

Reward circuitry in the brain

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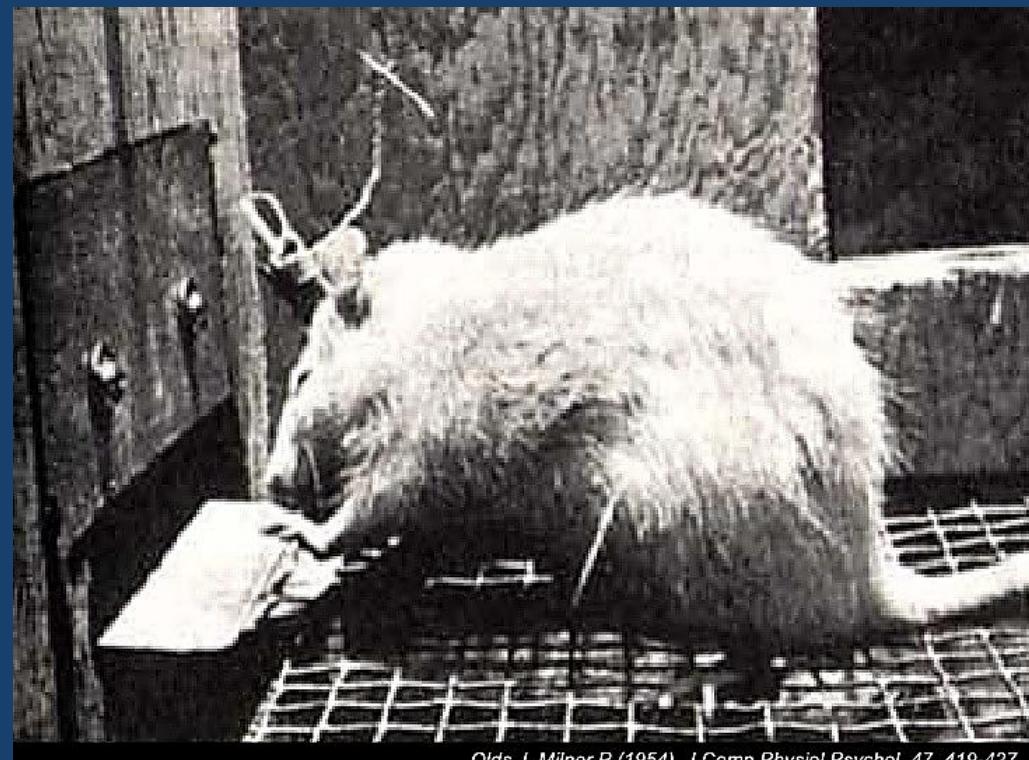
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Reward and aversion

➤ James Olds and Peter Milner (1954):

- Electrodes into the brains of rats
- Rats in chambers equipped with a lever
- When pressed delivered current to the electrodes
- implantation in certain regions of the brain
- Animals work for food when they were hungry, for water when they were thirsty, but even when sated would work for electrical stimulation of their brains.

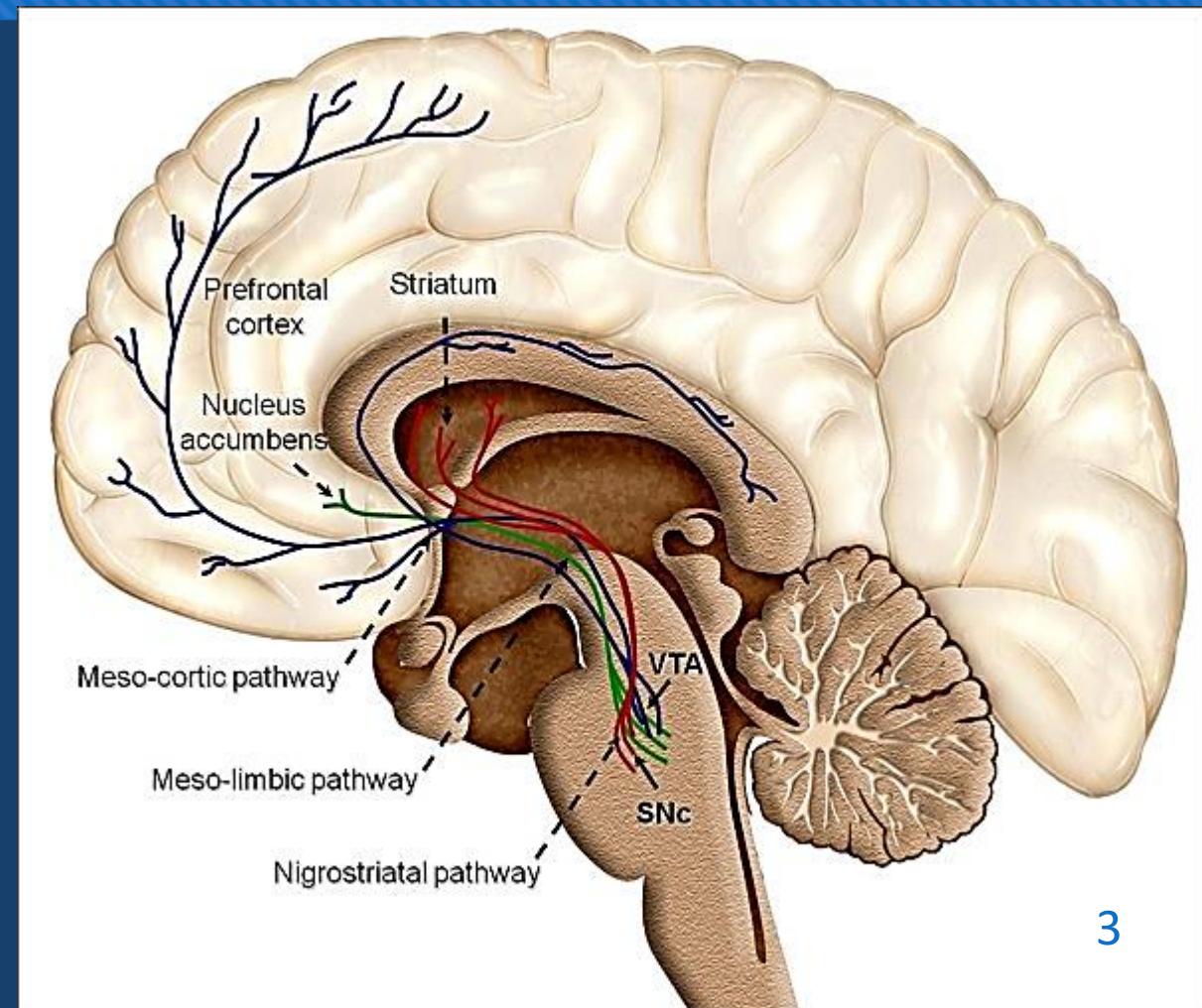


Olds J, Milner P (1954) J Comp Physiol Psychol, 47, 419-427.

Reward and aversion

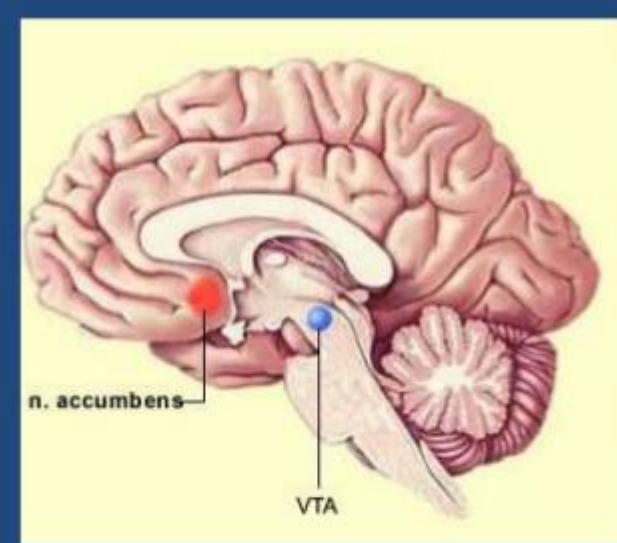
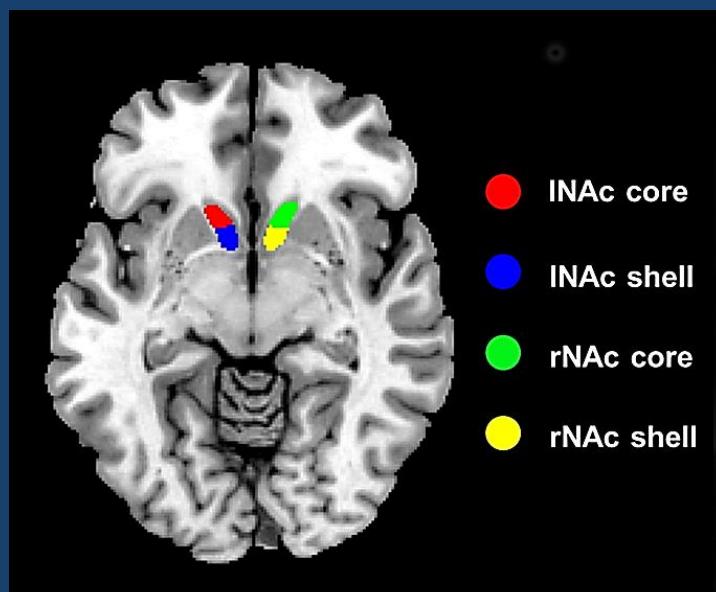
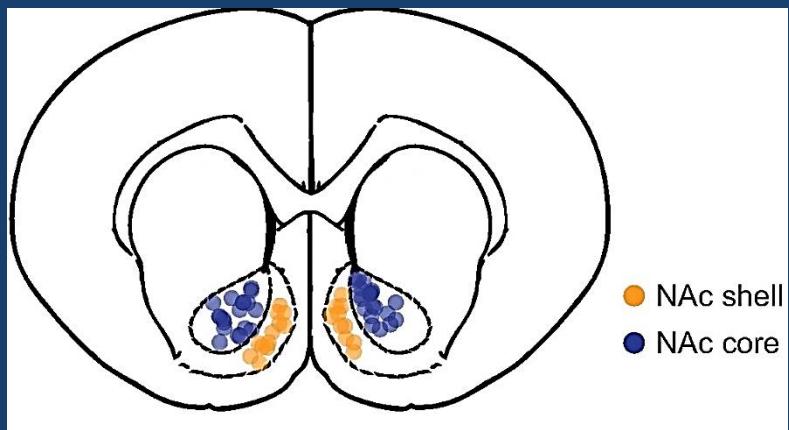
The mesocorticolimbic system:

- Nucleus accumbens (NAc), the ventral tegmental area (VTA) and the PFC: implicated in reward
- The amygdala (AMG), periaqueductal gray (PAG), and the locus coeruleus (LC): implicated in aversion.



