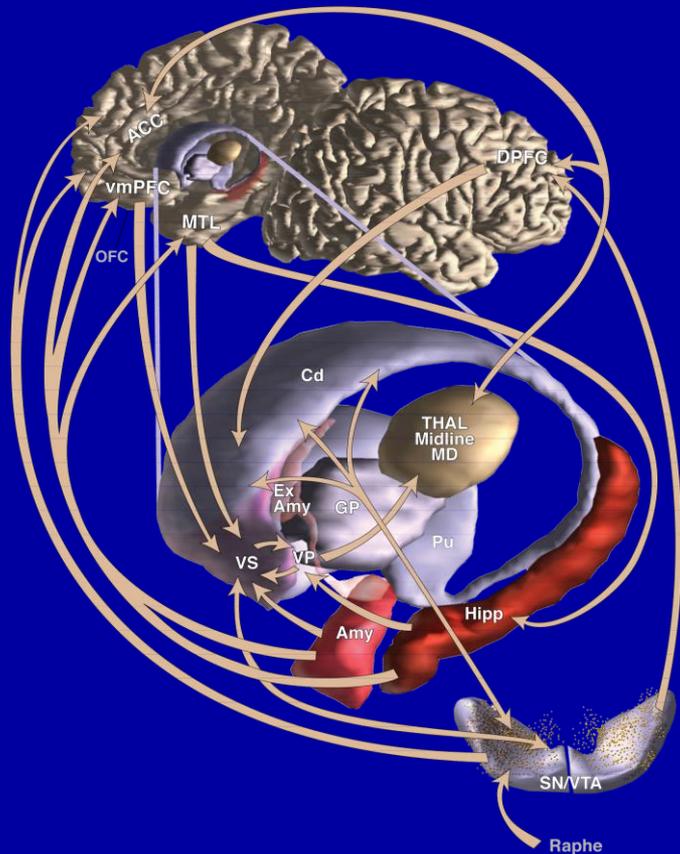


# Neural circuits and the study of addiction: molecules to disease and back again.



Haber - The circuitry of addiction

Yule - Intracellular Calcium signaling and addiction

Lalor - modelling attentional bias in addiction.

Conner & Wiegand - The addicted individual

Portman - modeling DA function in worms

Foxe - Imaging the addicted brain

Padmanabhan - physiology of addiction

Xia - NMDA and CREB-mediated gene transcription in addiction

Bidlack - Structure and function of opiate receptors

Glading - BBB and drugs

# Drug addiction: a complex and chronic disease.

Addiction is characterized by drug seeking and use that is compulsive, and difficult to control, despite the harmful consequences.

