Dopamine, Reward and Addiction

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The Ghost of Mark Thomas
Departments of Neuroscience and Psychology

How do we define addiction?

Religion

politics

ethics

How do we define addiction?

Context matters!

Psychology

biology

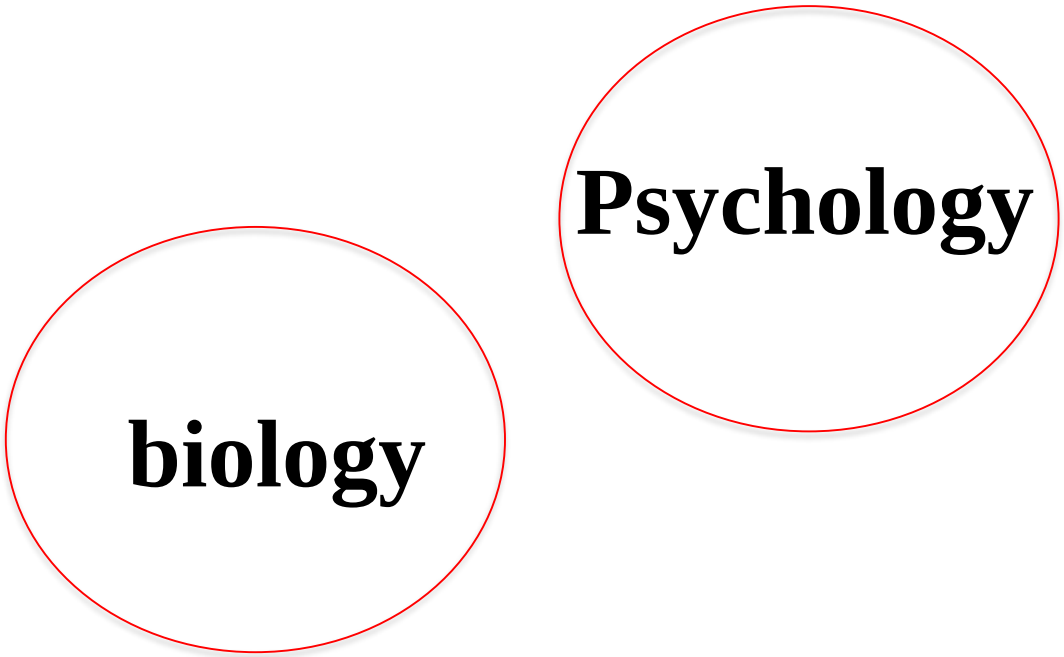
Sociology

politics

Religion

ethics

How do we define addiction?



Sociology

How do we define addiction?

- Psychology: “addiction can best be defined as the loss of control over drug use, or the compulsive seeking and taking of drugs despite adverse consequences.” –Nestler 2001
- Biology: TBD?

Plan

- Reward Systems
- Role of dopamine in reward systems
- How drugs affect dopamine in reward systems
- Experimental models for assessing drug effects on the brain

Reward Systems

With tablemates, discuss the purpose and/or function of reward systems.

What use is a reward system

Direct behavior towards
"advantageous" stimuli

Food

Sex

Social network

Which ultimately leads to....

SURVIVAL!!!

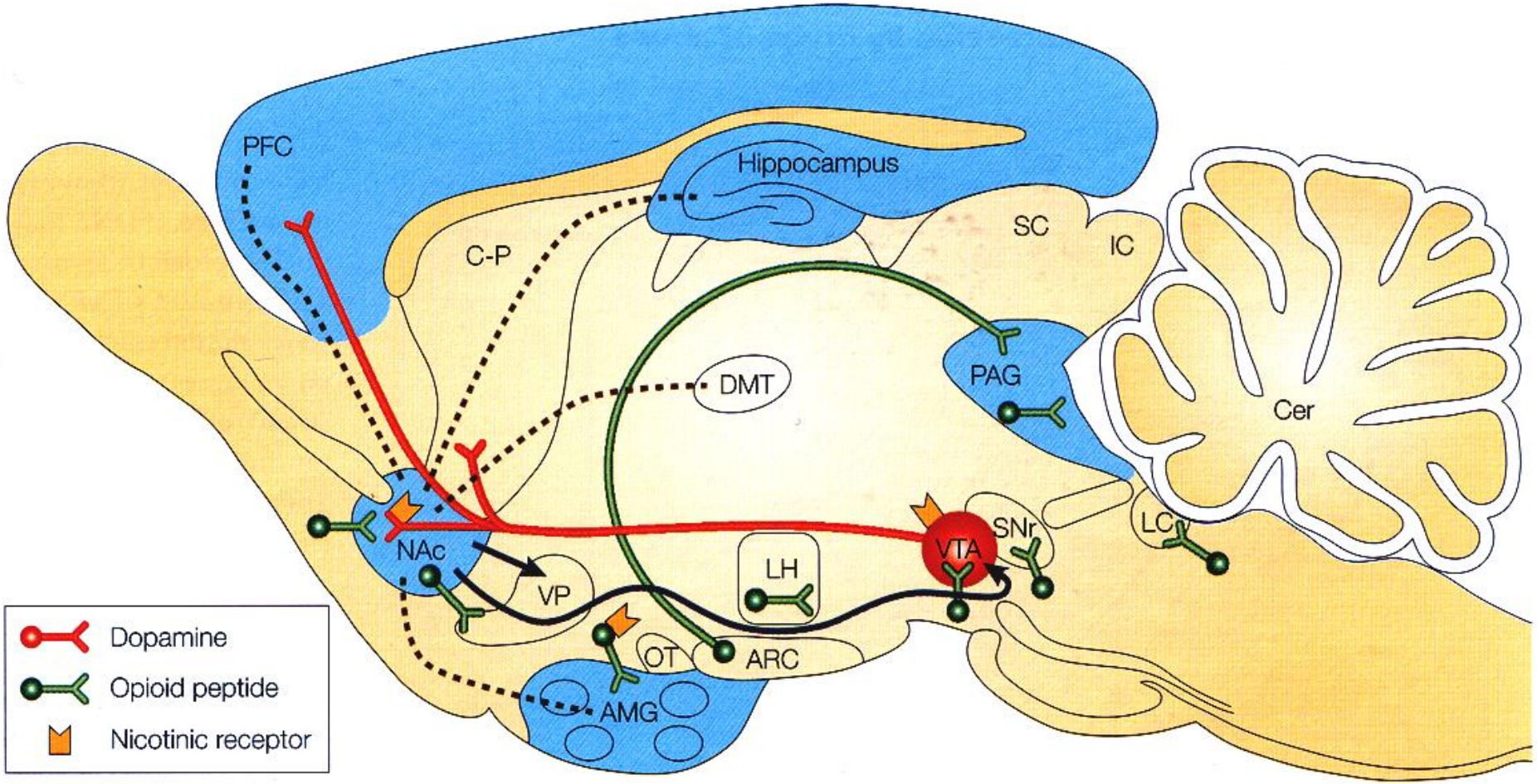
Season 37???

What use is a reward system

- Reward circuitry directs us towards "advantageous stimuli" that are necessary for survival.
- So, where IS the reward circuitry???

Reward Circuitry interconnects many areas of the brain. With tablemates, list these brain areas and their known functions.

Reward Circuitry



(from EJ Nestler, Nature Reviews Neuroscience, 2001)

The reward system interconnects many areas of the brain.

- **Nucleus Accumbens: motivation, reward, reinforcement**
- **Ventral Tegmental area: reward, motivation**
- Prefrontal Cortex (PFC) : decision-making
- Hippocampus: learning and memory
- Amygdala: emotion
- Dorsal Striatum (caudate/putamen): motor function, stimulus-response learning

The reward system would not be useful without connections to diverse areas of the brain

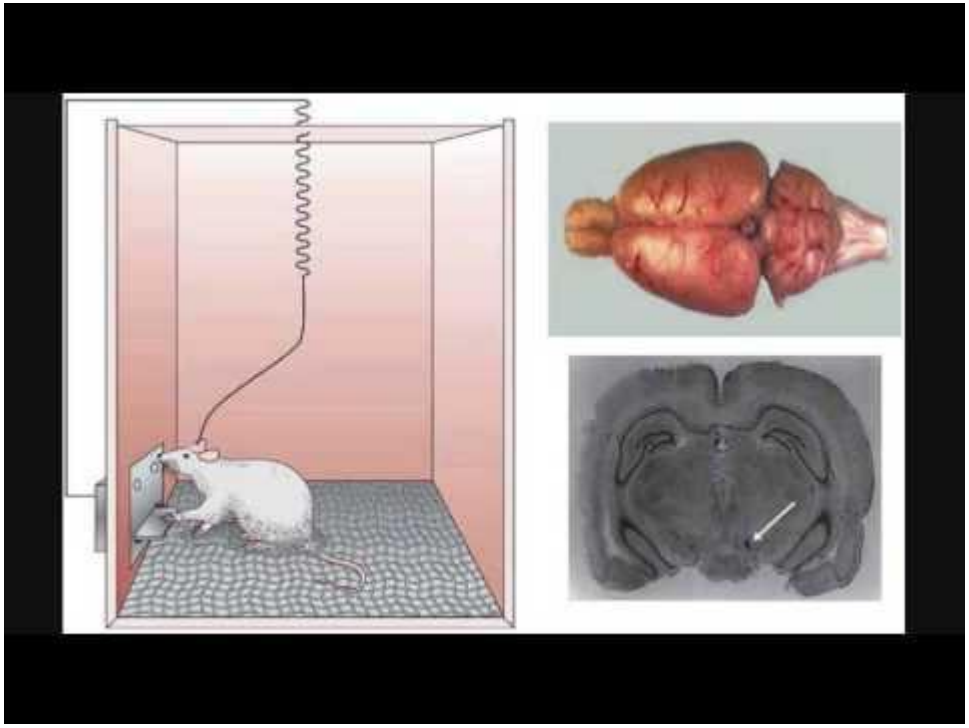
- **Nucleus Accumbens: Am I motivated to eat chocolate?**
- **Ventral Tegmental area: Am I motivated to eat chocolate?**
- Prefrontal Cortex (PFC) : do I eat the reward of chocolate or not? Do I eat something else?
- Hippocampus: Do I remember if I find chocolate rewarding or tasty?
- Amygdala: Does eating chocolate relieve my anxiety
- Striatum (caudate/putamen): What stimuli will result in me eating chocolate?

How were these circuits identified?