Reward and aversion

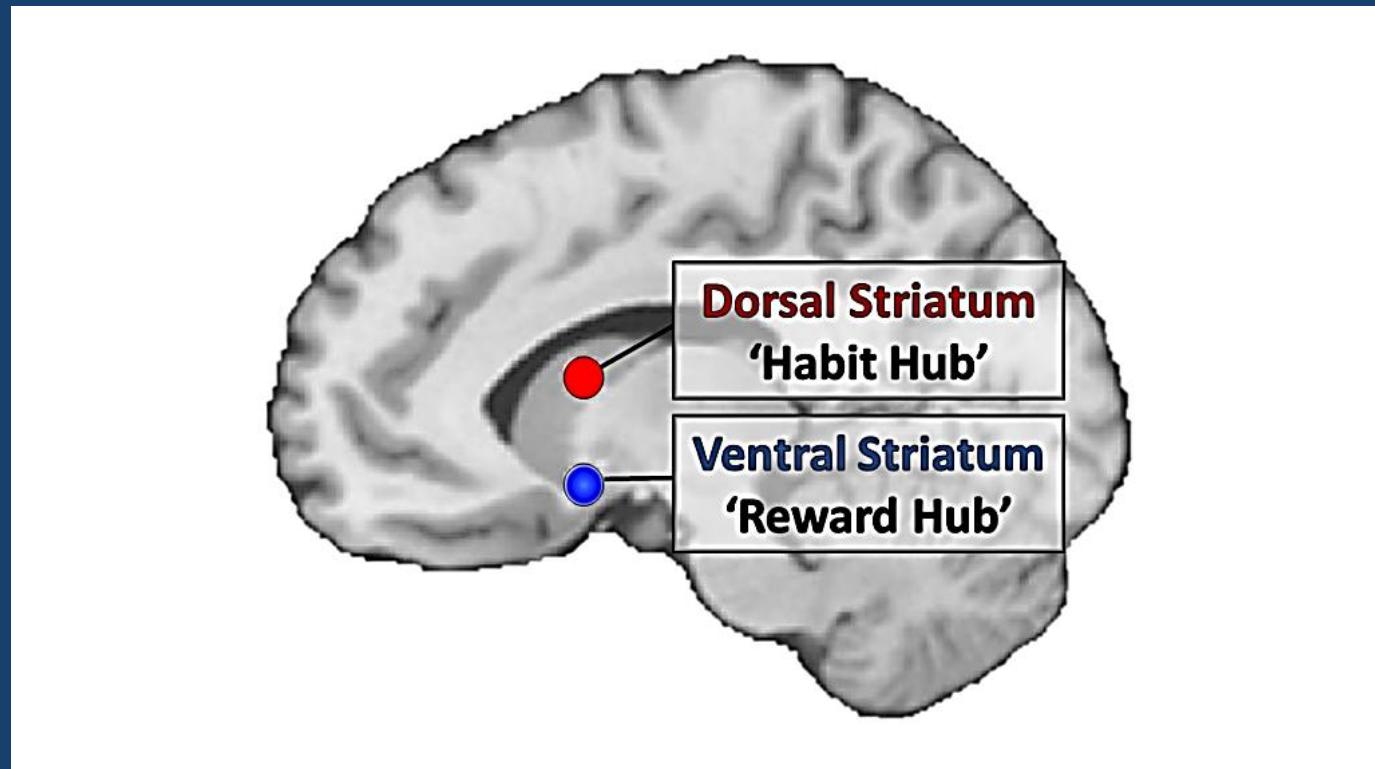
- The NAc, especially its shell: assigning motivational properties on rewards and to the stimuli that predict them.
- Rat and mouse models: intact NAc is required if the animal is to learn to work (lever pressing) to obtain natural rewards, like palatable foods, or to learn how to self-administer drugs.



- Behind the Prefrontal Cortex
- On the top of the brain stem

Reward and aversion

- Once an animal learns how to obtain a reward, and the relevant behaviors become embedded:
 - Reward seeking no longer depends on the Nac.
 - Dorsal striatum (the caudate and putamen in humans), structure for well-learned behaviors and habits.



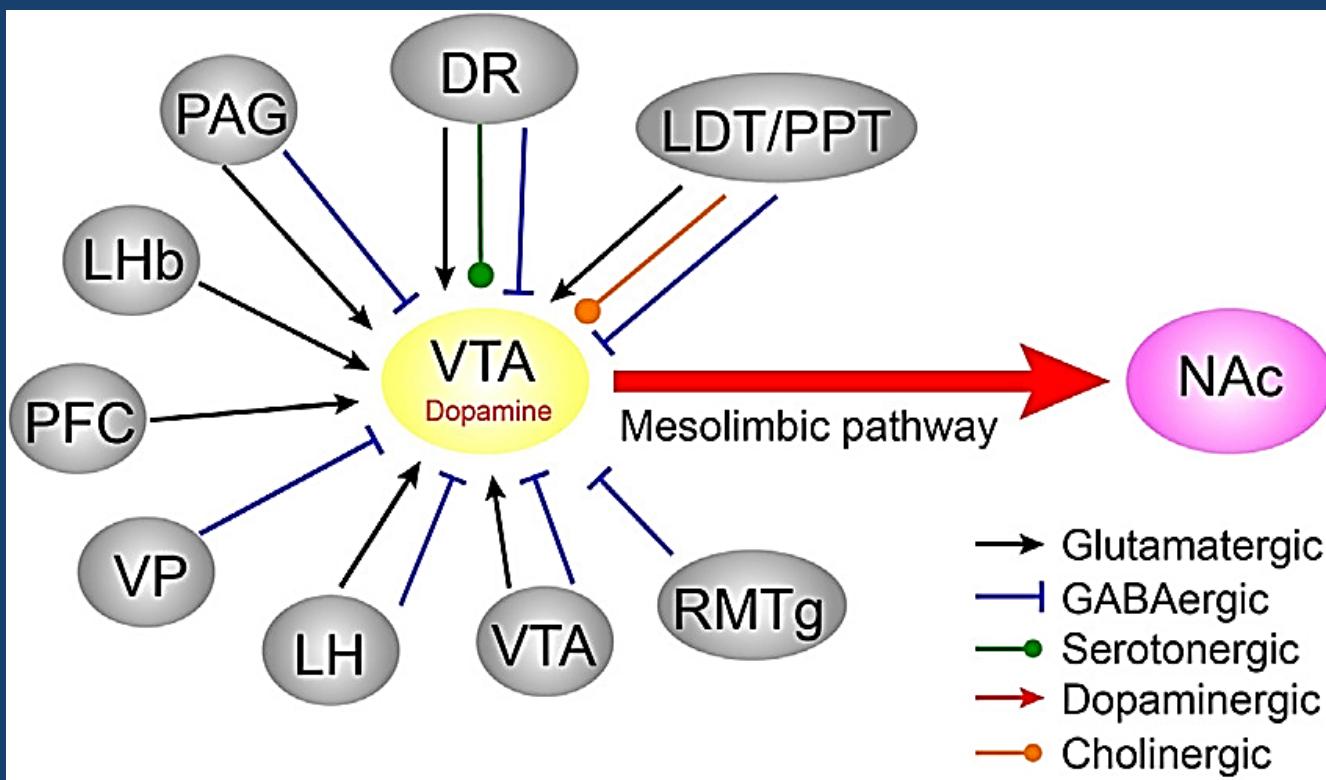
Reward and aversion

- Speed and efficiency in gaining food, water and shelter improve the probability of survival.
- Reward circuitry facilitates the rapid learning of:
 - Cues that predict the proximity of reward
 - Behaviors maximizing the chances of successfully obtaining it.
- Once learned, predictive cues activate **cognitive, physiologic and behavioral** responses aimed at obtaining the predicted reward.



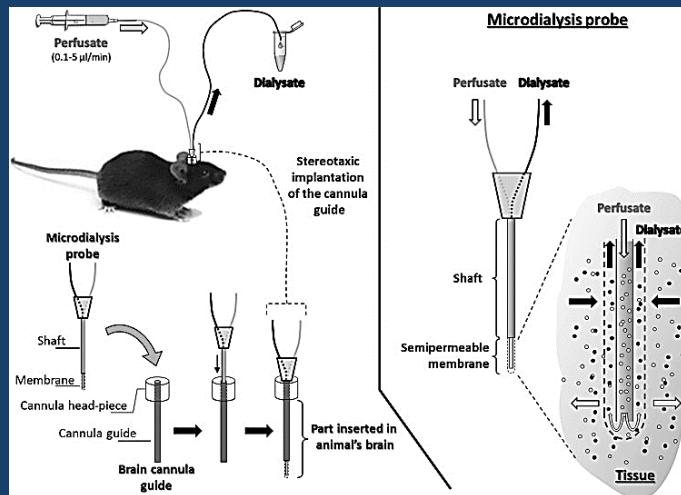
VTA DA neurons

- Primary source of DA in medial PFC, NAc, and etc.
- Important roles in motivating behaviors and neuropsychiatric disorders.
- DA released from VTA neurons in the NAc plays the key role in binding rewards and reward associated cues to adaptive reward-seeking responses.