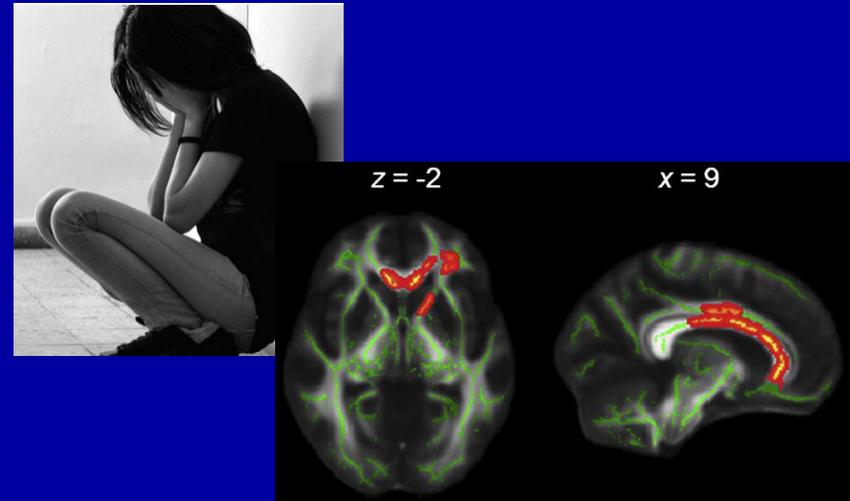
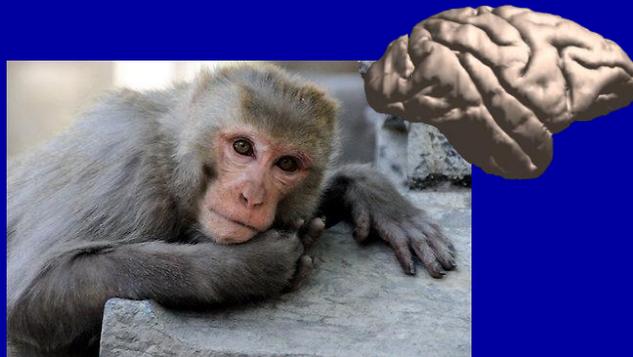
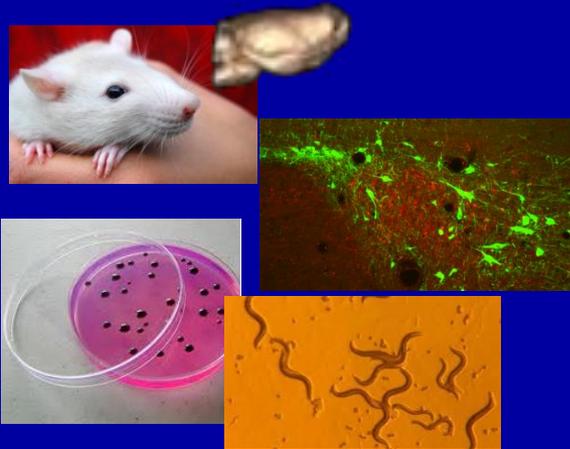
Repeated drug use leads to brain changes that challenge an addicted person's self-control and interfere with their ability to resist intense urges to take drugs.

These brain changes are persistent, which is why drug addiction is considered a "relapsing" disease—people in recovery from drug use disorders are at increased risk for returning to drug use even after years of not taking the drug.

Research shows how drugs affect the brain at molecular, physiological and behavioral levels.

A key goal is to understand more about these mechanisms and to develop strategies for treatment.

# Animals to man: circuits linked to addiction



## Drug addiction: a complex and chronic disease.

Addictive drugs affect the brain's "reward circuit" by flooding it with the chemical messenger **dopamine**. This overstimulation of the reward circuit causes the intensely pleasurable "high" that leads people to take a drug again and again.

Cells in key brain regions of the **midbrain and striatum** adjust to the excess dopamine in complex ways, reducing the ability of cells in the reward circuit to respond appropriately. This reduction of the high, an effect known as tolerance, increases drug use.

Chronic use leads to the development of the habit, a stimulus-response link, that is particularly difficult to break.