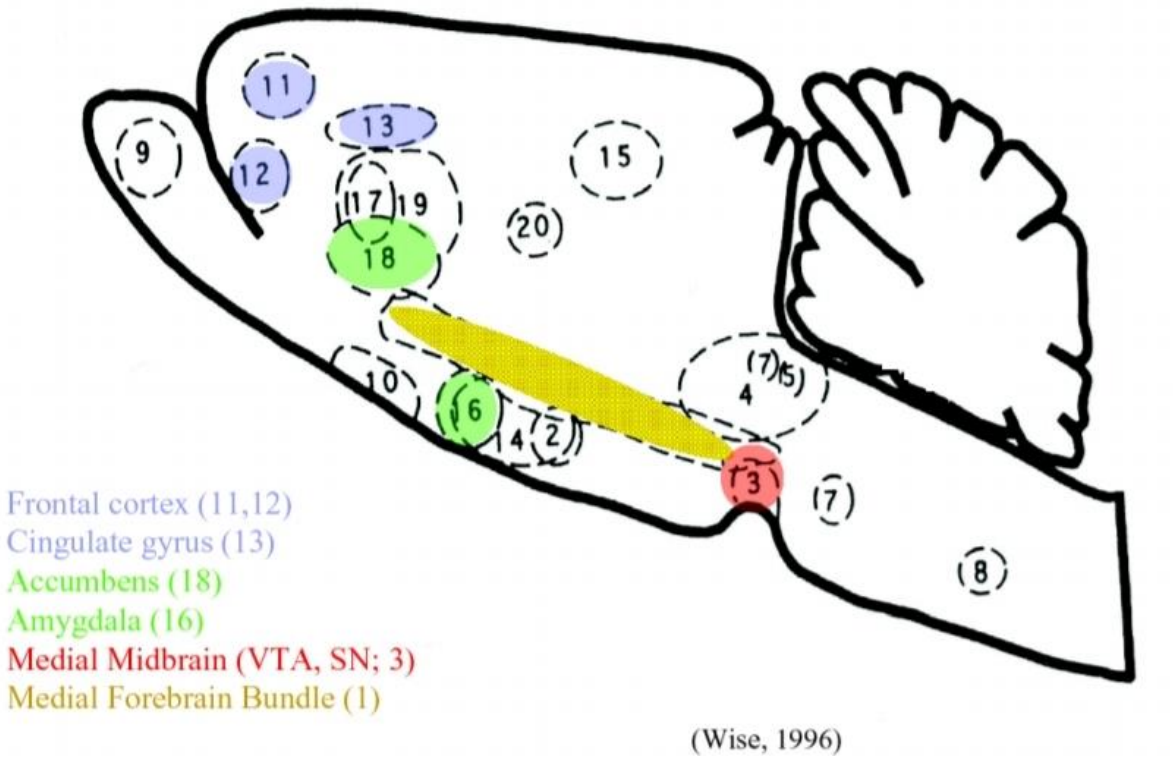
- Lesions in certain areas and the resulting behavior informed scientists about areas involved in reward circuitry.
- fMRI would have been an option, but was not around during early studies.
- A more direct approach targeted brain areas for electrical stimulation and observed the resulting behavior.

Brain Stimulation Reward (BSR)

- Place permanent electrode in region of interest.
- Teach animal to associate lever press with an electrical stimulation of that area.
- Record lever presses, correlate number of presses with level of pleasure or reward.
- Reward circuitry was identified based on stimulated areas that yielded more lever presses



Brain Stimulation Reward (BSR) regions

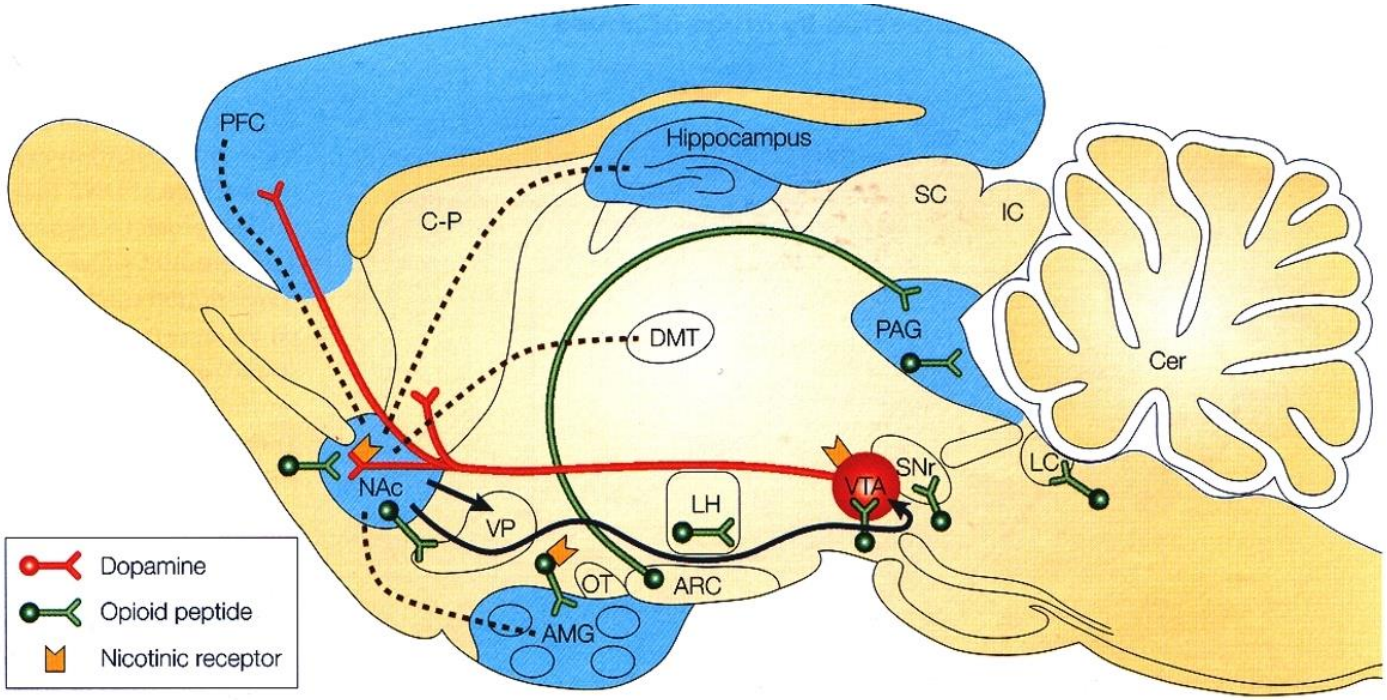


(Wise, 1996)

- When stimulating areas 20, 15, 10, etc, rodents would not press the lever for more stimulation.
- When stimulating frontal cortex, cingulate gyrus, accumbens, VTA, etc, rodents would continually press the lever to receive more electrical stimulation in that area, which was indicative of reward.

With tablemates, list common neurotransmitters found in reward circuitry

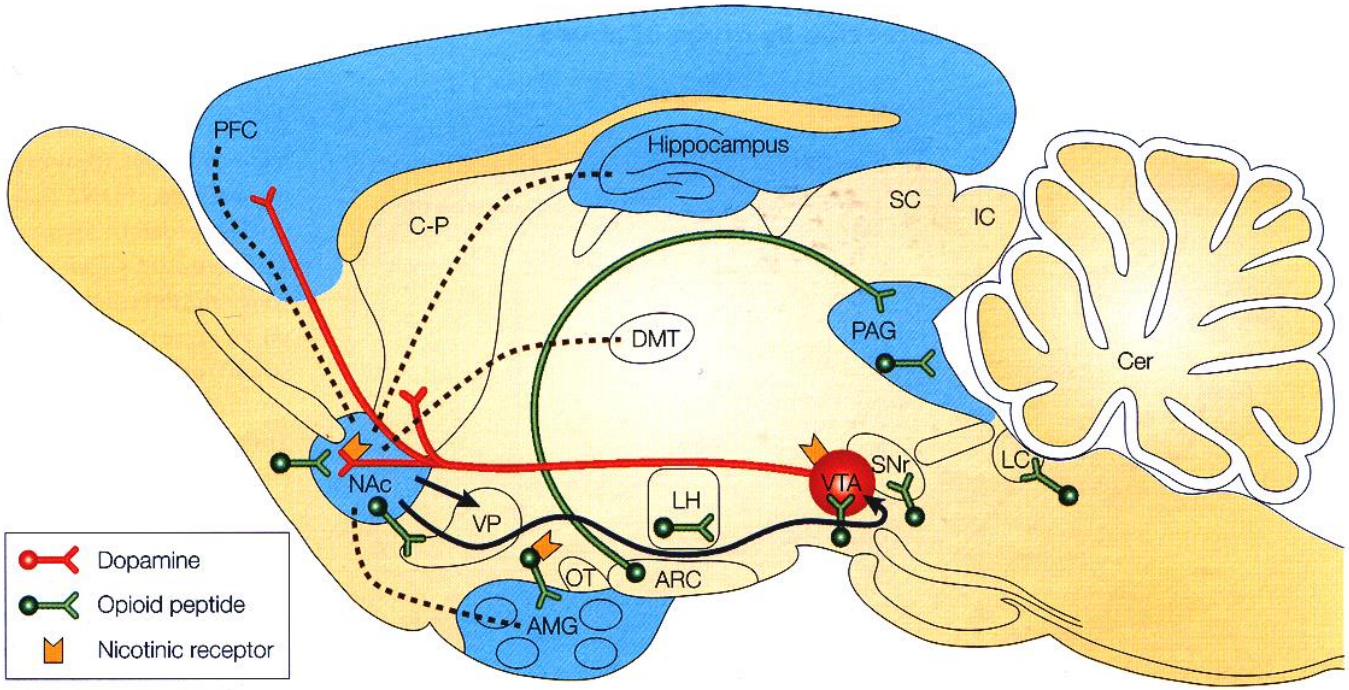
With tablemates, list common neurotransmitters found in reward circuitry



