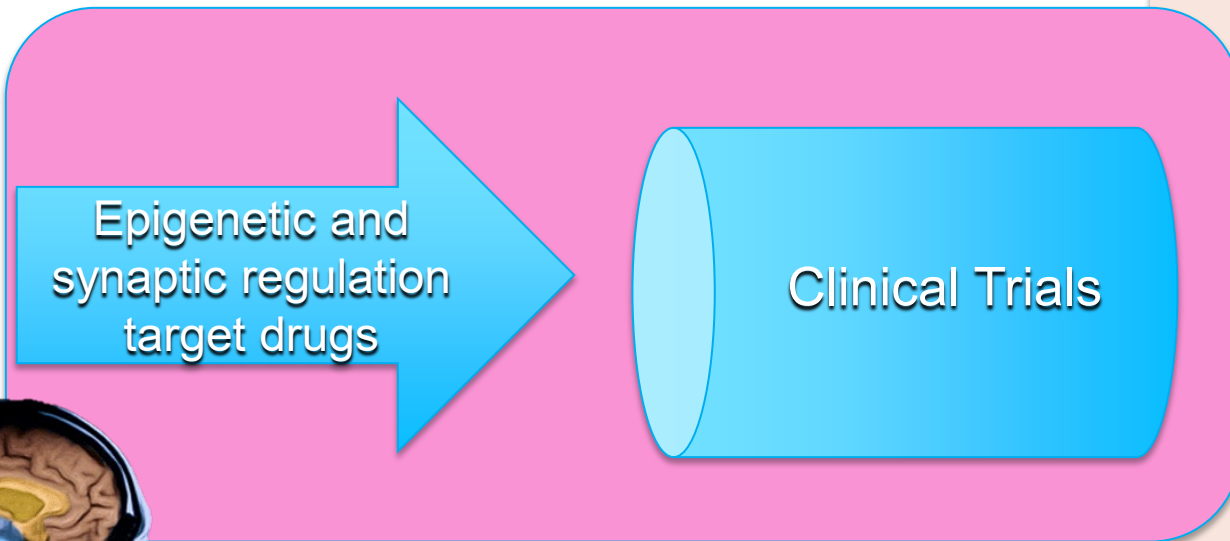
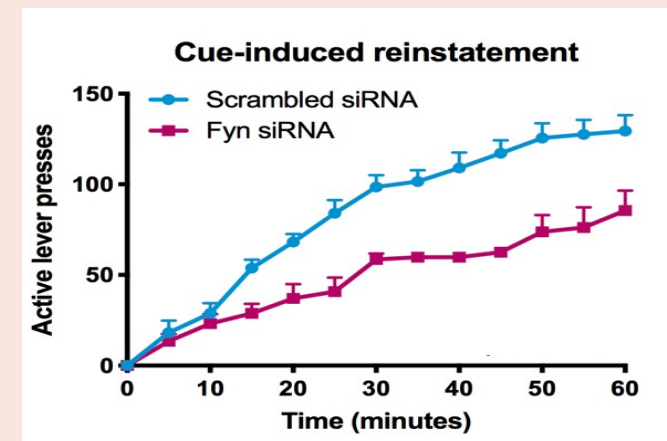
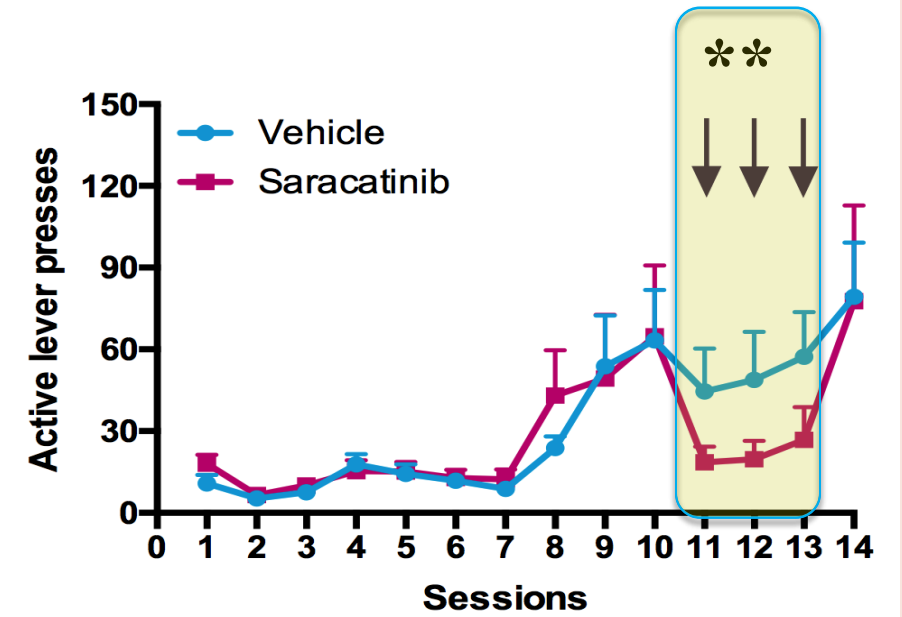
Egervari et al., Nature Communications, 2020