In animals:

- Implanted electrodes can record the firing of DA neurons
- Microdialysis catheters and electrochemical methods to detect DA

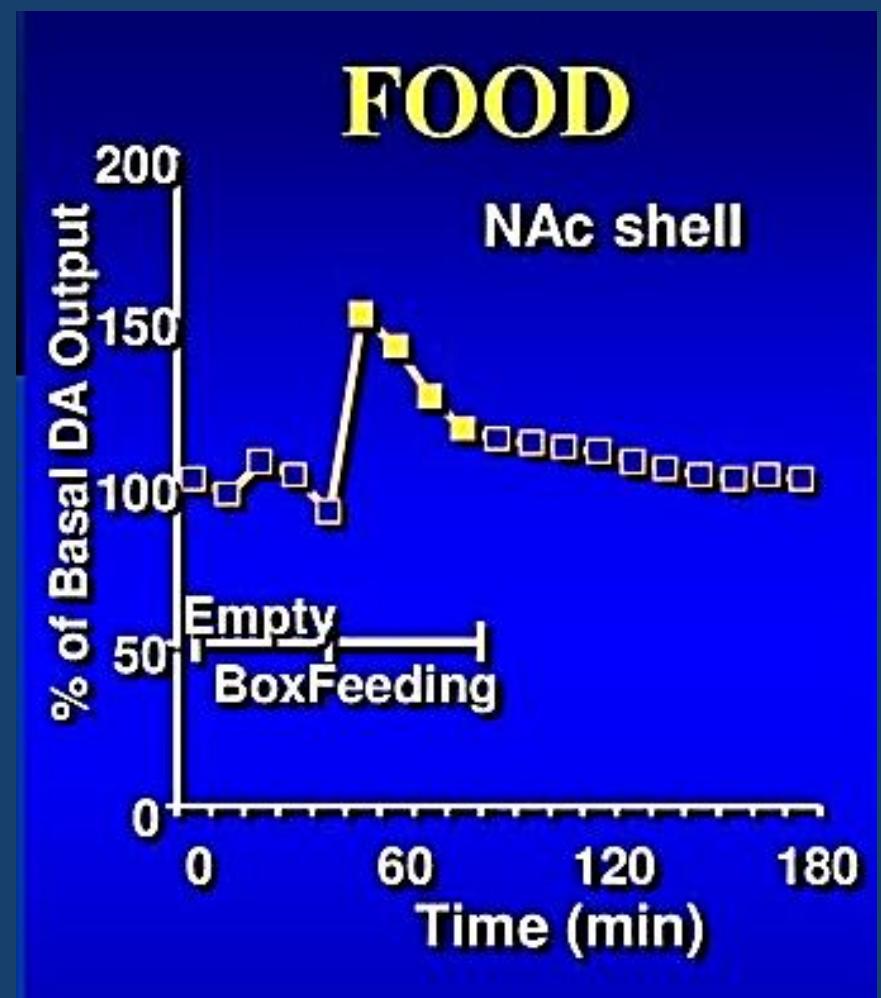


In humans:

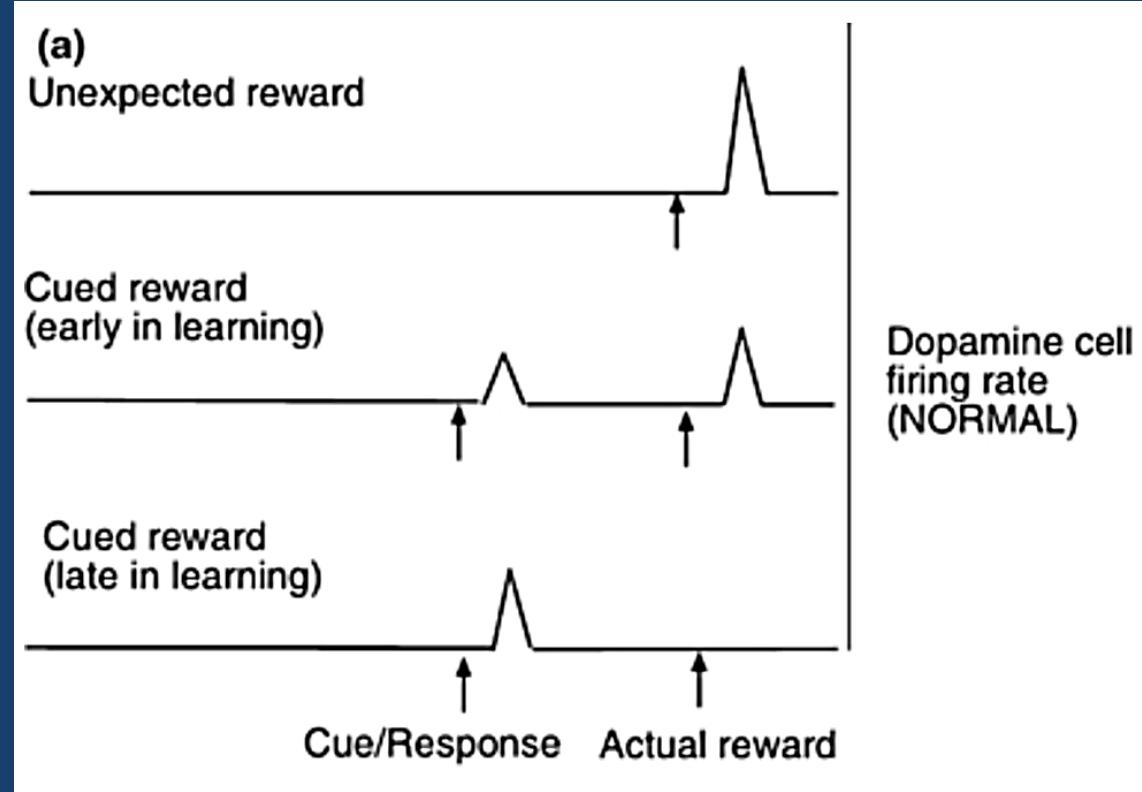
- Positron emission tomography (PET) permits indirect measures of DA release by observing the displacement of a positron-emitting D2 DA receptor ligand previously bound to receptors following a stimulus or pharmacologic challenge.



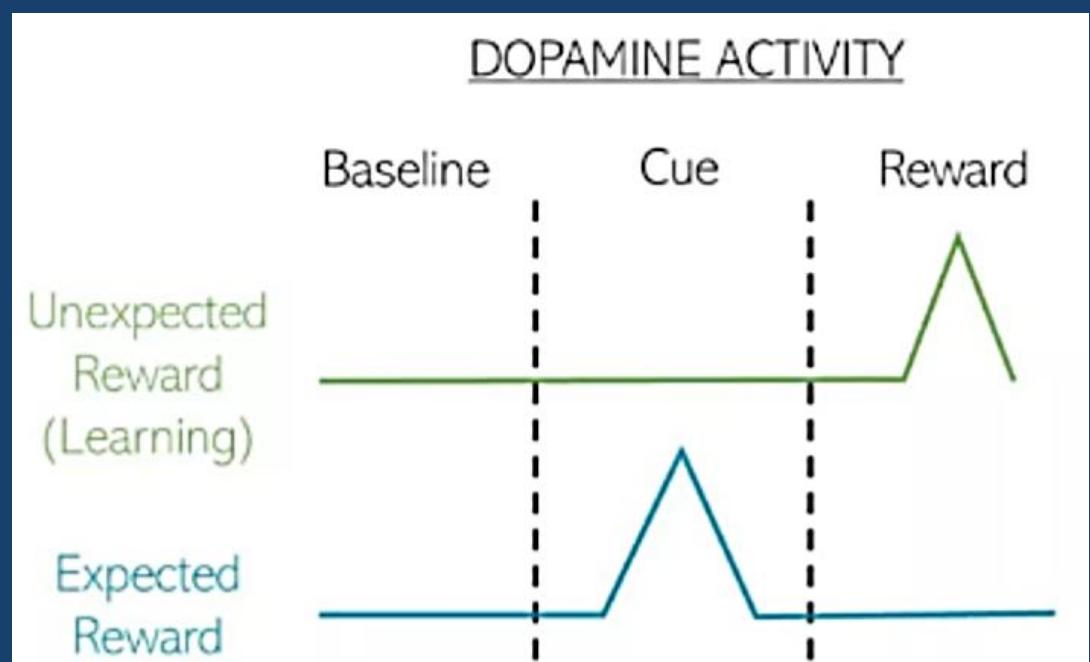
- Using such methods in multiple paradigms:
- ***Natural rewards cause firing of neurons and DA release in the NAc***
- DA blocked (by lesioning DA neurons, blocking post-synaptic DA receptors, or inhibiting DA synthesis):
 - **Rewards no longer motivate the behaviors necessary to obtain them.**
- The pattern of DA neuron firing, and the resulting synaptic release of DA in relatedn circuits, act to shape behavior so as to maximize future reward.



- Basal state: DA neurons have a slow tonic pattern of firing.
- A new, unexpected, or greater than expected reward: a phasic burst of firing of DA neurons causing a transient increase in synaptic DA.
- When a reward is predicted from known cues and is exactly as expected: no change from the tonic pattern of firing, no additional DA release.
- When a predicted reward is omitted or less than expected: DA neurons pause their firing to levels below their tonic rate.



- ✓ Phasic increases in synaptic DA signify that the world is better than expected, facilitate learning of new predictive information and bind the newly learned predictive cues to action.