An important feature of the habit is the lack of cognitive control

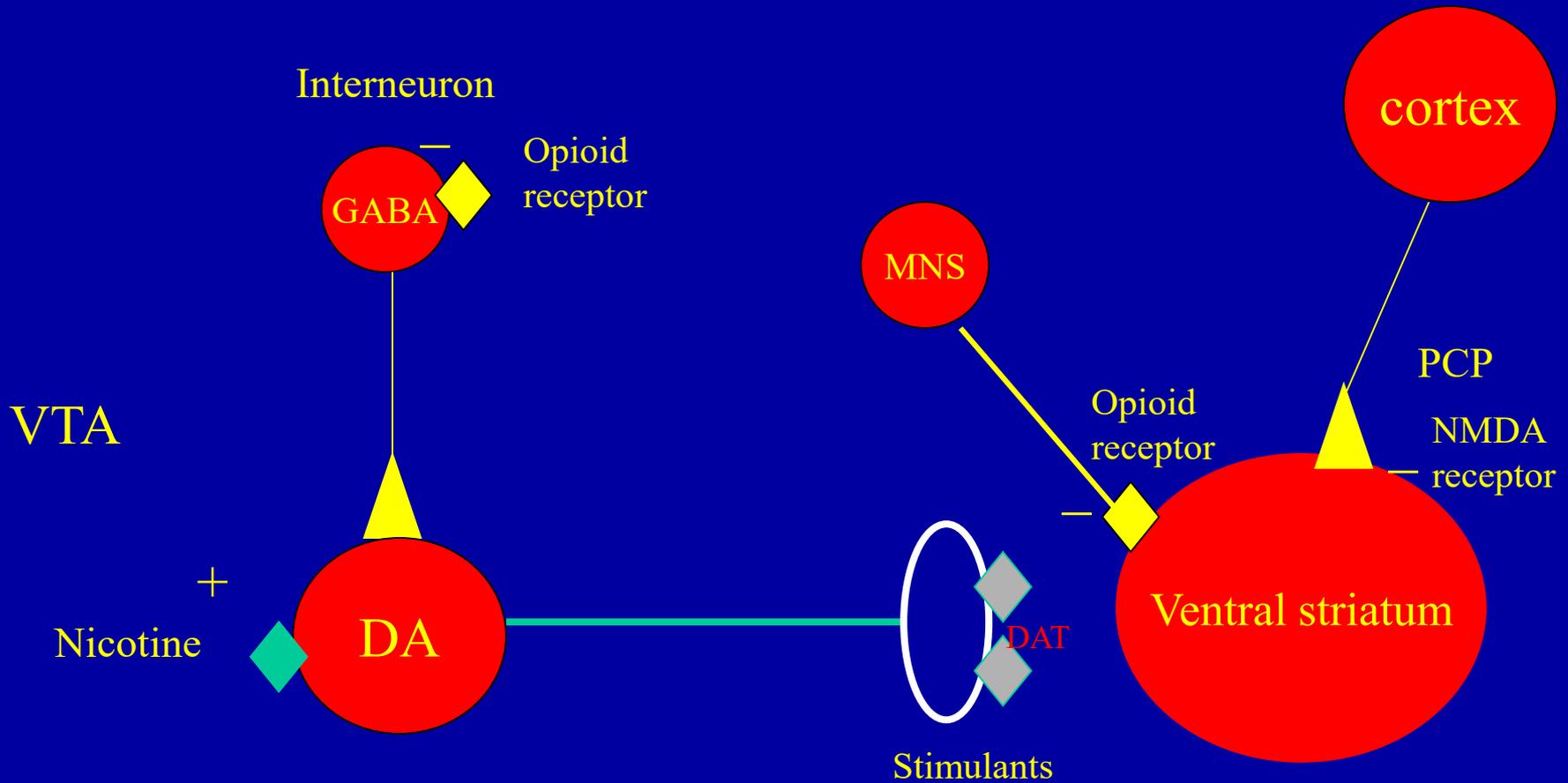
# Drugs of abuse act directly or indirectly on midbrain dopamine pathways

Cocaine and amphetamine bind to the dopamine transporter (DAT), increasing extracellular dopamine. (They also act on the NE and 5HT transporters.) Low D2 levels predict working for drugs (cocaine).