- **Dopamine**
- Glutamate
- Endogenous opioids
- Acetylcholine

Role of Dopamine in Reward Systems

Dopamine projections in Reward Circuitry

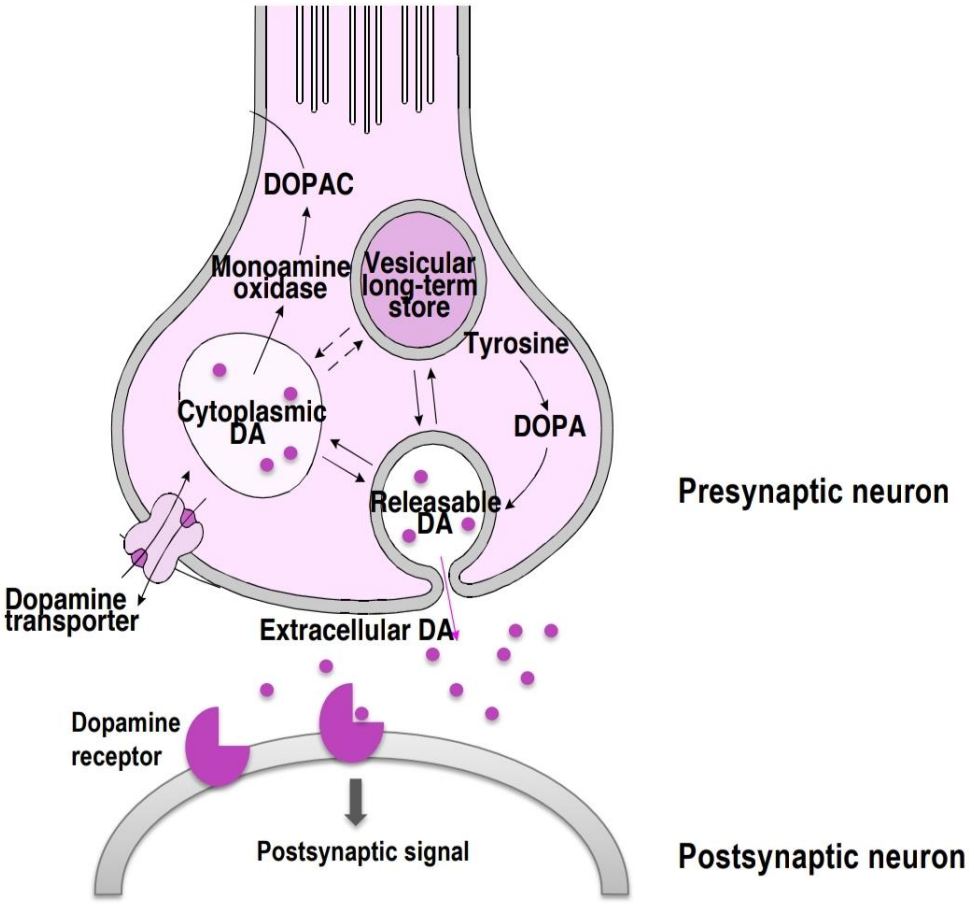


- VTA -> NAc
- VTA -> PFC
- VTA -> Caudate/putamen

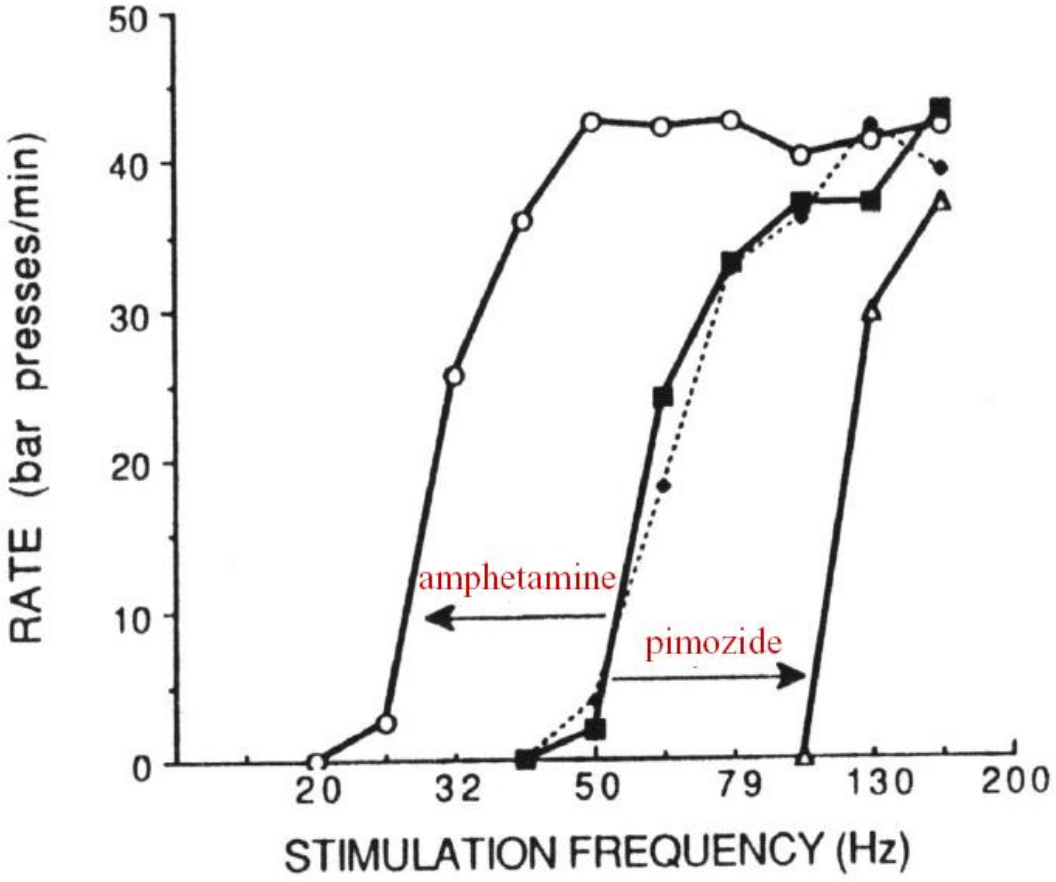
(from EJ Nestler, Nature Reviews Neuroscience, 2001)

Dopamine synapse – form and function

- Dopamine synapses have the same properties as any other typical synapse:
  - Neurotransmitter
  - Neurotransmitter vesicles
  - Precursor molecules and enzymes necessary to make neurotransmitter
  - Machinery to release vesicles into extracellular space
  - Reuptake transporters
  - Postsynaptic terminal with receptors



Dopamine signaling enhances BSR



- BSR experiment with addition of amphetamine (elevates extracellular dopamine) OR pimozide (dopamine antagonist).
- With amphetamine/more extracellular dopamine, a lower stimulation frequency is necessary for rodents to detect the rewarding stimulus.

Gallistel and Karras (1984)

Discuss with tablemates: does dopamine mediate or represent pleasure or liking? Why or why not?

Is dopamine necessary for "liking" responses?

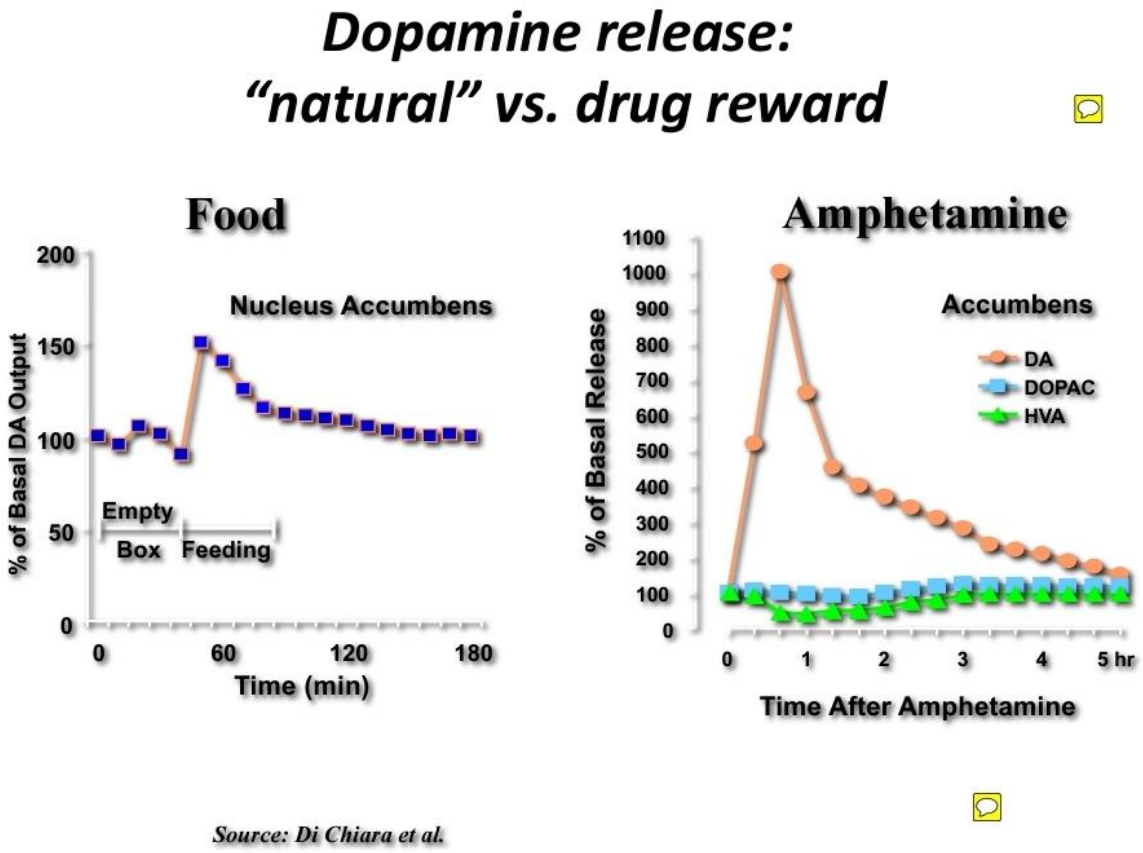
- Rodents given sweet tastant, facial expressions analyzed.Knocking out majority of dopamine neurons did not change their facial expressions in response to a sweet tastant.
- Dopamine is NOT necessary for "liking."