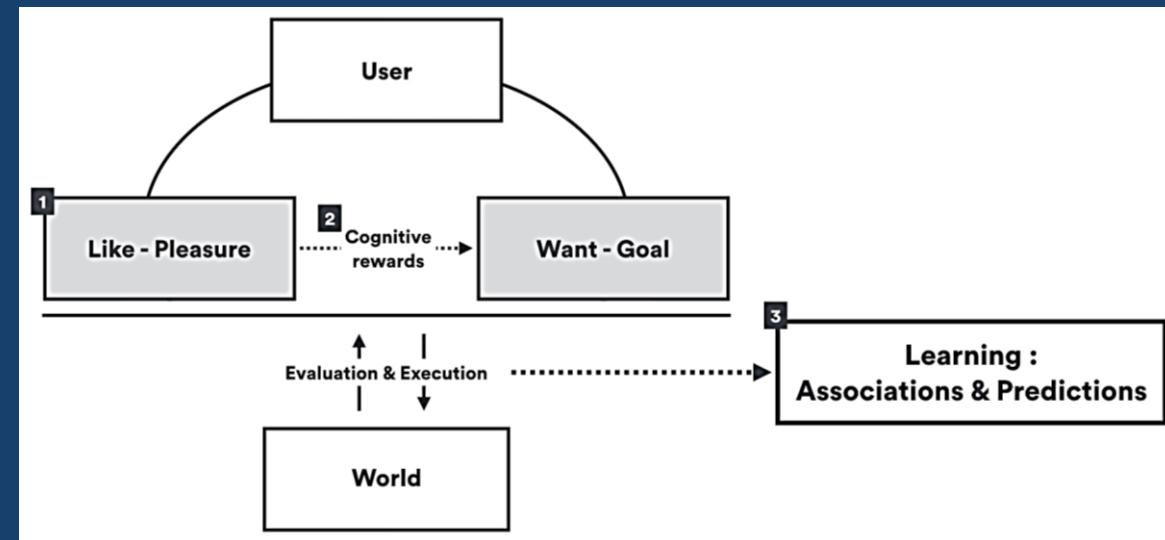
- ✓ Two distinct patterns of DA neural activity:
 - ✓ Midbrain DA neurons typically fire at low frequencies of 1-5 Hz, to produce a tone on the high-affinity DA D2 receptor in the mesolimbic DA system, including the NAc.
 - ✓ When animals are presented with conditioned cues that predict drug availability, midbrain DA neurons fire in high frequency bursts (>20 Hz): transient increases in NAc DA that occupy low affinity DA D1 receptors.

The pleasure–reward system

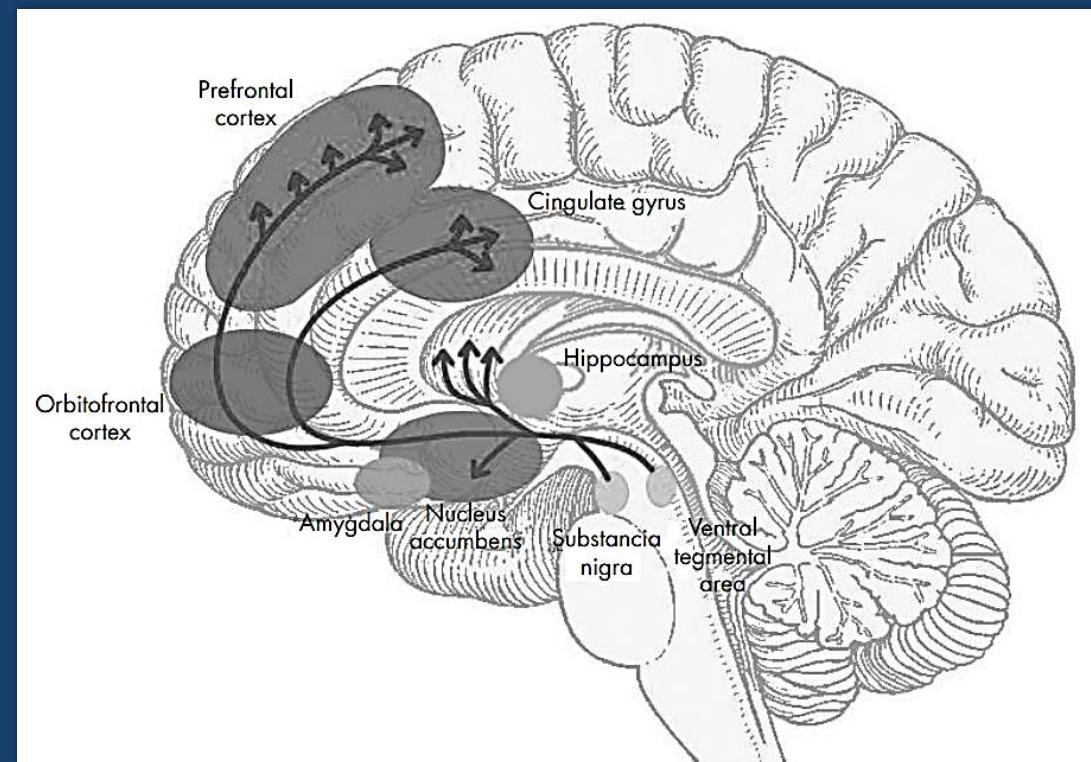
Reward involves multiple neuropsychological components:

1. ***the hedonic sensation of pleasure***
2. ***the motivation to obtain the reward (incentive component)***
3. ***the reward-related learning***

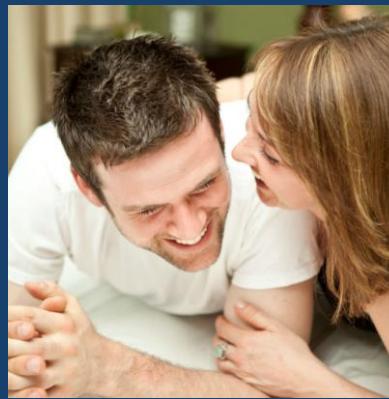
- Pleasure represents the subjective hedonistic value of rewards; can either be rewarding when it follows satisfaction, or incentive when it reinforces behaviors.
- Pleasure is not merely a sensation.
- Even a sensory pleasure such as a sweet taste requires the co-recruitment of additional specialized pleasure-generating neural circuitry to add the positive hedonic impact to the sweetness that elicits liking reactions.



- Different rewarding stimuli may elicit qualitatively and quantitatively different reward values.
- Increased DAergic activity in the VTA: either from an unexpected reward or, after recognition of the reward characteristics, from the anticipation of the reward
- Anticipation of a satisfaction activates neurochemical pleasure mechanisms and reinforces the obtaining behavior.



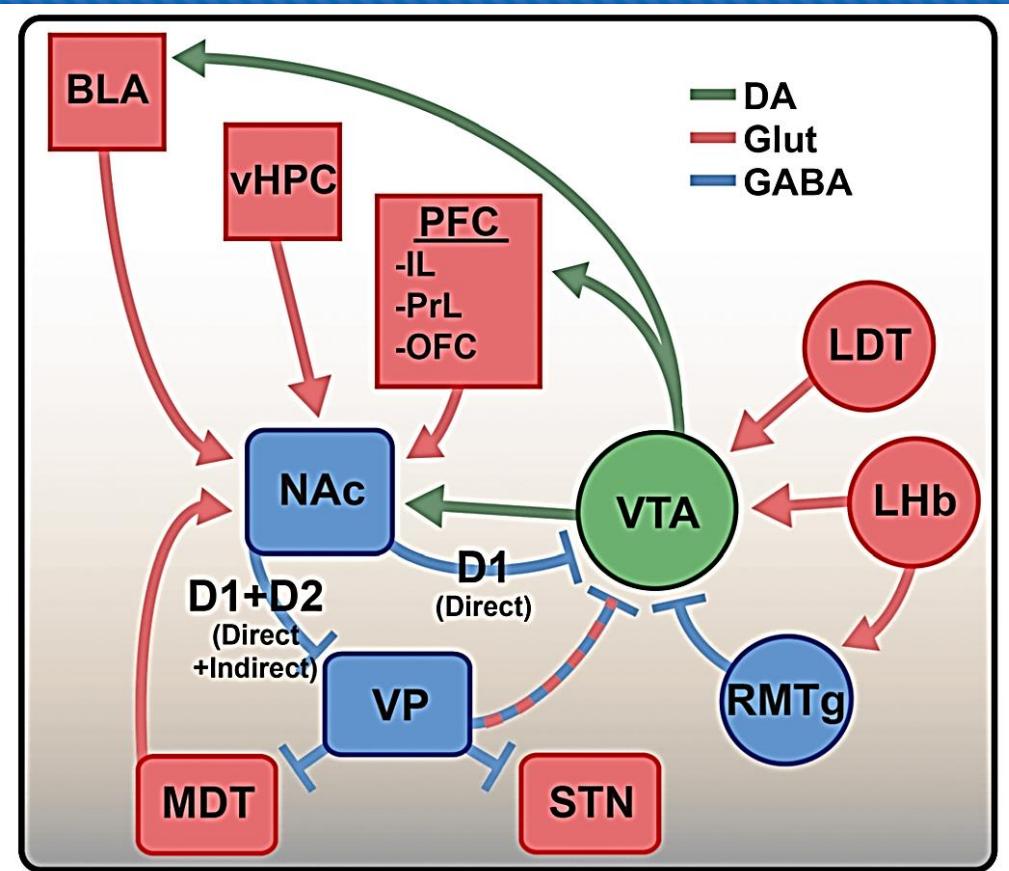
- Much of what we know of the structure of the reward circuit, and the generation of pleasure, was identified in the context of drugs of abuse.
- Our understanding of the circuitry underlying the rewarding aspects of drug use informs the greater understanding of general reward mechanisms.