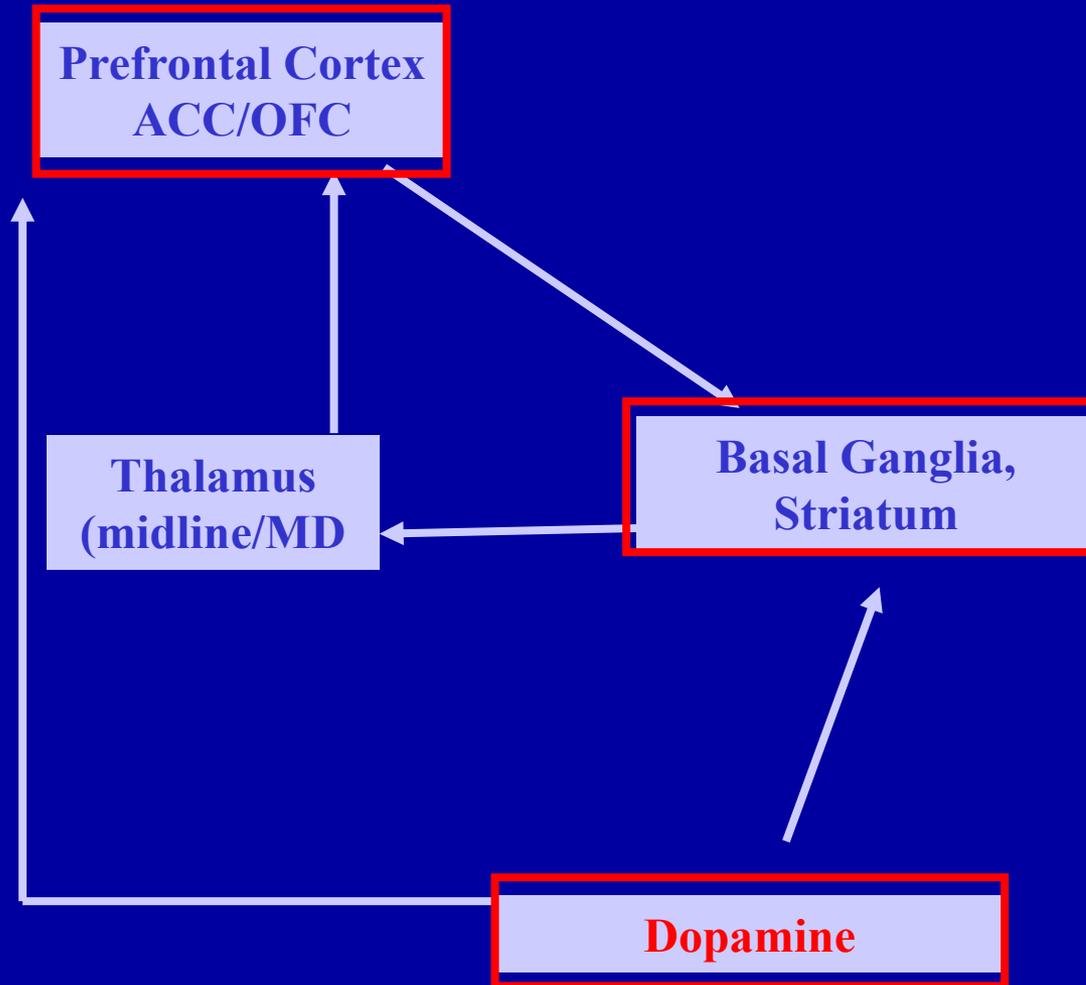
Opiate drugs bind to the endogenous opioid receptors, (mainly the  $\mu$  receptor) in the VTA and in the VS

Nicotine activates ACH nicotinic receptors in the VTA.

# Proposed sites of action



# The addiction Network



Prefrontal and basal ganglia areas most associated with habit formation and addiction.