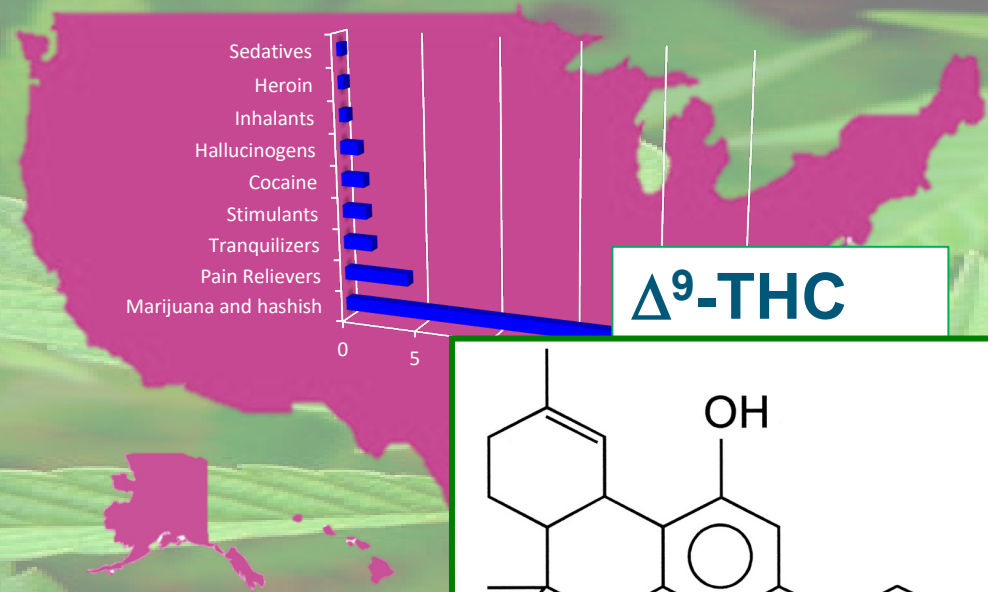
FYN – (tyrosine kinase) is a component of the synaptic machinery that regulates the phosphorylation of Tau; **hyperphosphorylated Tau** is a pathological feature of **neurodegenerative disorders (tauopathies)**



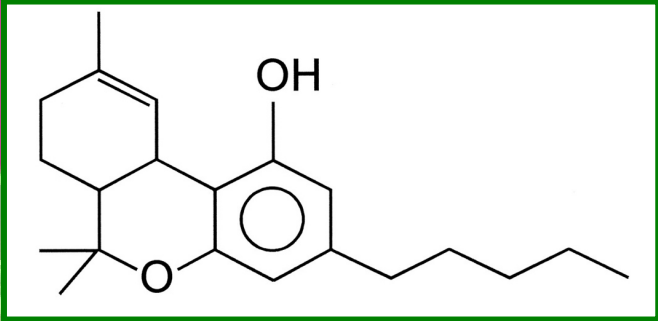


Inhibiting FYN (that reduces pTau) reduces heroin self-administration in animal models