Wiring of the Reward Circuitry

VTA

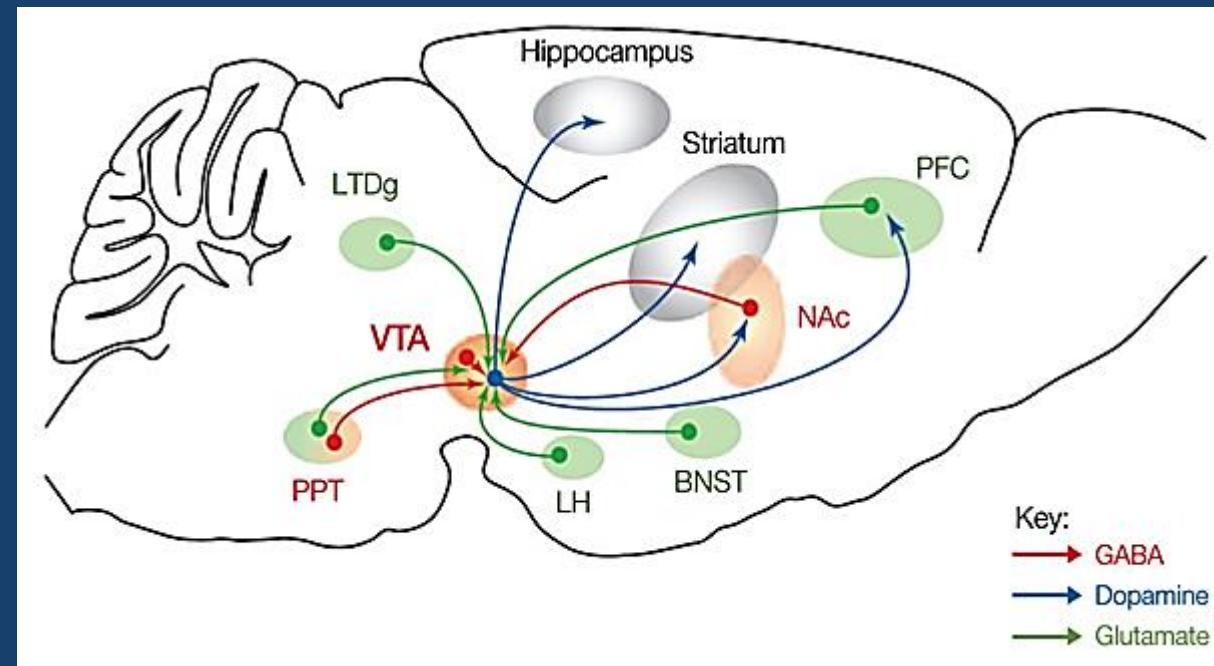
- A heterogeneous brain region composed of DA (60–65%), GABA (~30–35%), glutamatergic neurons (2–3%).
- stimulation of VTA DA neurons and the release of DA in projection sites, most notably the NAc, produces reward.
- Drugs of abuse increase DA release in the NAc, blocking the action of the DA (via receptor blockade) blocks many behavioral effects of drugs.



behaviors. BLA = basolateral amygdala; D1 = dopamine type 1 receptor; D2 = dopamine type 2 receptor; LDT = laterodorsal tegmentum; LHb = lateral habenula; MDT = mediiodorsal thalamus; PFC = prefrontal cortex; RMTg = rostromedial tegmentum; STN = subthalamic nucleus; Thal = thalamus; vHPC = ventral hippocampus; VP = ventral pallidum; IL = infralimbic; PrL = prelimbic; OFC = orbitofrontal cortex; VTA = ventral tegmental area;

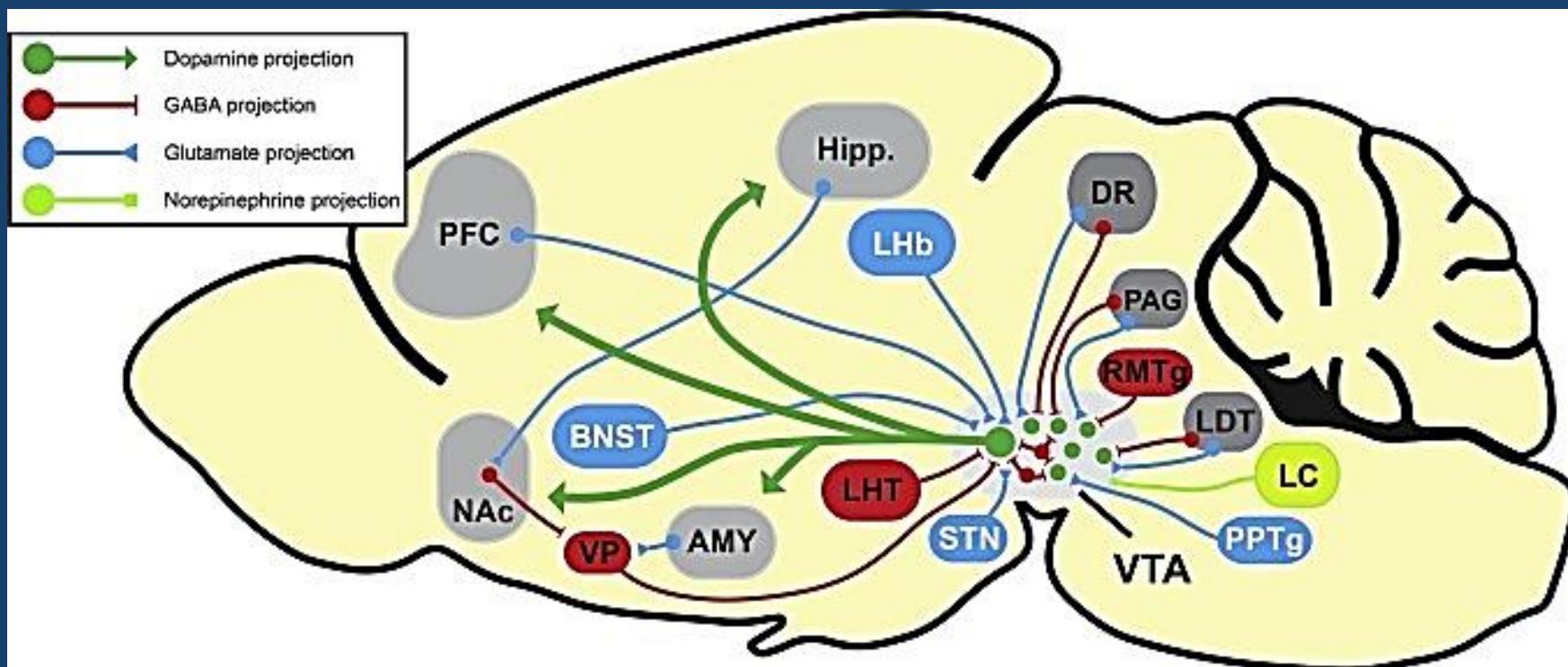
VTA

- VTA DA neurons are subdivided by projection target.
 - *Those that project to the NAc (mesolimbic)*
 - *Those that project to the PFC (mesocortical)*
 - *Additional projection sites, including the amygdala and hippocampus.*
- Distinct electrophysiological properties and functional outcomes



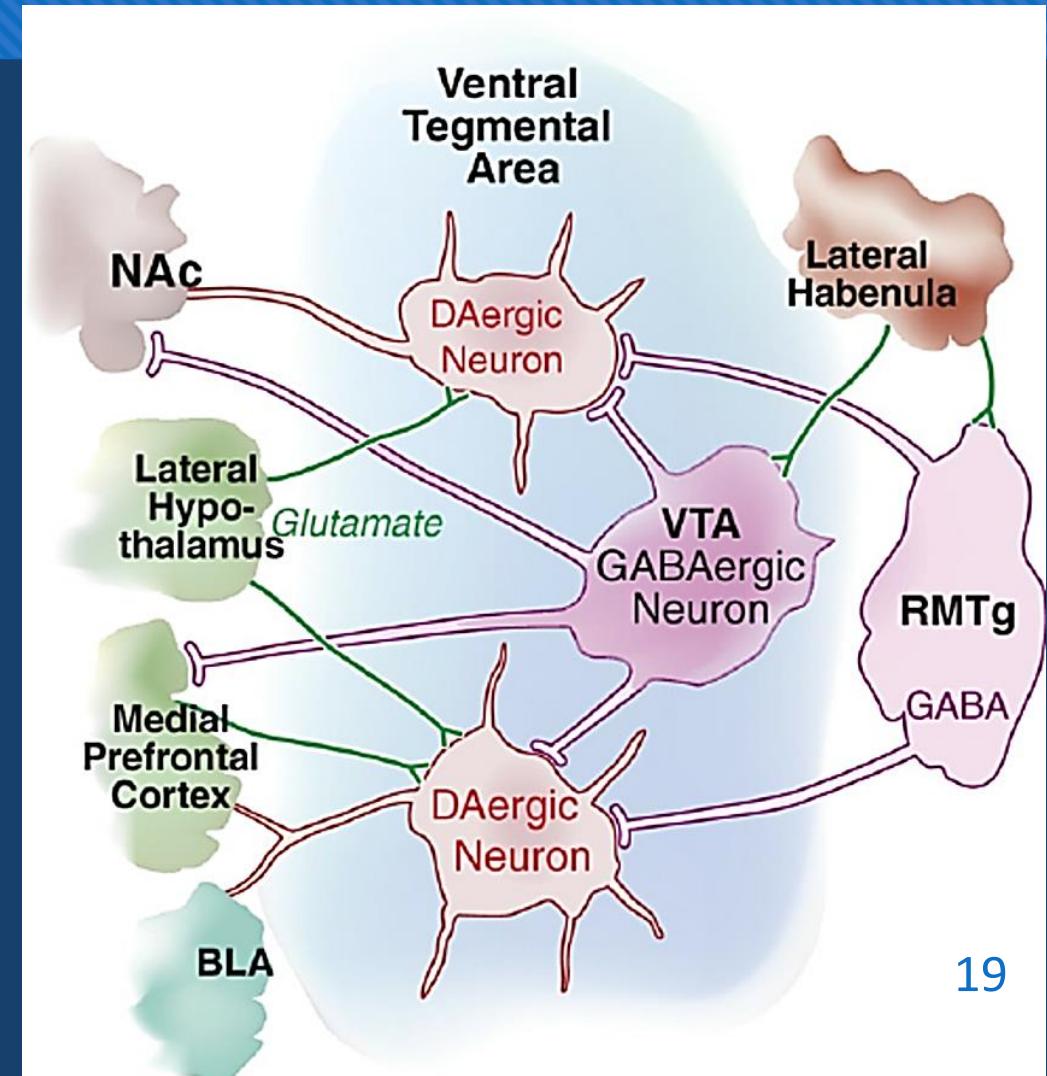
VTA

- A rewarding stimulus (cocaine) modulates excitatory input to VTA DA neurons that project to Nac.
- An aversive stimulus (formalin injection) modulates synaptic input onto VTA DA neurons that project to mPFC.
- Activation of Glu neurons in LDT synapsing onto VTA DA neurons projecting to NAc increases reward behavior.
- Activation of Glu lateral habenula neurons that innervate VTA DA neurons that project to the mPFC induces aversive behavior.