Midbrain dopamine system, reward/motivation/learning

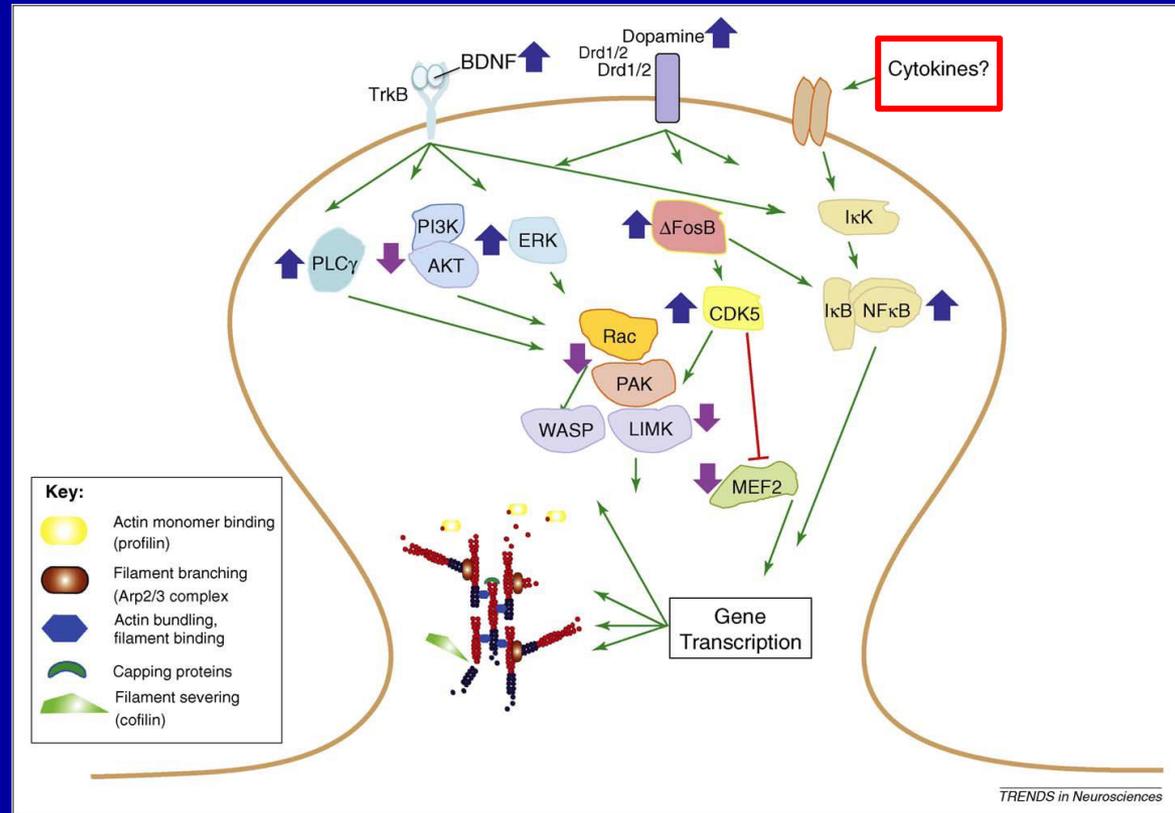
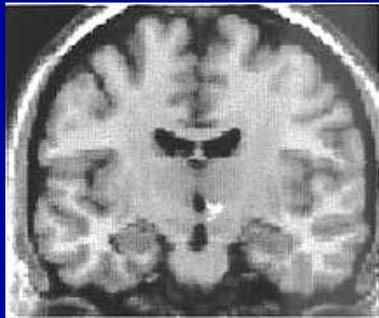
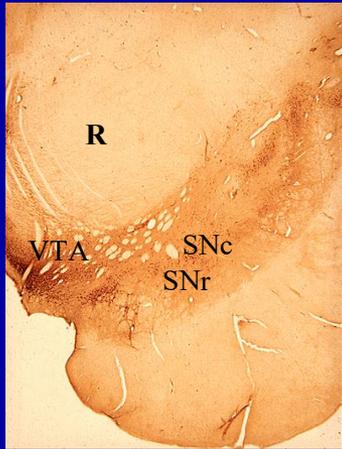
Ventral striatum (VS), reward/motivation.

Dorsal, rostral striatum (DS), cognitive control.

Orbitofrontal cortex (OFC), links stimuli to their values.

dPFC (dlPFC, ACC), cognitive control, attentional switching.

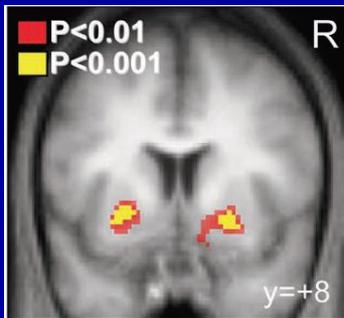
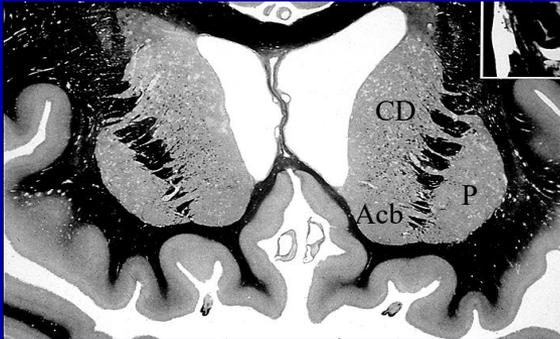
# Midbrain dopamine neurons