Berridge and Robinson, Trends in Neurosci, 2003

How drugs affect dopamine in reward systems

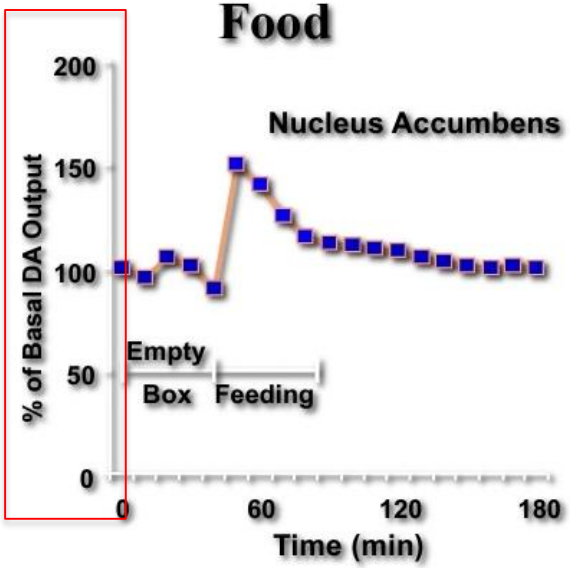
Drug reward leads to large increases in dopamine release.

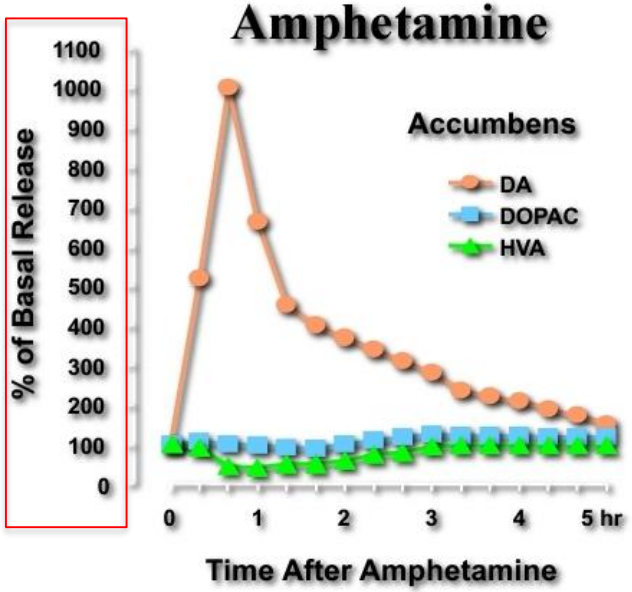
- Dopamine levels in the NAc increase in response to food.
- Dopamine levels in NAc increase much more in response to amphetamines.



- Note the difference in scale! Imagine your chocolate addiction multiplied by 18!

Dopamine release: "natural" vs. drug reward



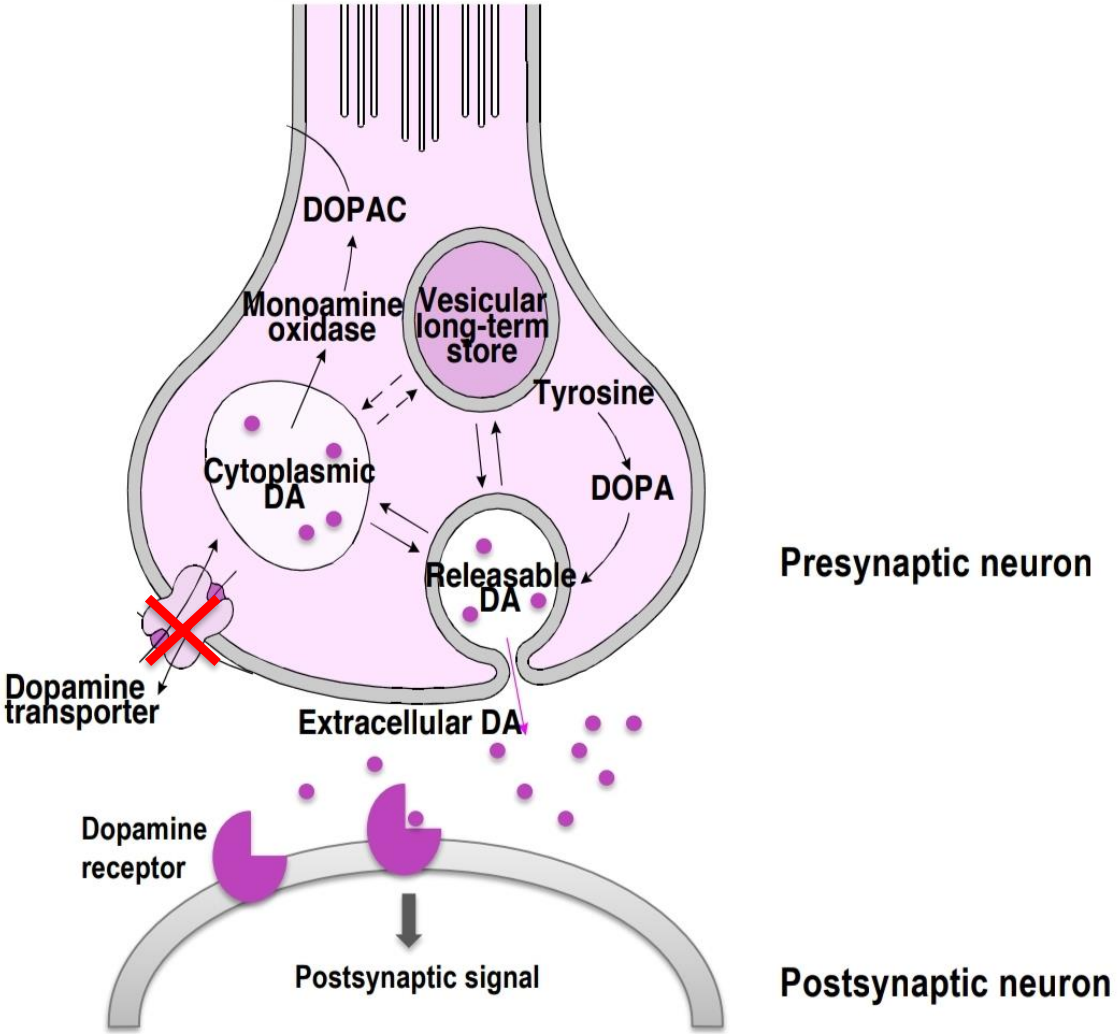


Source: Di Chiara et al.

With tablemates, discuss the drug action of cocaine

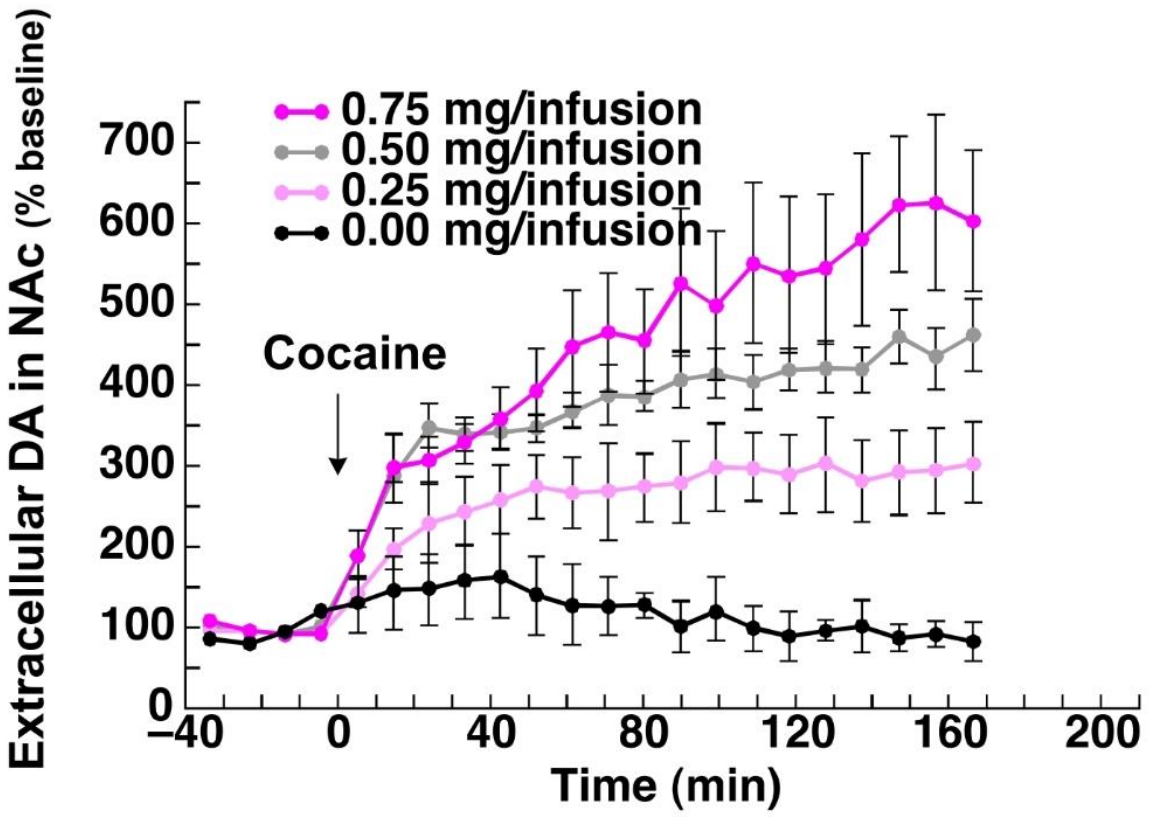
Dopamine synapse – form and function

Cocaine blocks the function of dopamine reuptake transporters, which allows for dopamine to stay longer in the synapse to and continue to bind to dopamine receptors.