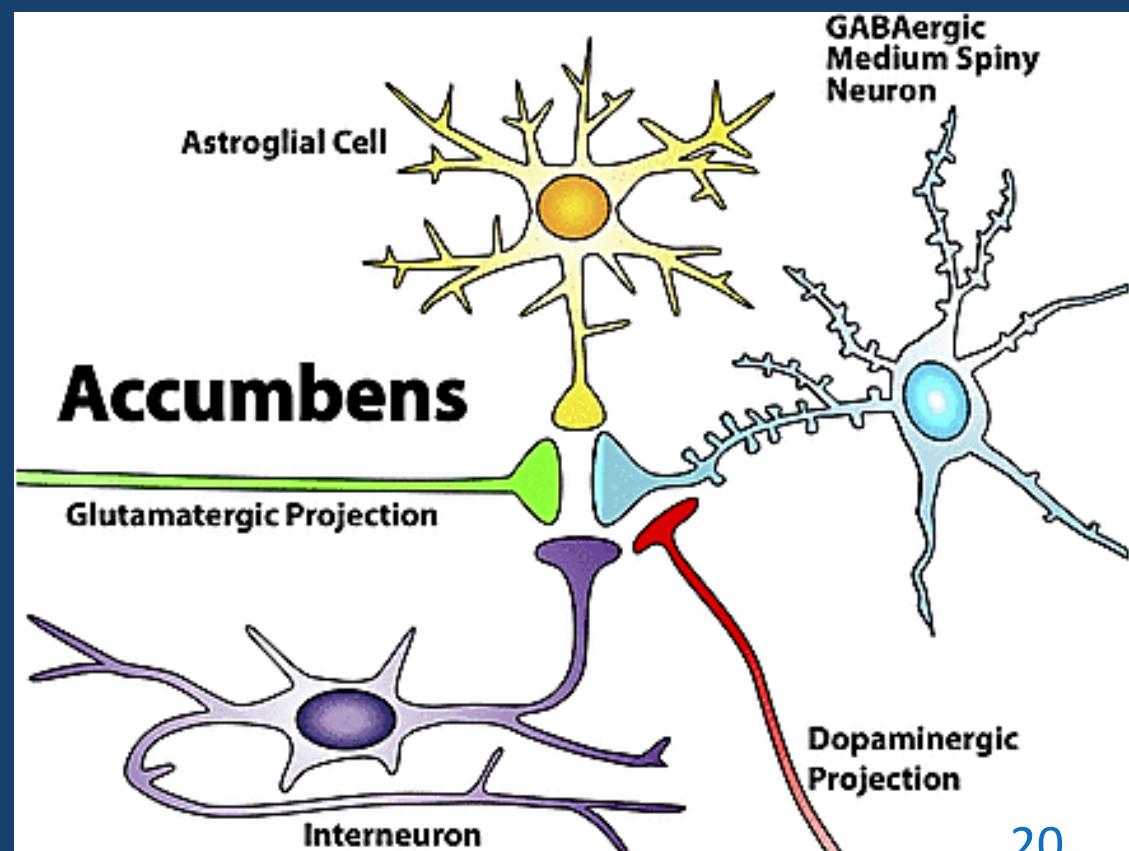
VTA

- VTA GABA neurons: critical for reward processing
- Their activation produces real-time aversion
- Their inhibition produces preference.
- VTA GABA activation inhibited VTA DA neuronal activity and produced a concomitant decrease in DA release in NAc



NAc

- A major reward-related output of VTA DA activity is Nac (ventral striatum).
- Here, DA activates DA receptors on medium spiny neurons (MSNs), the predominant cell type in NAc.
- MSNs are GABAergic projection neurons, their expression of either D1- or D2- like DA receptors.
- D1 MSNs constituting the “direct” pathway (ultimately increasing thalamocortical drive)
- D2 MSNs forming the “indirect” pathway (ultimately decreasing thalamocortical drive).



NAc

- Direct versus indirect pathway distinction is not as clear in NAc as it is in dorsal striatum:
- Only NAc D1 MSNs project to the VTA
- Both D1 MSNs and D2 MSNs project to the ventral pallidum (VP).
- Cellular heterogeneity (D1 vs D2 cells)
- Regional heterogeneity (core and shell subregions)

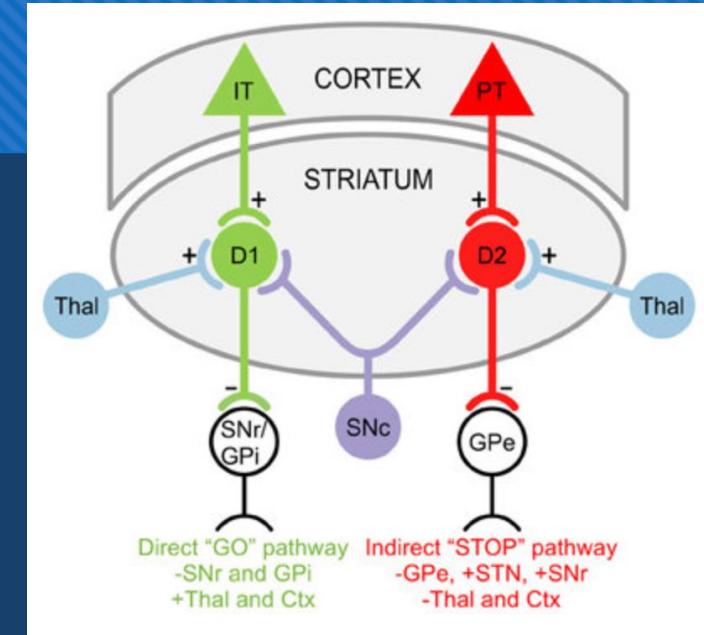


Figure 1: Striatal projection pathways. In the direct "GO" pathway, MSNs expressing DA D1 receptors receive inputs from intratelencephalically projecting (IT) neurons in the cortex (Ctx) and project to the substantia nigra pars reticulata (SNr) as well as the internal segment of the globus pallidus (GPi). In the indirect "STOP" pathway, MSNs expressing DA D2 receptors receive inputs from pyramidal tract (PT) neurons in the Ctx and project to the external segment of the globus pallidus (GPe). The GPe, in turn, projects to the STN and SNr. Both D1 and D2 MSNs also receive afferents from the substantia nigra pars compacta (SNC) and thalamus (Thal).

NAc

- **MSNs in NAc core:**

- Assigning motivational value to discrete stimuli associated with reward or aversion
- Updating these values as circumstances change

- **MSNs in NAc shell:**

- Drive behavioral responses to repeated exposure to rewarding experiences, such as chronic drug administration.
- NAc MSNs also receive a large amount of glu input from PFC, vHIPP, and BLA.

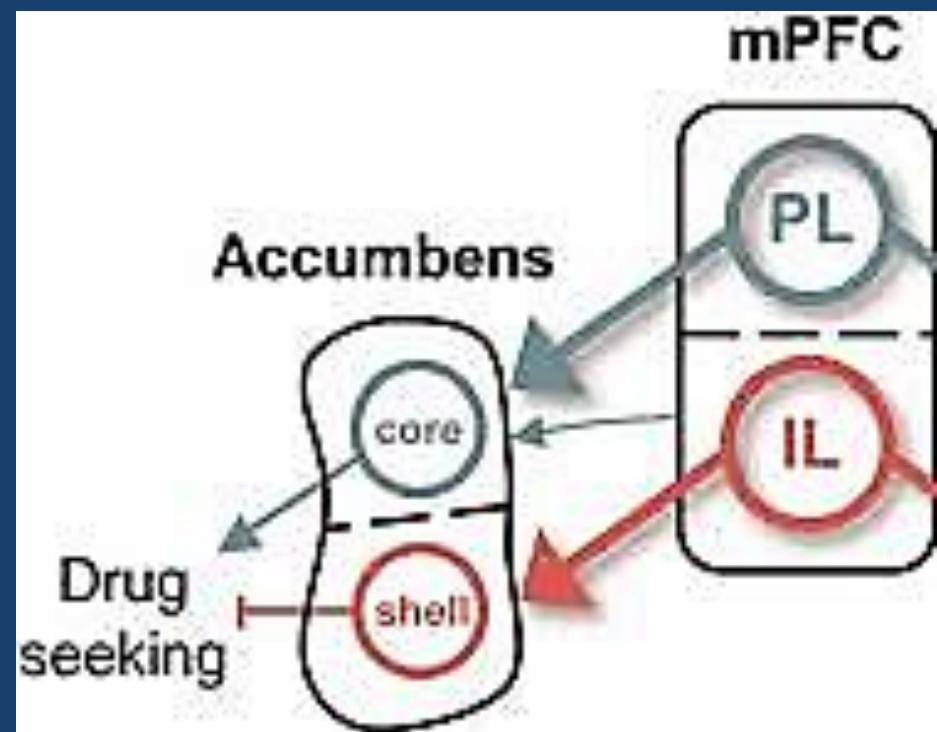
PFC

- **PFC input to Nac:**

- Associated with executive control
- Mediate goal-directed behaviors such as the seeking and planning of action to obtain reward-related substances (like drugs of abuse).