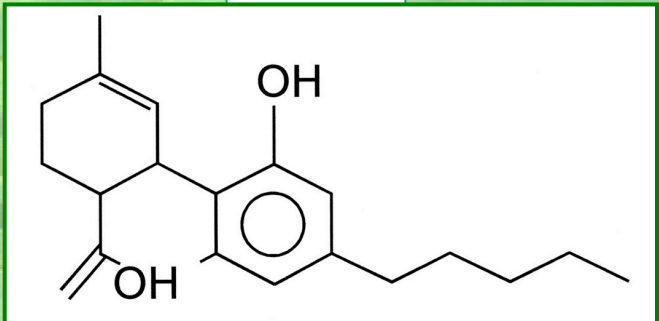
Δ^9 -THC



Δ^9 -tetrahydrocannabinol



CBD

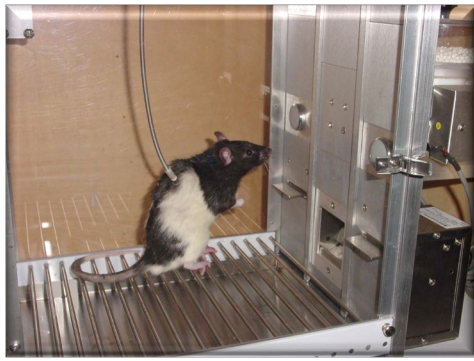


Cannabidiol

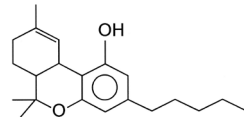
Cannabis contains over 500 chemicals including >140 cannabinoids which have a greater or lesser degree of psycho-pharmaco-activity



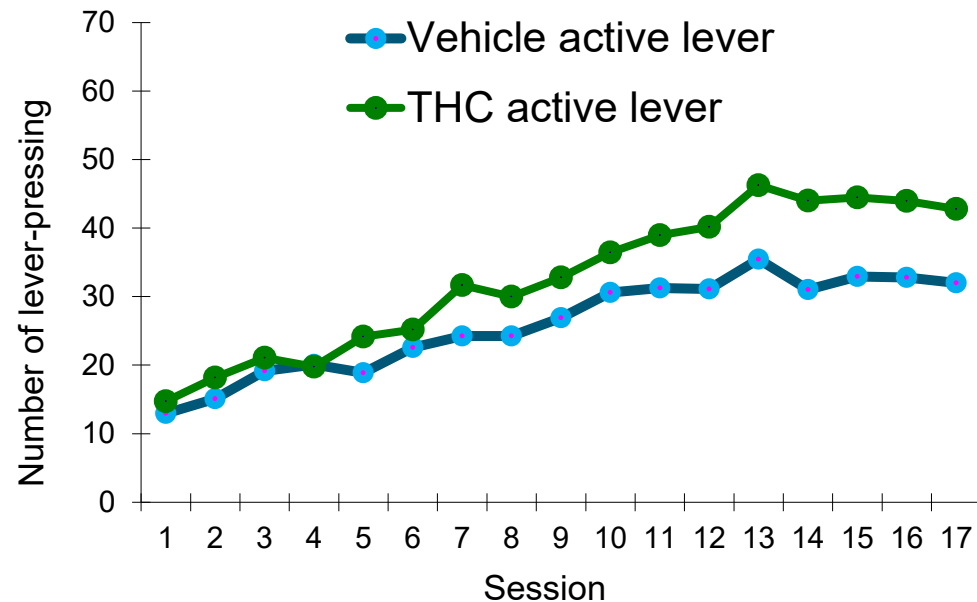
Distinct Effects of THC and CBD Relevant to Heroin Vulnerability