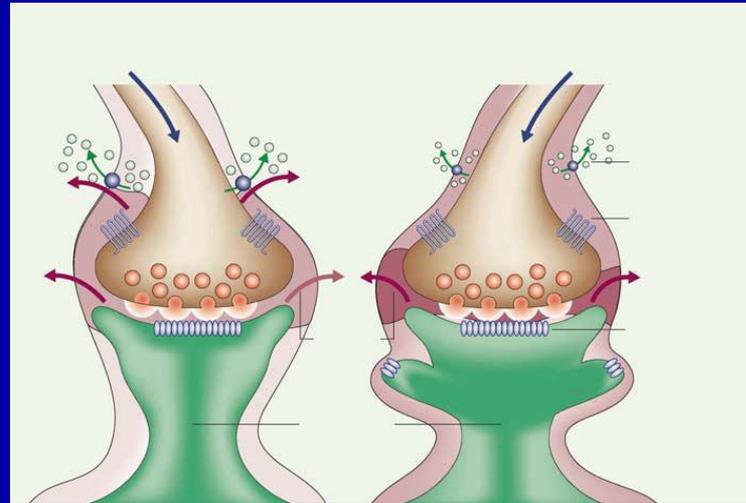
Midbrain activation related to reward level during a gambling task with financial rewards and penalties. Elliott et al, '00, JNS.

Signaling pathways involved in addiction-related cytoskeleton reorganization (Russo, Malenka, Nestler '11).

# Nucleus accumbens/ventral striatum

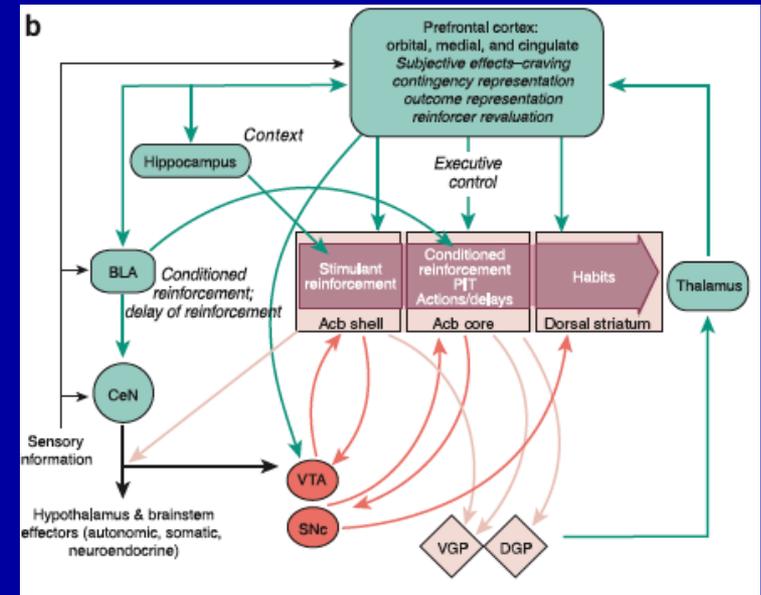
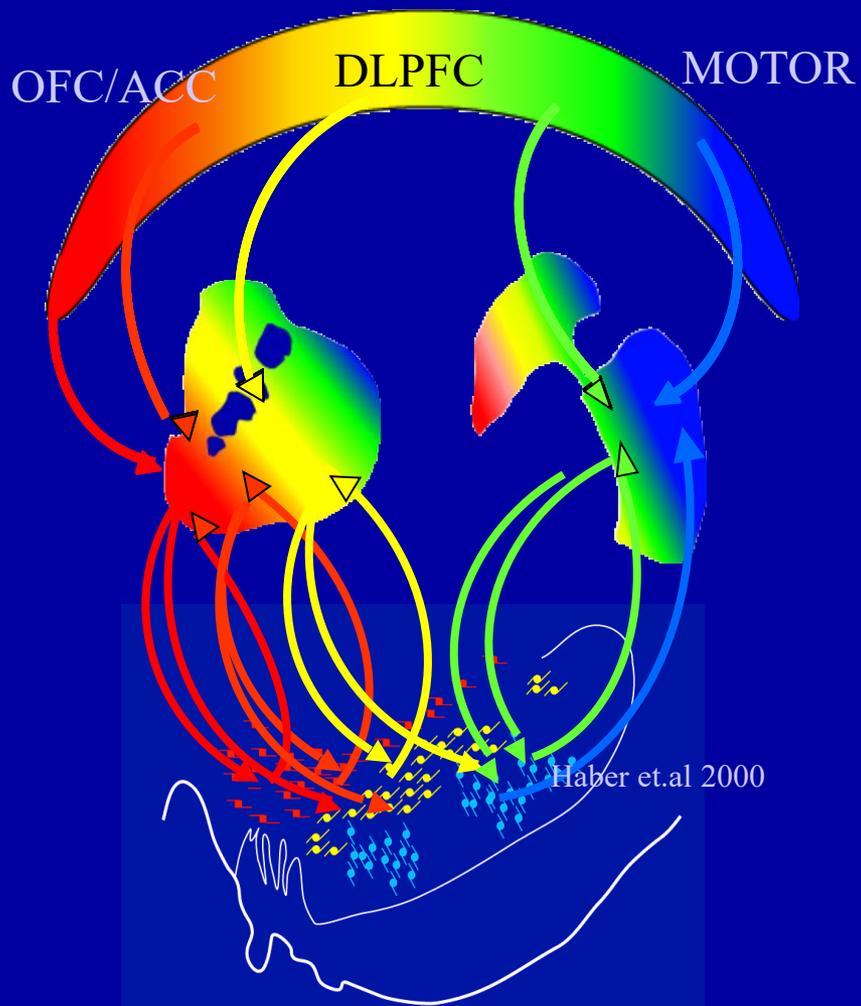