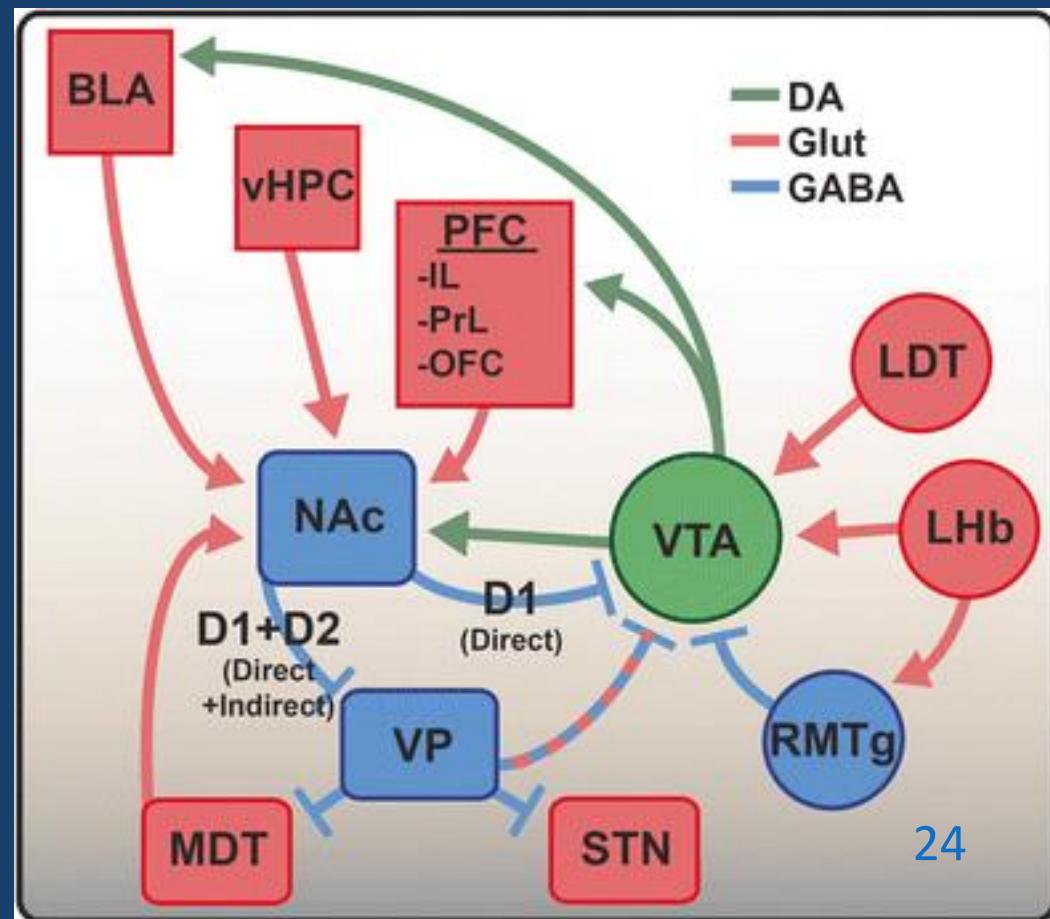
- **PFC subregions:**

- Infralimbic (IL) mPFC preferentially projecting to NAc shell
- Prelimbic mPFC (PrL) to NAc core



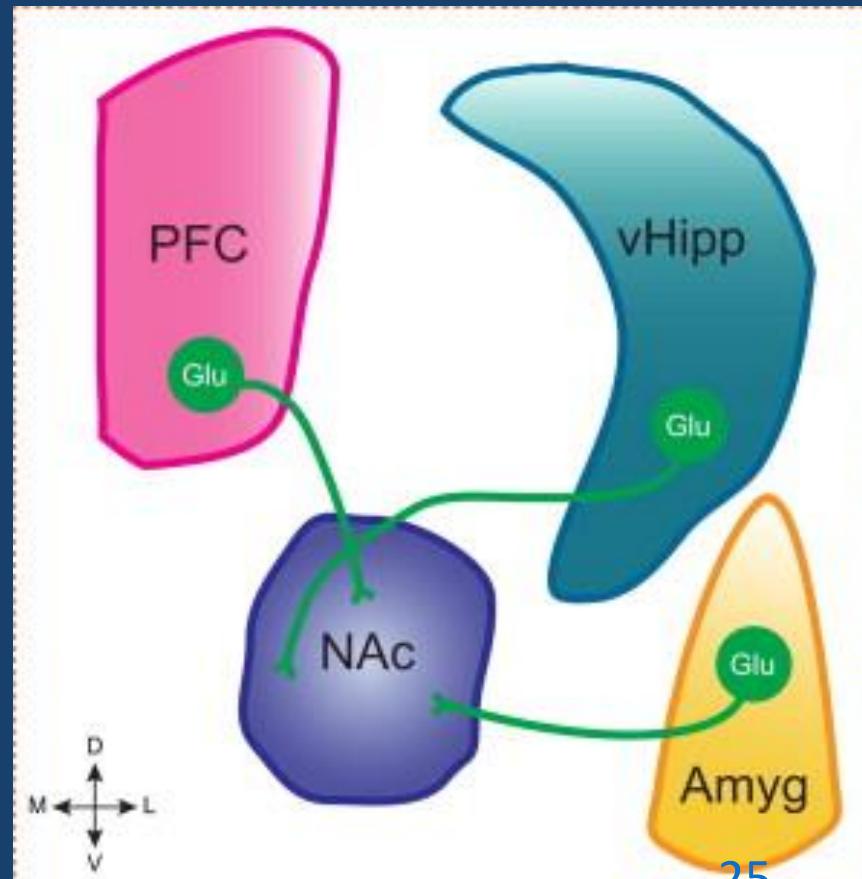
vHIPP

- ✓ vHIPP sends glu projections to Nac
- ✓ Act as a site of integration between spatial / contextual information from dorsal HIPP and emotional information from BLA and LC.
- ✓ vHIPP–NAc connection provides contextually relevant emotional information to influence goal-directed behavior.
- ✓ This circuit is implicated in both reward and aversive behaviors
- ✓ Its modulation impacts cue-induced drug seeking behavior.



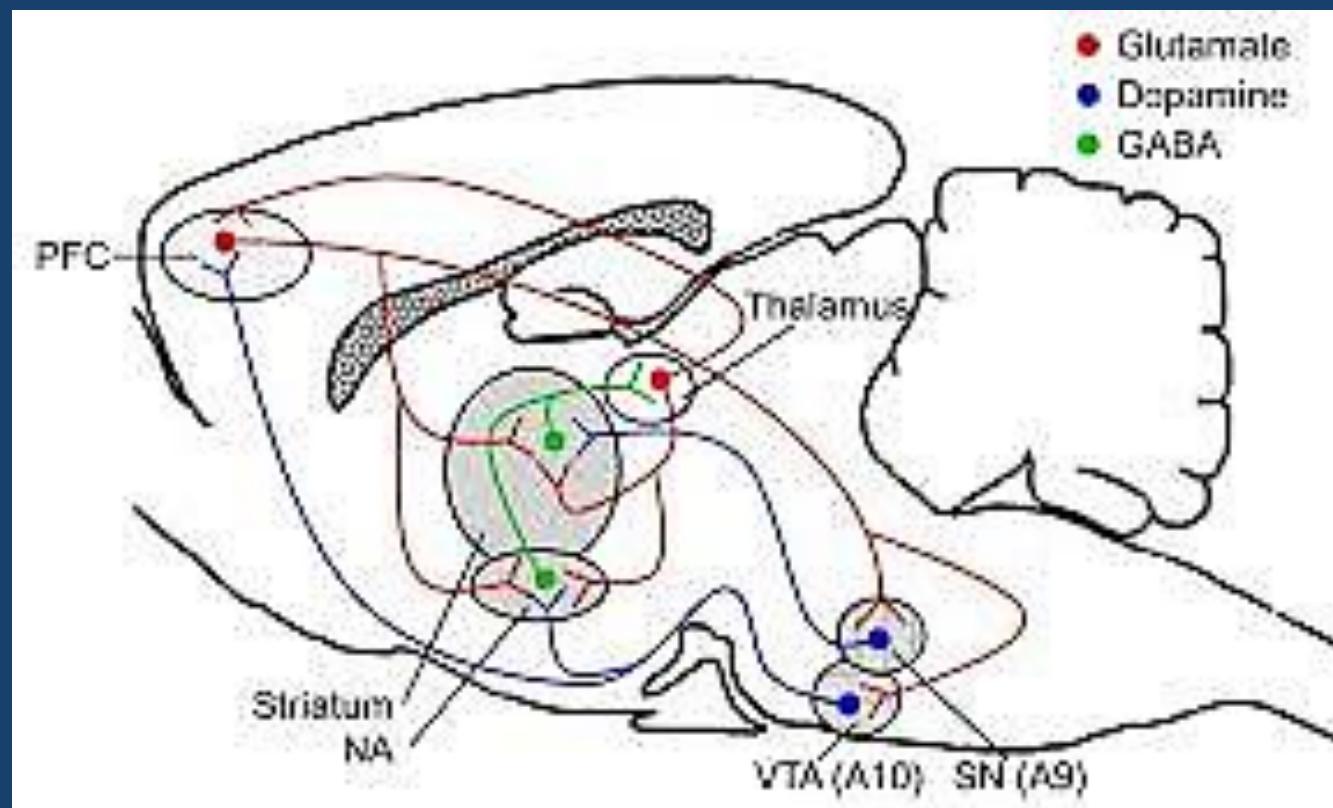
Amygdala

- The amygdala also sends glu input to Nac
- BLA–NAc projections facilitates reward seeking and supports positive reinforcement.
- Role of amyg in emotional learning and projections from the BLA to mediate fear- and anxiety-behaviors, are mediated distinctly from those of BLA projections to NAc, BLA–NAc microcircuit drives reward and reinforcement.