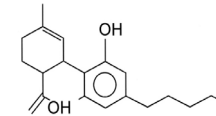
Δ^9 -THC



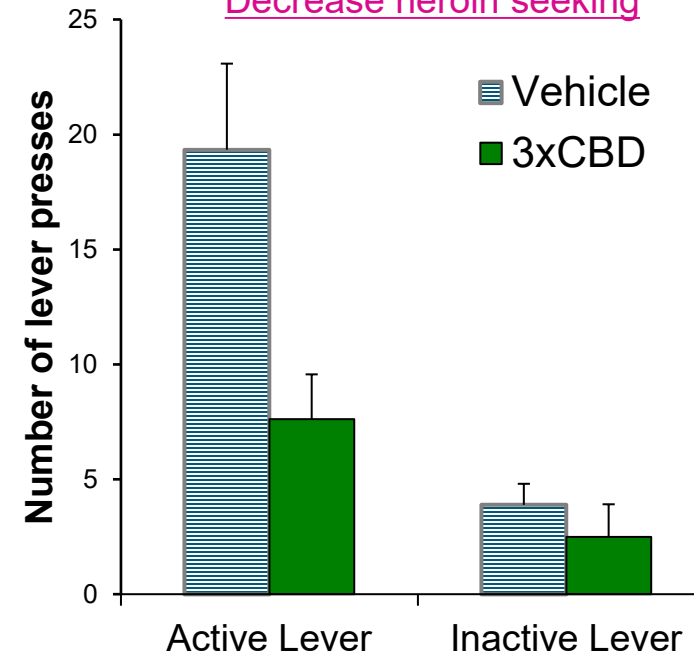
Enhance heroin self-administration



CBD



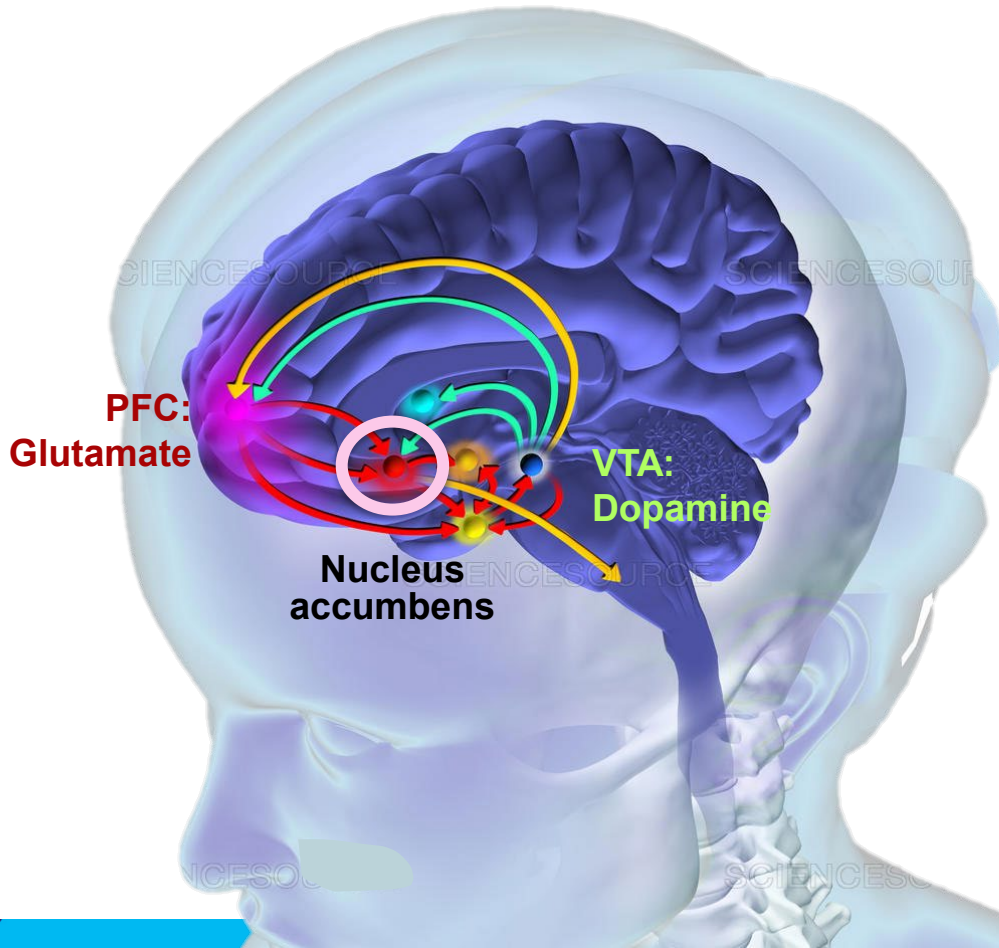
Decrease heroin seeking



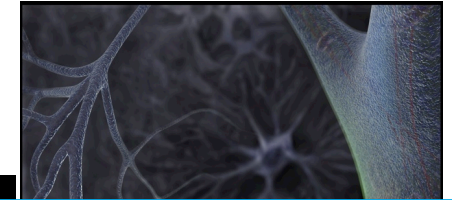
Opioid Abuse is Characterized by Impairments of Glutamatergic Transmission