Reward prediction error responses in VS,  
(O'Doherty et al, Sci. '04).



Molecular neuroplasticity associated with excitatory synapses in the NA hypothesized to underlie the vulnerability to relapse to cocaine (Kalivas , NPP,'08).

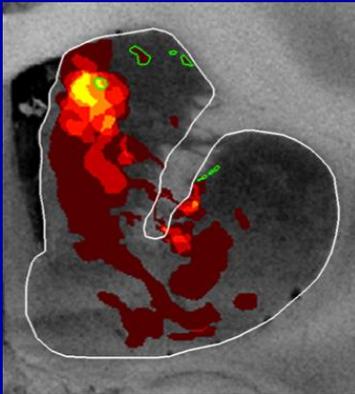
# Anatomical substrates for transferring information from the reward circuit to habit formation



Exposure to addictive drugs recruits serial and dopamine dependent, striato-nigro-striatal ascending spirals from the n. acb to more dorsal regions of the striatum that underlie a shift from action-outcome to stimulus-response mechanisms in the control over drug seeking.

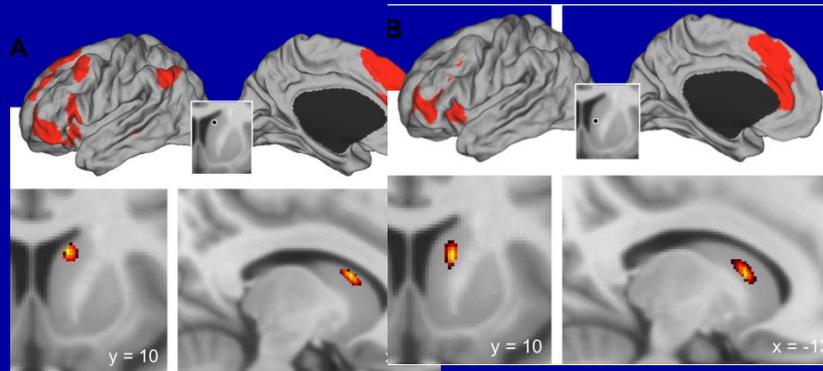
# A hub in the striatum to start:

Prefrontal, cingulate, and parietal inputs converge in the striatum: where emotion, cognition, and perception interface and habit formation occurs.