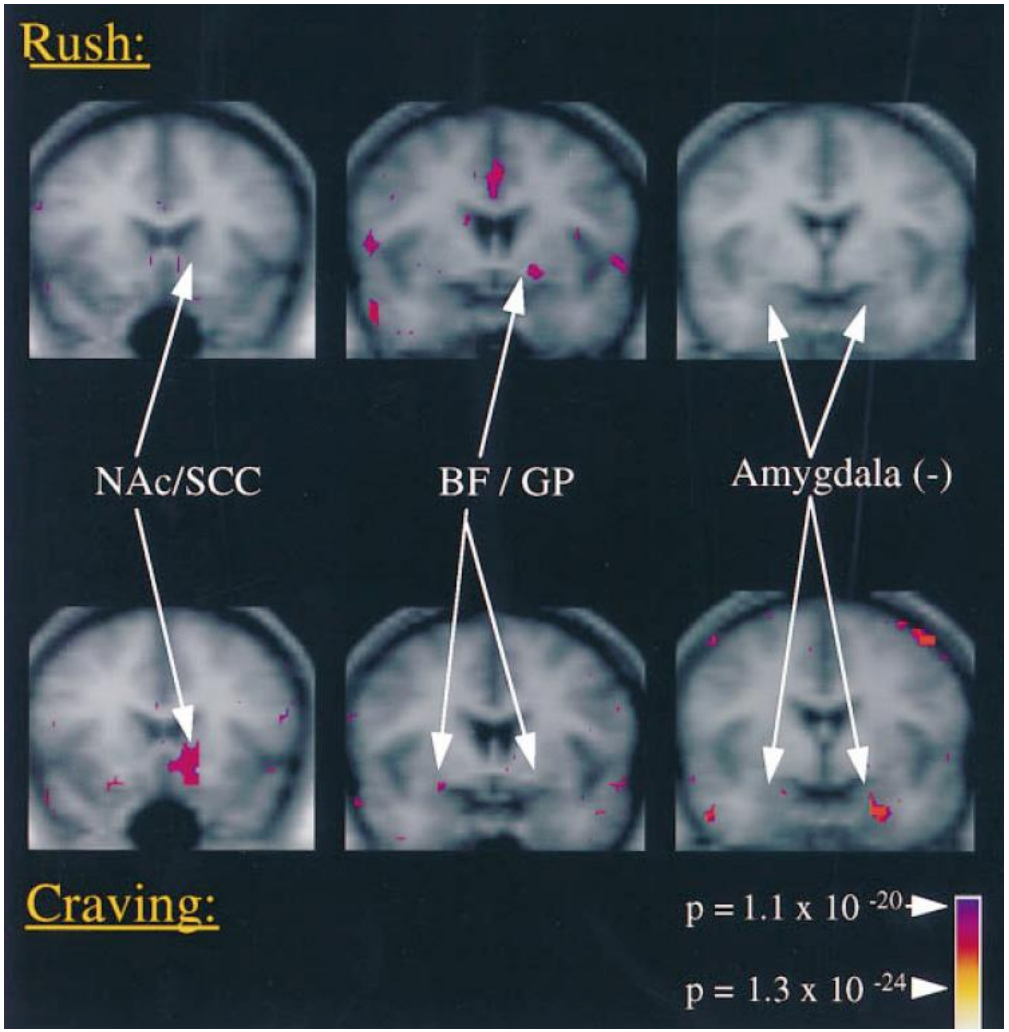


Do addictive drugs affect dopamine signaling?

Cocaine blocks the function of dopamine reuptake transporters, which allows for dopamine to stay longer in the synapse to and continue to bind to dopamine receptors.



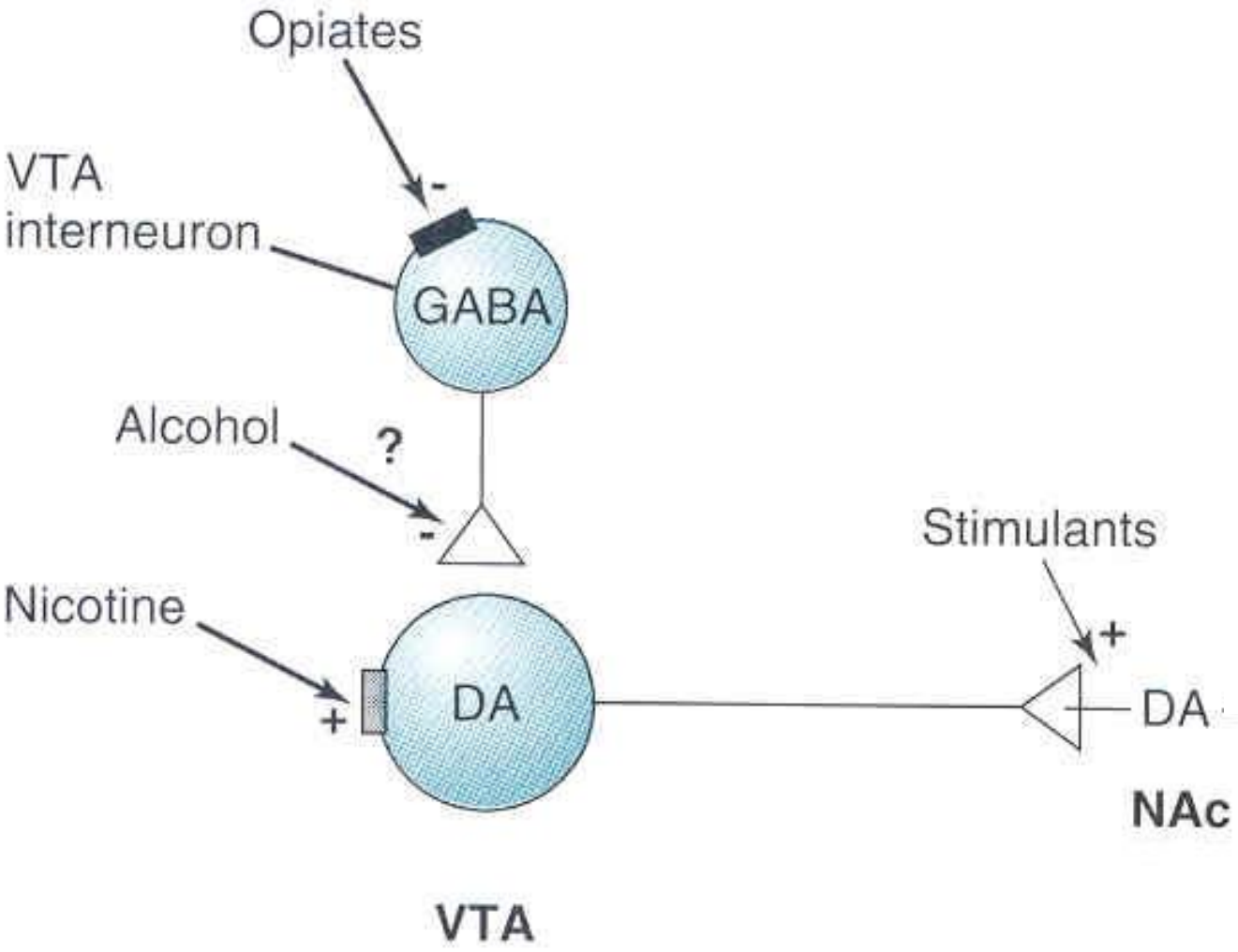
Cocaine= higher levels of dopamine. How does this translate into behavior?



- fMRI
- Gave subjects cocaine, reported when subjects felt rush vs. craving.
- More NAc activity during craving period.
- We know that cocaine increases extracellular dopamine levels in the NAc.
- Cocaine-mediated increases in dopamine levels in NAc correlated with “do this again” signal rather than “liking” signal.

Breiter et al., Neuron, 1997

Different drugs, different mechanisms → same result



Different drugs, different mechanisms → same result

Table 1 | **Acute actions of some drugs of abuse**

Drug	Action	Receptor signalling mechanism
Opiates	Agonist at μ-, δ- and κ-opioid receptors*	G_i
Cocaine	Indirect agonist at dopamine receptors by inhibiting dopamine transporters‡	G_i and G_s§
Amphetamine	Indirect agonist at dopamine receptors by stimulating dopamine release‡	G_i and G_s§
Ethanol	Facilitates $GABA_A$ receptor function and inhibits NMDA receptor function‖	Ligand-gated channels
Nicotine	Agonist at nicotinic acetylcholine receptors	Ligand-gated channels
Cannabinoids	Agonist at CB_1 and CB_2 cannabinoid receptors¶	G_i
Phencyclidine (PCP)	Antagonist at NMDA glutamate receptors	Ligand-gated channels
Hallucinogens	Partial agonist at 5-HT_{2A} serotonin receptors	G_q
Inhalants	Unknown	

(from EJ Nestler, Nature Reviews Neuroscience, 2001)

Experimental models for assessing drug effects on the brain

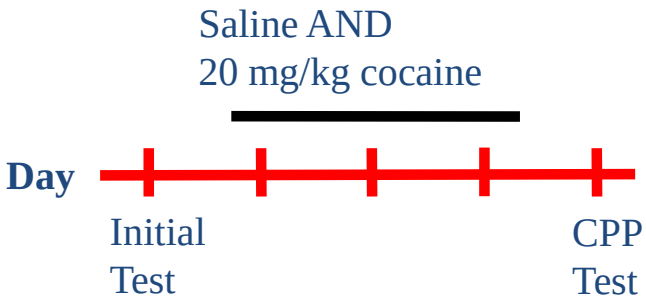
With tablemates, discuss methods for evaluating the effect of drugs on the brain. In your discussion, consider:

- Behavior
- Structure
- Genetics

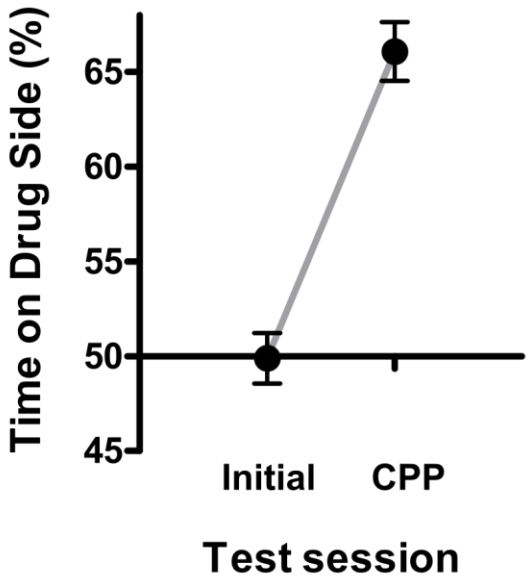
Behavioral Models of Drug Addiction

- Conditioned Place Preference and Self Administration models assess how addictive a drug may be.