Dopamine – reward

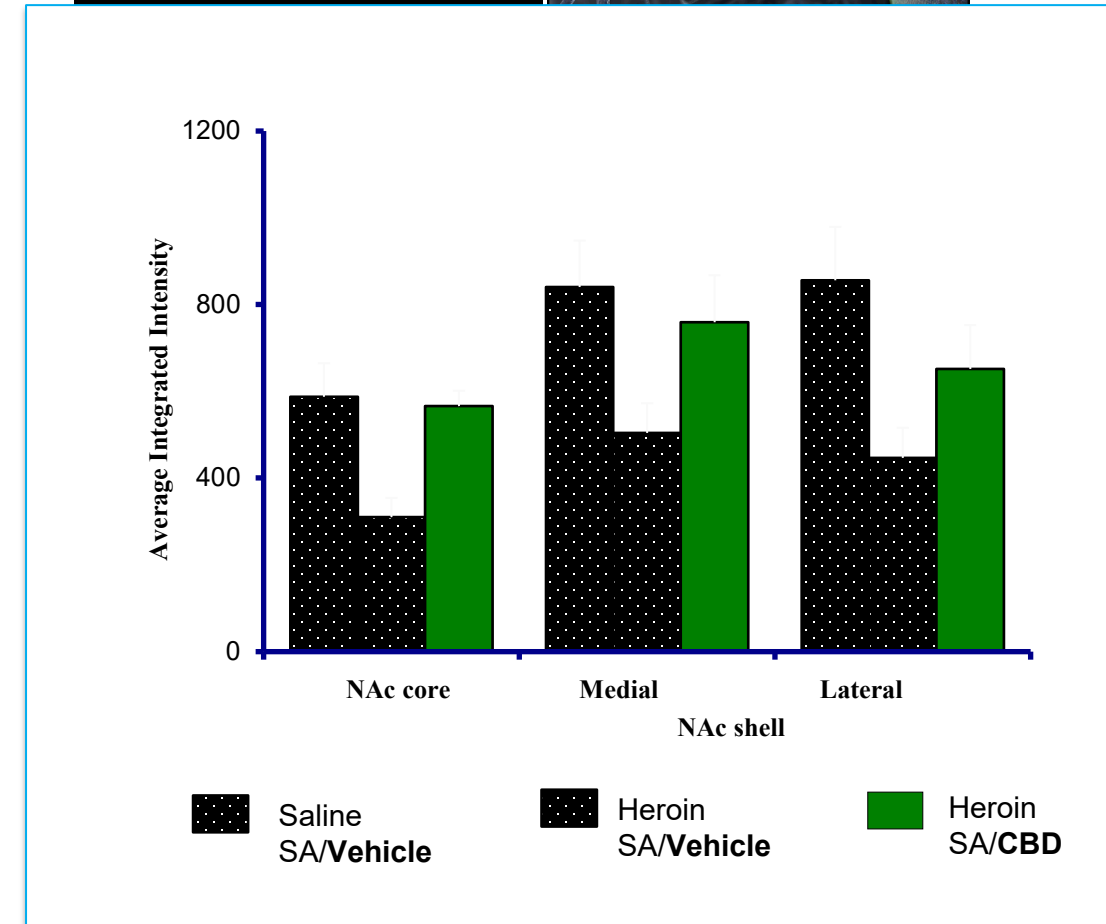
Glutamate – excitatory neurotransmission; modulate reward system; drug seeking



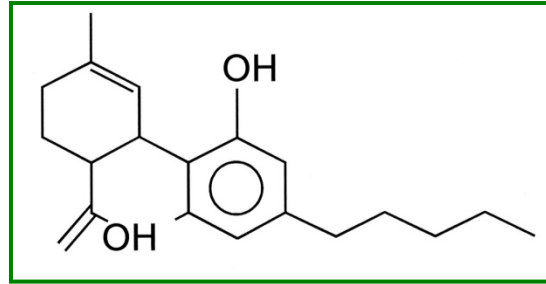
Nucleus accumbens



Synaptic plasticity



Cannabidiol as Potential Treatment Intervention for Opioid Relapse



- ▶ FDA Approval
- ▶ IRB Approval
- ▶ NIH Grant – R21, R01

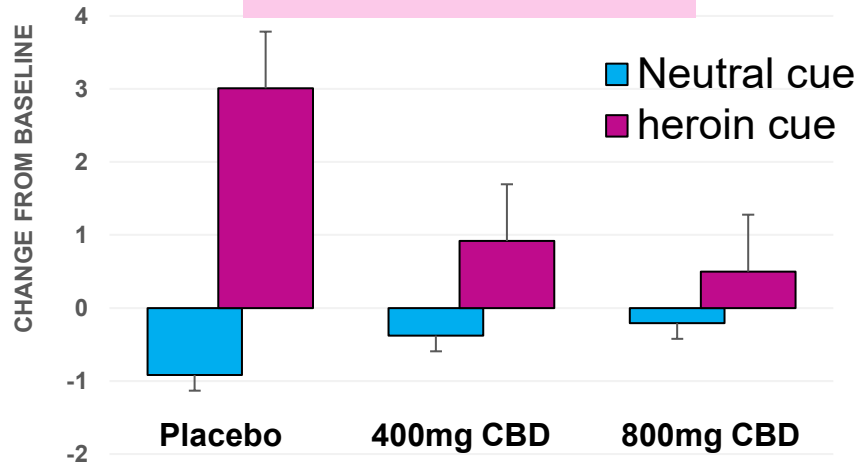


Clinical Lab Study

CBD Reduces Cue-Induced Craving and Anxiety in Individuals with Heroin Use Disorder