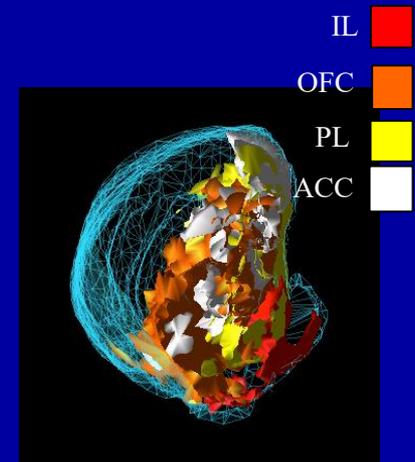


Convergence off prefrontal, cingulate, and IPL terminals in monkeys.

Choi et al, Neuroimage '16



Resting-state correlations in the human striatum (A) rdCaud or (B) vCaud seed regions



Rat terminal convergence  
Mailly, et al 'JNS,13

# Goals of the Center

1. To understand mechanistic changes in the striatum and cortex that lead to the drug habit:

What are the key striatal regions most vulnerable to habit formation? How do these regions change over time with addiction?

What are the cortical areas most vulnerable to loss of cognitive control during habit formation. How do these regions change over time with addiction

What are the molecular mechanisms (cell signaling) that underlie changes to chronic dopamine in the those striatal areas?

# Goals of the Center

## 2. Therapies and drug development.

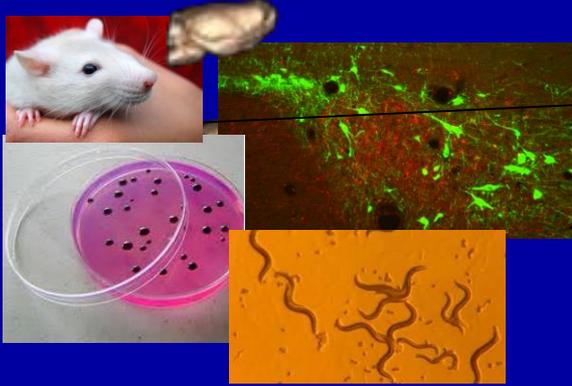
Are there specific regions where drugs enter the brain? How do drugs change that system?

What are the key structure-function relationships that can be manipulated.

Are there key cell-signaling mechanisms that can be manipulated

# How drugs get into and act in the brain.

## Cellular/Molecular



Bidlack-Structure and function of opiates receptors

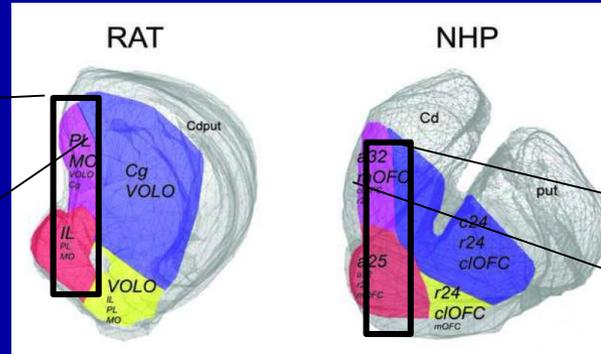
Glading- BBB and drugs

Portman-modeling DA function in worms

Xia-NMDA and CREB-mediated gene transcription

Yule-Intracellular Calcium signaling in addiction

## Circuitry/physiology



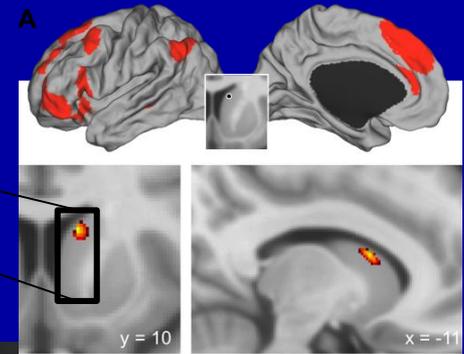
Homologous regions across species (Heilbronner et al, '16).

Haber-addiction circuitry

Lalor- modelling perception and attentional bias in addiction.

Padmanabhan-Physiology of addiction

## Imaging/disease



Foxe-Imaging the addicted brain

Conner & Wiegand-The addicted individual