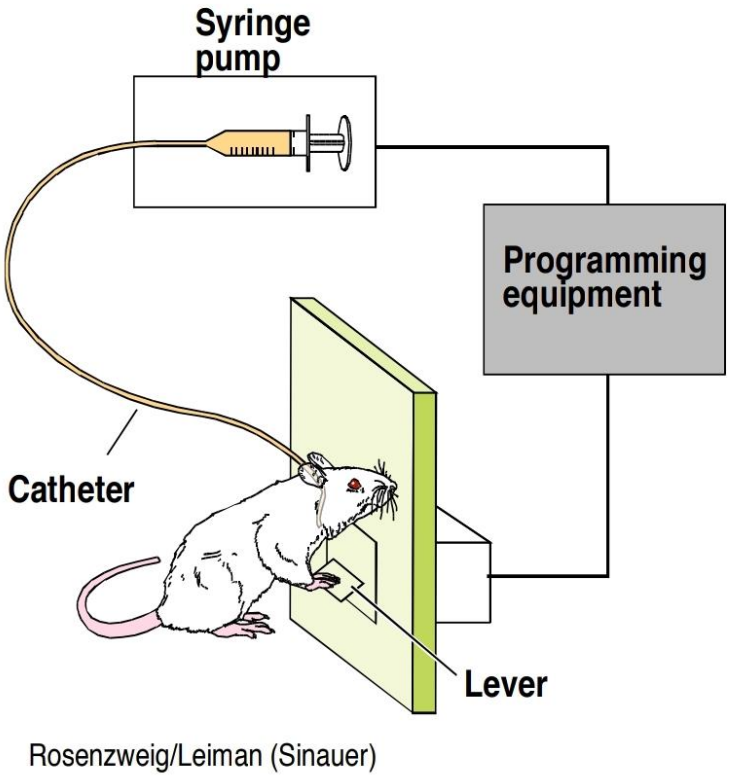
Conditioned place preference (CPP)



Basic paradigm: 1. Have animal learn to associate drug with one side of cage, saline with the other side. 2. Measure amount of time the animal spends on one side or another.



Drug self administration



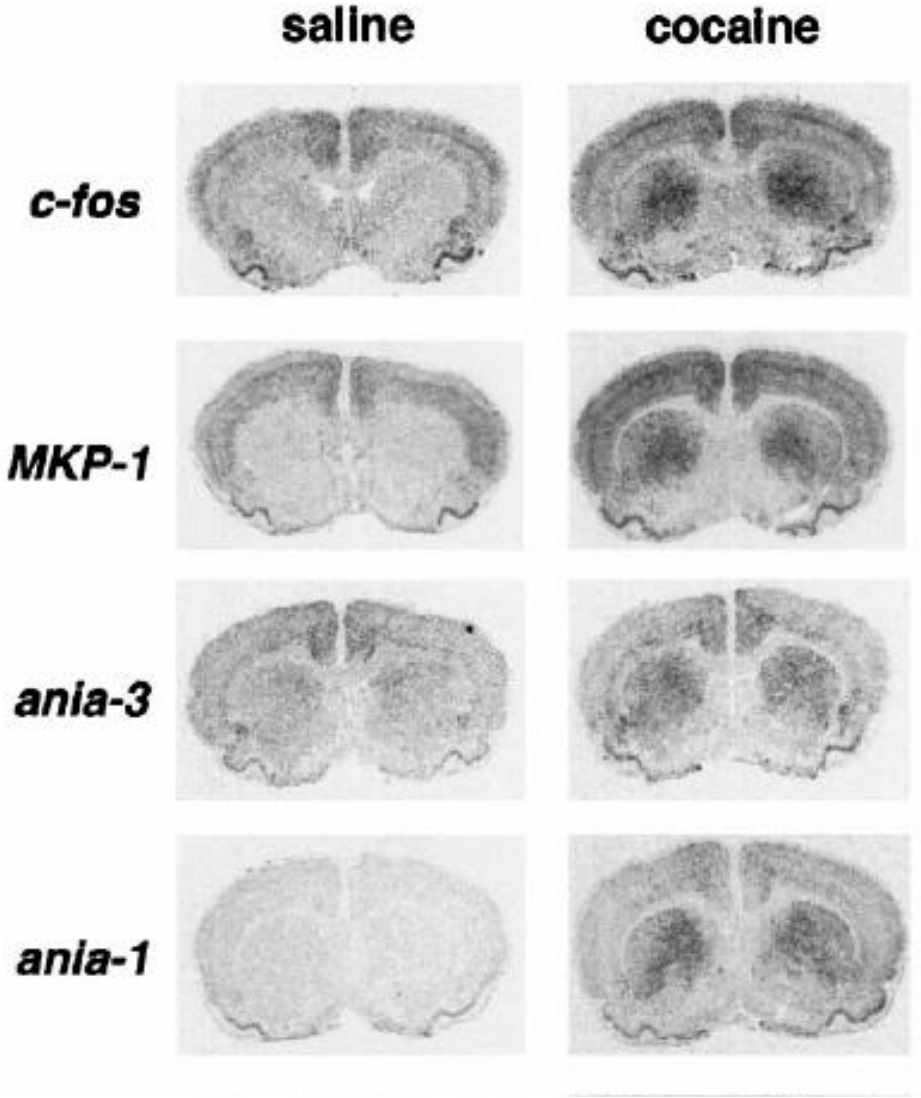
Basic paradigm: Teach animal to associate lever with the drug. Present animal with on demand access to drug through lever press. Count amount of times lever is pressed in a session.

Genetic Approach to Studyig Addiction

Genetic Approach to Studying Addiction

- Two basic strategies:
- 1. Change the genetics, observe differences behavior.
- 2. Change or manipulate behavior, observe differences in genetics.

Changes in gene expression occur with a single exposure to cocaine

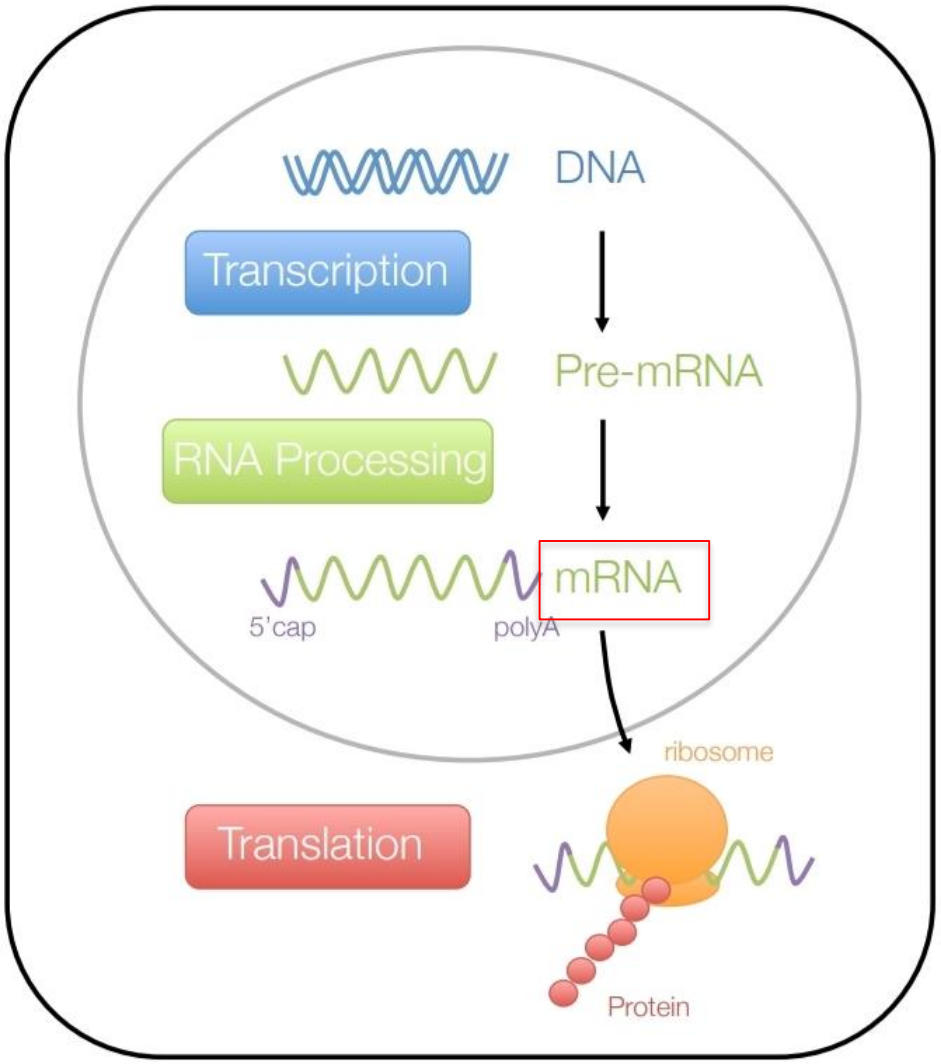


Berke et al., J Neurosci, 1998

Example of stragety #2: Change behavior by introducing drug, observe differences in genetics in striatum.

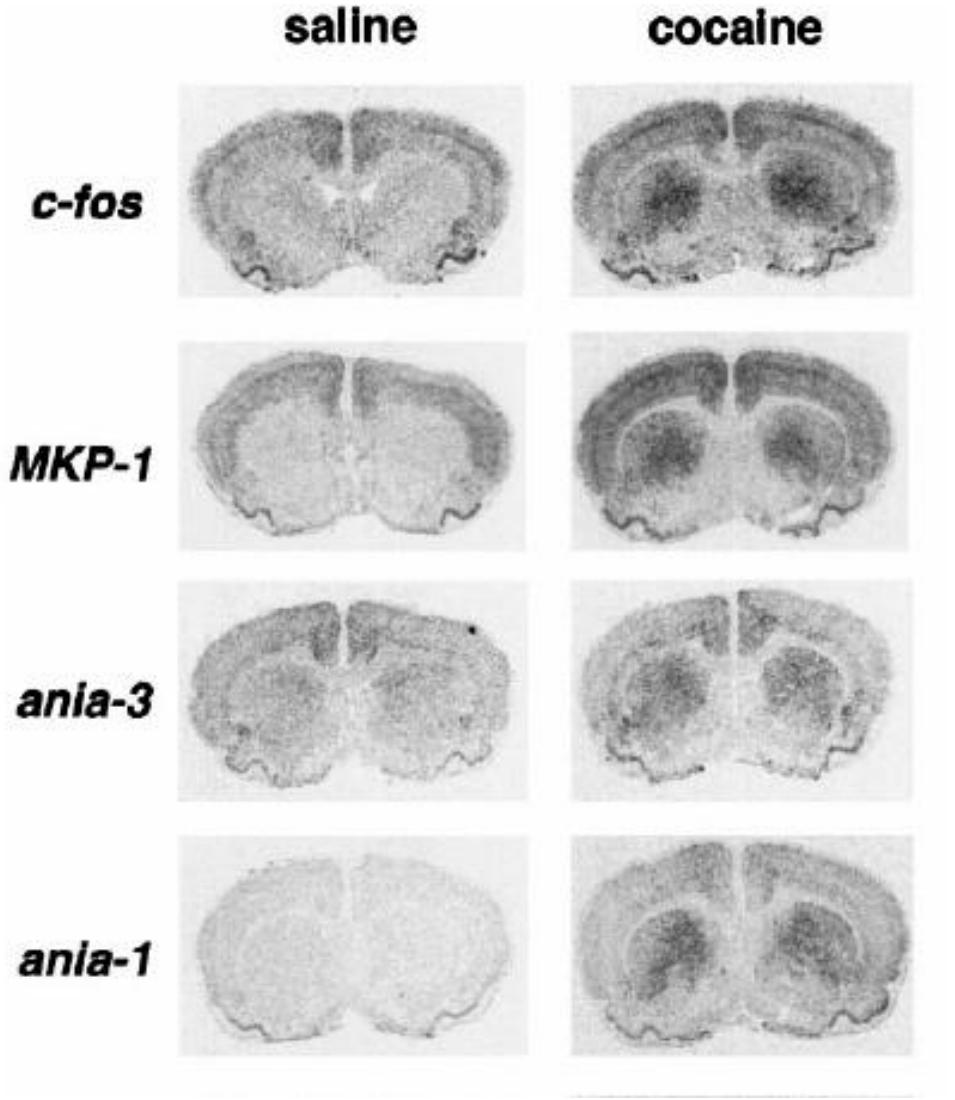
This example is labeling mRNA. Increased darkness in an area indicates increased mRNA transcripts.