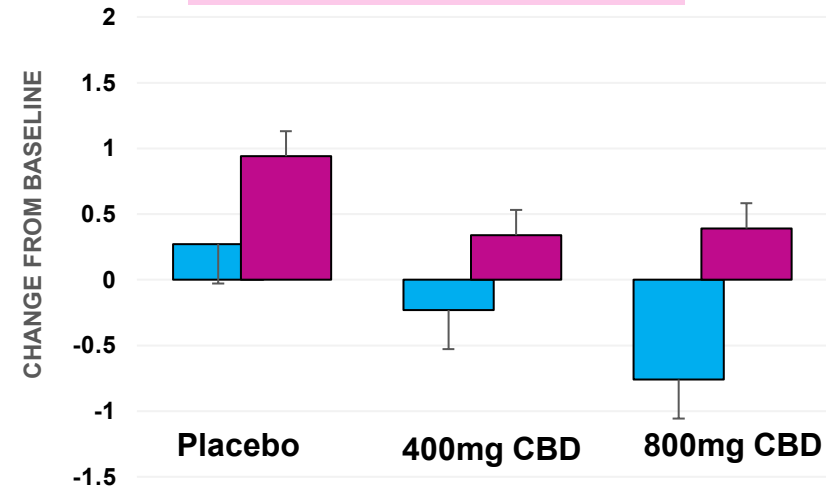


(1-2hr post CBD/Placebo)

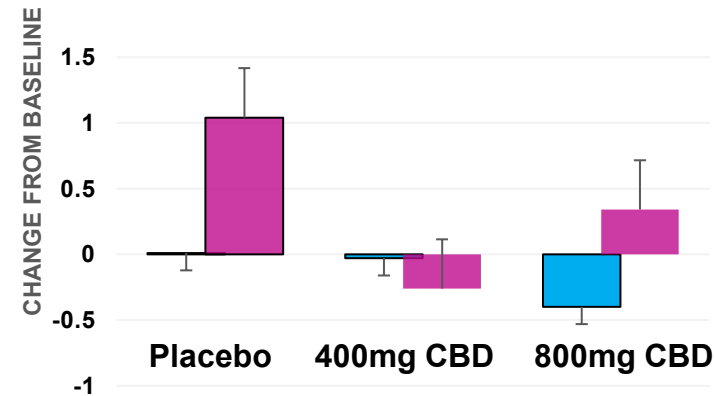
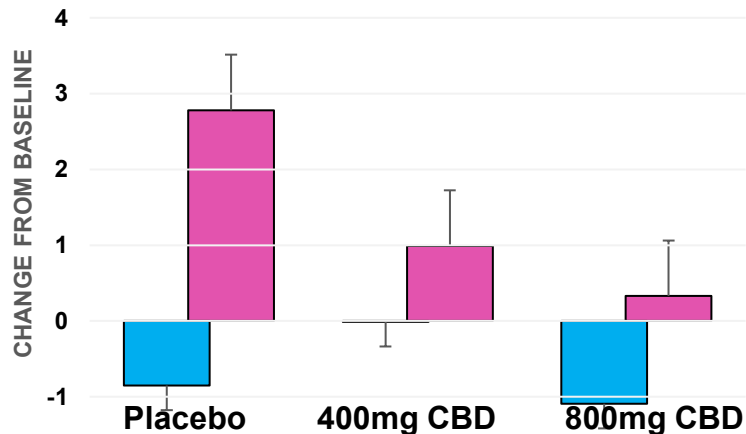


CRAVING

(7 days post CBD/Placebo)



ANXIETY



Reduced
cue-
induced
increase
of cortisol
and heart
rate

The PathForget the Stats and Rules

- ▶ Embrace being different..... Being an 'outlier' is not always bad
- ▶ Get out of your comfort zone..... science requires people who think differently
- ▶ Success requires bravery Focus on your passion, not just what is popular [*though important to have insight about the direction of the field*]
- ▶ Seek out all opportunities, even those that seem out of reach
- ▶ Scientific discoveries are dependent on training different types of people....especially those who are not our clones