Review on Gene Expression



- DNA is transcribed into RNA.
- RNA is spliced into mRNA.
- mRNA is brought to the ribosome for translation into protein.
- Changes in gene expression indicate a change in cellular function

Changes in gene expression occur with a single exposure to cocaine



What processes are these genes involved in?

- c-fos: marker of transient cellular activity
- MKP-1: memory formation
- ania-3: marker of transient cellular activity

Berke et al., J Neurosci, 1998

Structural Approach to Studying Addiction

Drug exposure leads to a larger dendritic tree with more spine. More spines= more synapses!

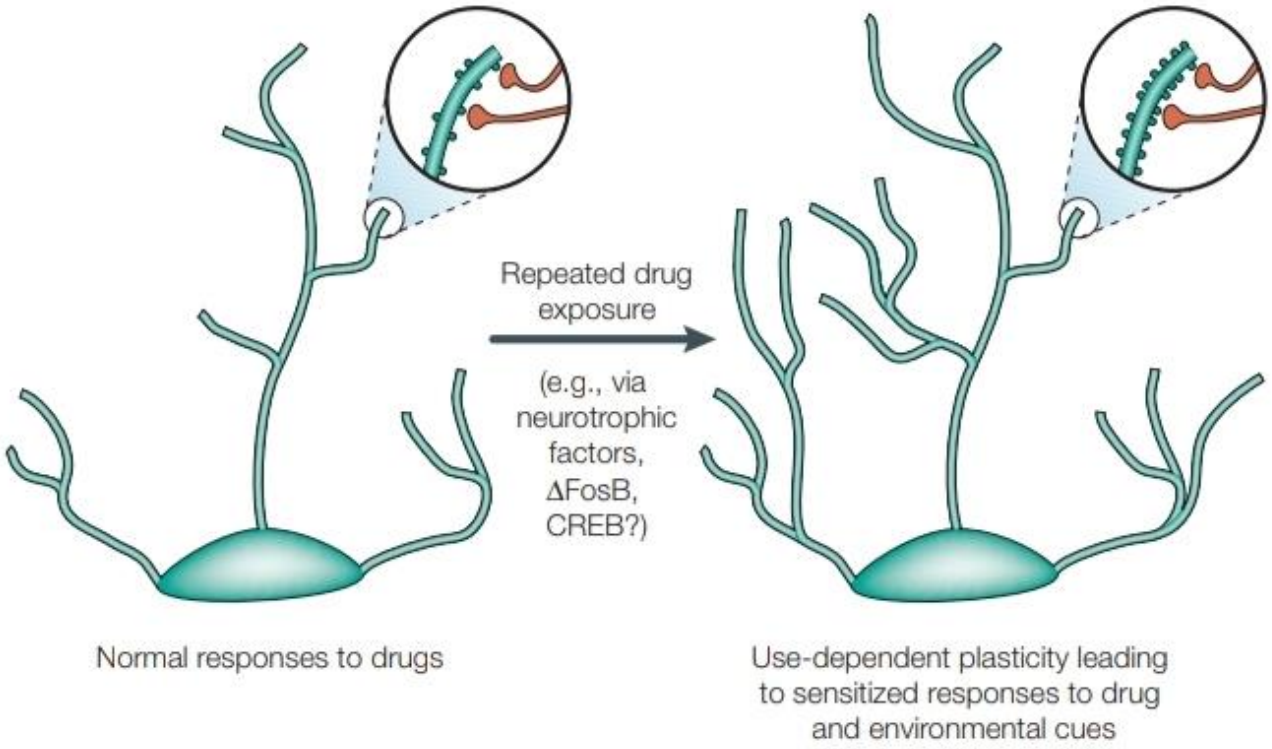
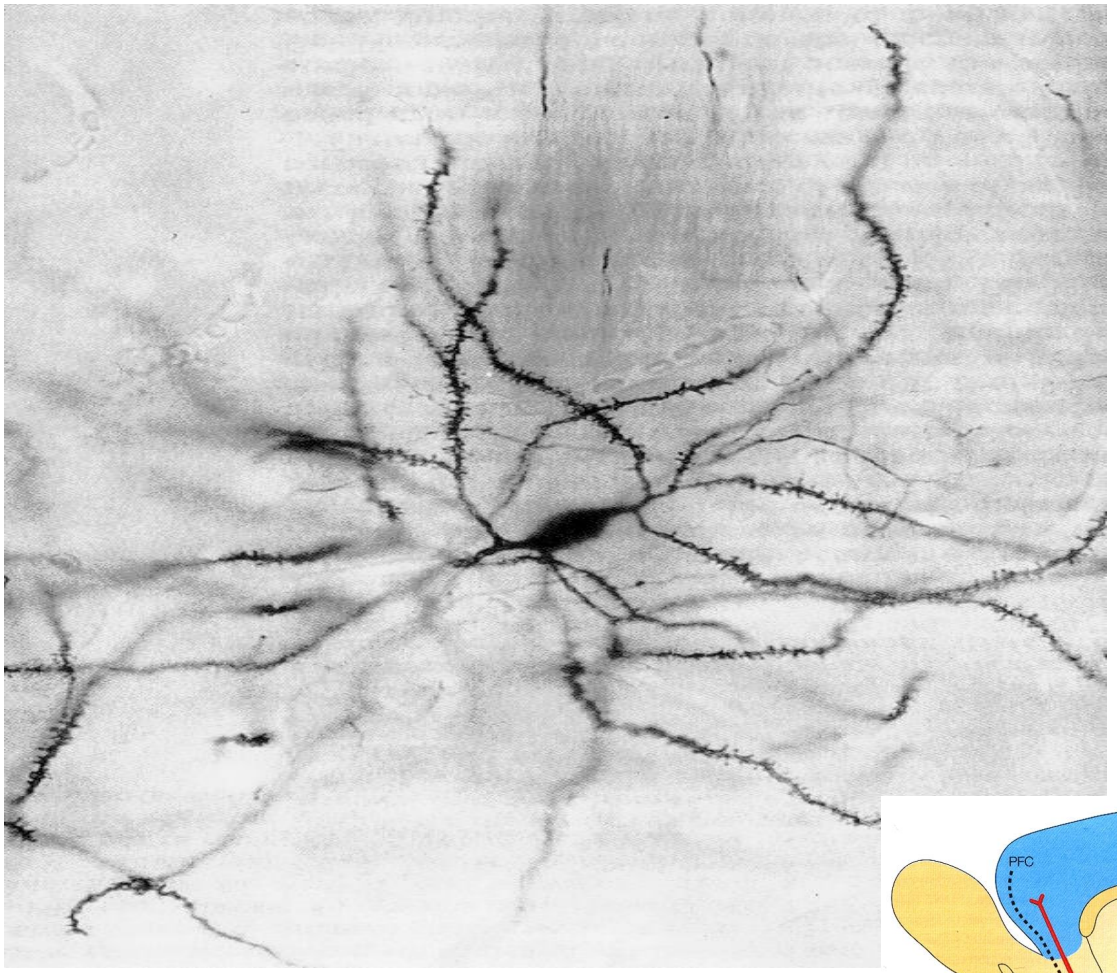


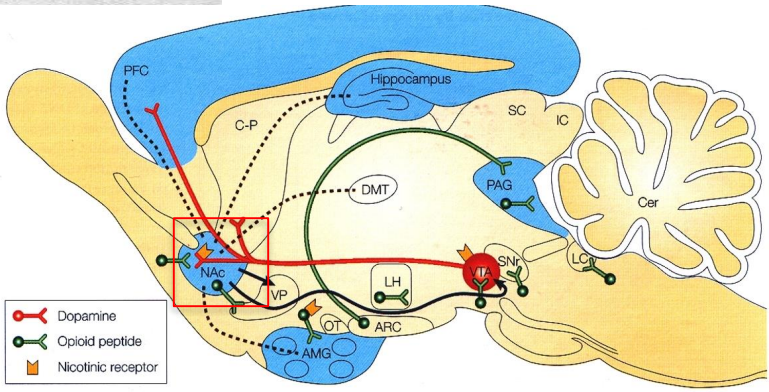
Figure 5 | **Regulation of dendritic structure by drugs of abuse.** The figure shows the expansion of a dendritic tree after chronic exposure to a drug of abuse, as has been observed in the nucleus accumbens and in the prefrontal cortex. The areas of magnification show an increase in dendritic spines, which is postulated to occur in conjunction with activated nerve terminals. Such alterations in dendritic structure, which are similar to those observed in other examples of synaptic plasticity such as long-term potentiation, could mediate long-lived sensitized responses to drugs of abuse or environmental cues.

(from EJ Nestler, Nature Reviews Neuroscience, 2001)

Normal structure of nucleus accumbens "medium spiny" neurons

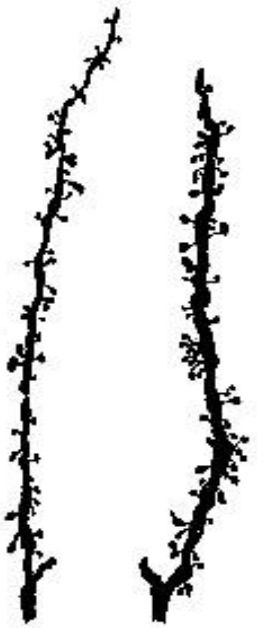


(from Smith & Bolam, *Trends Neurosci.*, 1990)

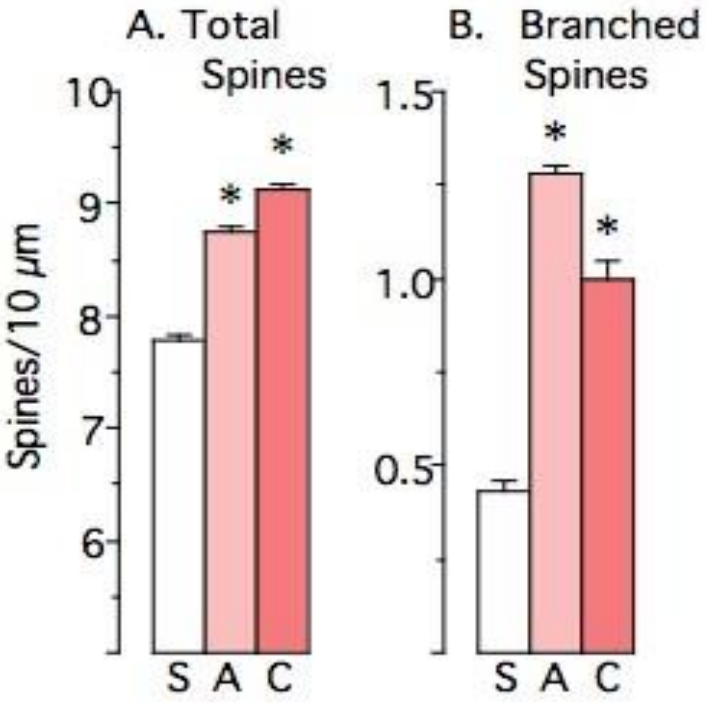


Addictive drugs alter structure of neuronal dendrites

Terminal tips of medium spiny dendrites

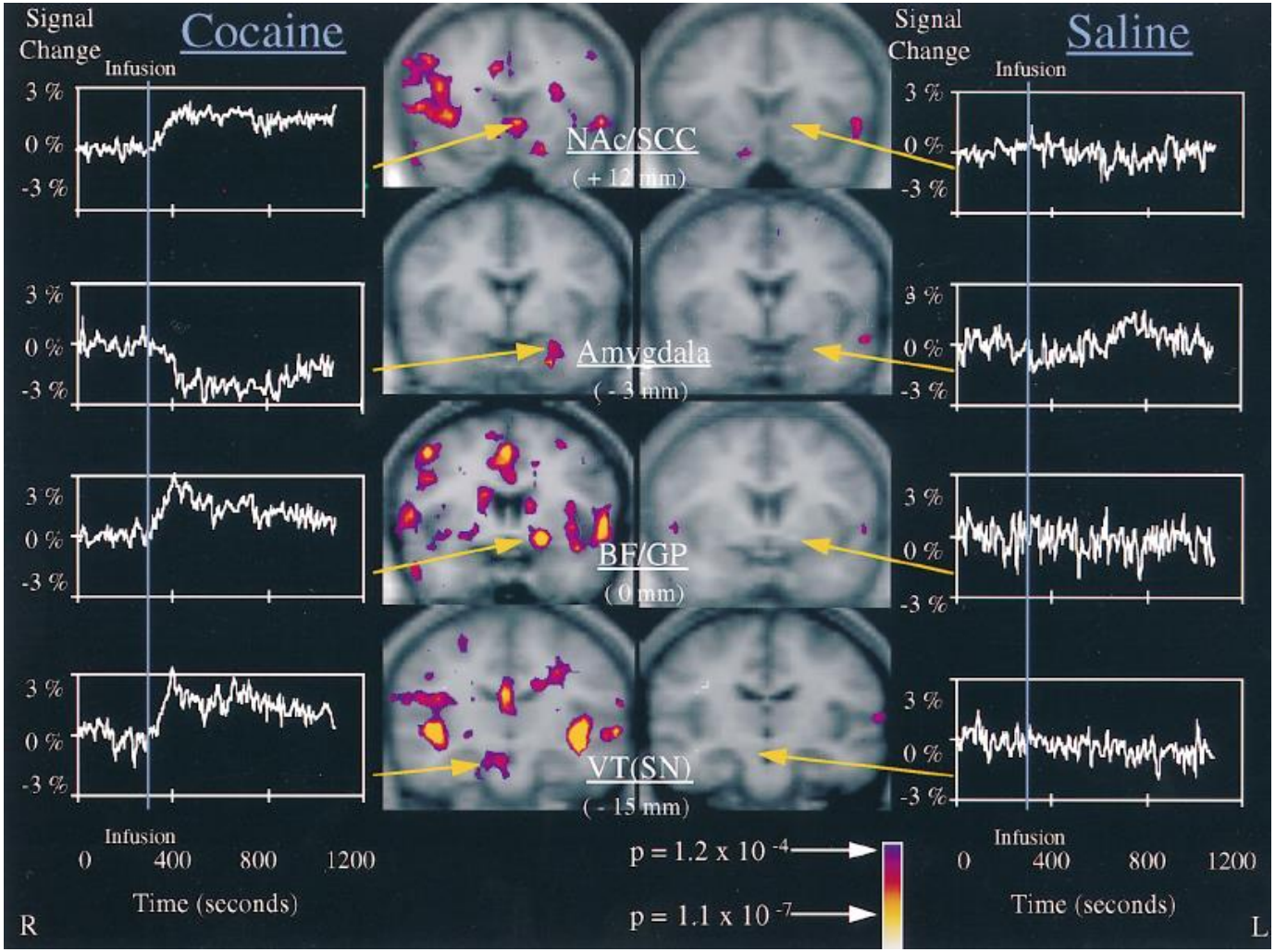


saline amph



T.E. Robinson & B. Kolb, J. Neurosci., 1997

How do drugs affect the brain?



As we have already discussed, fMRI can be used to study how drugs affect the brain.

Breiter et al., Neuron, 1997

MEDICAL SCHOOL | UNIVERSITY OF MINNESOTA

MEDICAL DISCOVERY TEAM
ADDICTION

WHY ADDICTION IS A LEARNING DISORDER AND WHY IT MATTERS

Maia Szalavitz

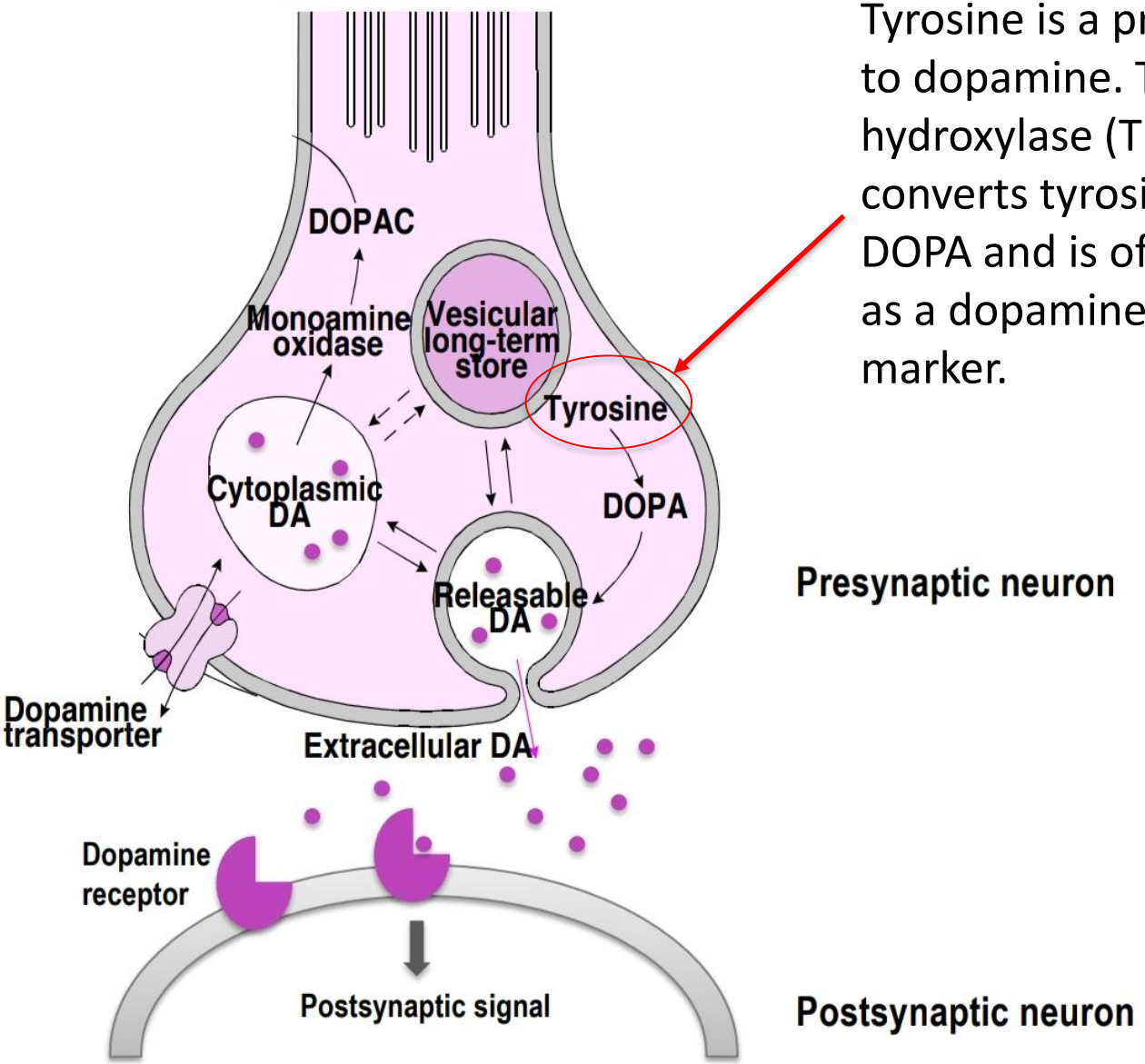
May 8, 2019

10:00-11:30 a.m.

Coffman Memorial Union Theater

If interested, you have to RSVP!!!

Dopamine synapse – form and function



Tyrosine is a precursor to dopamine. Tyrosine hydroxylase (TH) converts tyrosine to L-DOPA and is often used as a dopamine synapse marker.