Thalamus

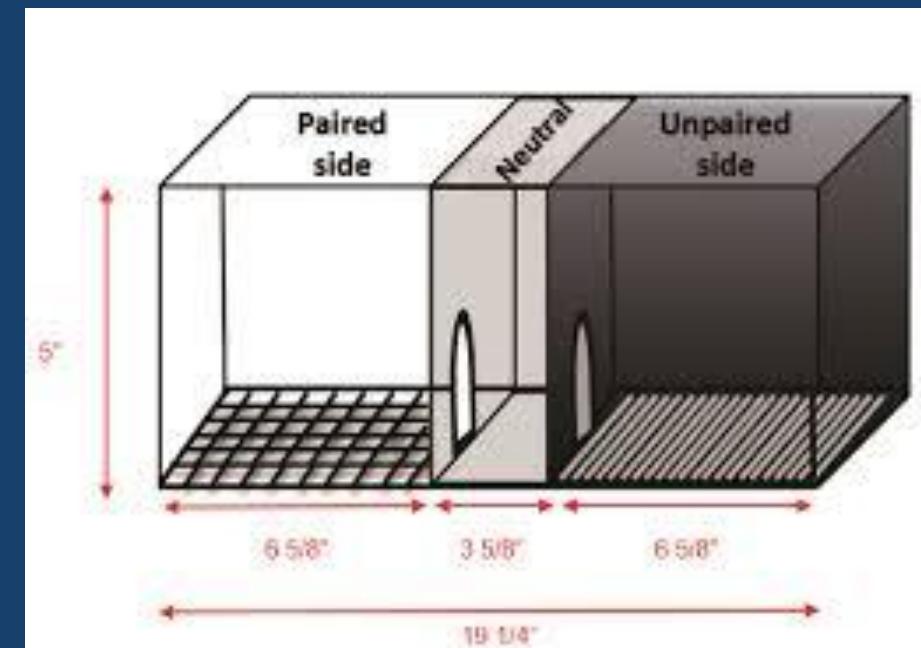
- Glu inputs into NAc from thalamus especially midline thalamic nuclei like the PVT
- PVT– NAc pathway is aversive, driving behavioral aversion in a place preference assay.
- Alteration of PVT activity alters drug-related behaviors like cocaine reward and seeking.



VTA DA Stimulation

Role of VTA DA neurons in reward-related behaviors:

- Stimulation of VTA DA neurons:
 - CPP
 - Increased DA release in the Nac
 - Positive reinforcement in a food-seeking operant task
 - Support intracranial self-stimulation



VTA DA Stimulation

The role of VTA DA activity in compulsive use despite negative consequences

- In an operant stimulation task:

An active lever press

Burst
stimulation of
VTA DA
neurons

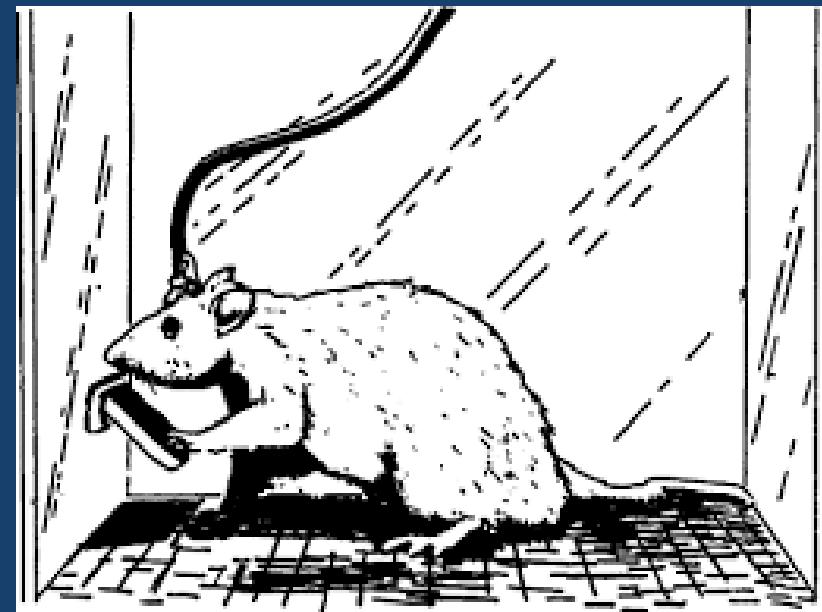
mice readily
acquired self
stimulation
behavior

reinforcement
relies on the
same circuits as
drugs of abuse

Cocaine
decreases self-
stimulation in a
dose dependent
manner

VTA DA Stimulation

- ***Similarity between self-stimulation and cocaine self-administration:***
- Similar cue-induced seeking behavior following 30 days of abstinence from VTA DA self-stimulation, similar to that following cocaine.
- VTA DA self-stimulation induces continued responding despite an electric foot shock punishment paired with the stimulation.

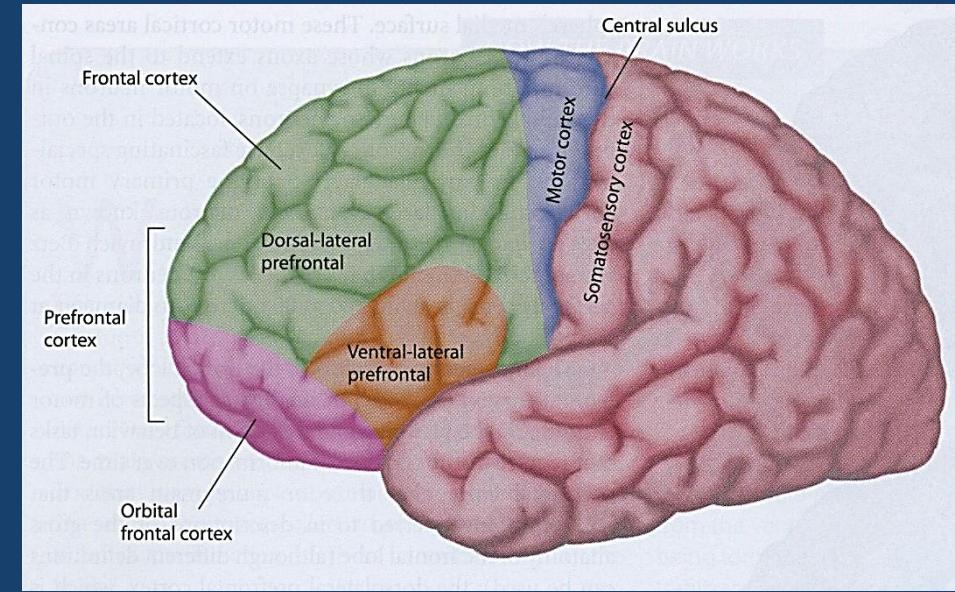


VTA DA Stimulation

Which brain regions contribute to the phenotype of continuing to self-stimulate in the presence of punishment?

Orbitofrontal cortex (OFC)

Silencing OFC neurons is sufficient to convert punishment resistant mice to susceptible.



NAc MSN Stimulation

- Activity of VTA DA neurons is critical to drive initial reward-related drug seeking.
- In Nac, reward-related information modulates glu inputs from cortical and limbic regions to produce behavior.
- In contrast to VTA DA neuron activation, D1 or D2 MSN activation did not generate place preference.

NAc MSN Stimulation

- Activation of D1 MSNs during cocaine exposure induces CPP to a subthreshold dose of cocaine
- D2 MSN activation produced the opposite result, decreasing CPP when administered during training.

PFC–NAc Stimulation

- ***Glu afferents to the NAc differentially support reward behavior.***
- ***Stimulation of NAc axonal terminals originating from BLA neurons promote self-stimulation***
- ***Simulation of terminals originating from mPFC neurons does not***
- PFC–NAc glu circuit changes play an integral role in drug-seeking behavior following forced abstinence or extinction from chronic cocaine.
- Activation of PrL–NAc projections is important for reinstatement behavior following cocaine extinction
- Inactivation of IL–NAc reinstates seeking behavior following extinction.

PFC–NAc Stimulation

- Glutamatergic regulation of NAc is critical for various aspects of addiction, including drug seeking and relapse.
- Results differ between the:
 - Region of PFC examined (PrL, IL, or orbitofrontal)
 - Cocaine-related paradigm and time point examined (reinstatement, seeking, or escalation)
 - Stimulation parameters
 - The species examined

Circuit-Based Therapeutics for Addiction

- Effects of drug addiction on the human reward circuitry using imaging approaches.
- Reports of drug-induced changes in structure and function of reward circuitry
- PFC activity is decreased in drug abusers
- Structural (decreased gray matter volume or cortical thickness) and functional (PET, fMRI,...) abnormalities in cocaine abusers.

Circuit-Based Therapeutics for Addiction

Alterations in the PFC subregions

Changes in limbic arousal, executive function, and reward valuation

Craving, risk taking, and outcome prediction errors

Addiction and relapse

Circuit-Based Therapeutics for Addiction

- Altered activity within PFC subregions: altered activity in the dorsal (caudate and putamen) and ventral (NAc) striatum.
- **Changes in dorsal striatal activity are associated with changes in:**
 - Movement
 - Cognitive processing
 - Habit formation
- Stronger connectivity to the dlPFC
- **Changes in activity in ventral striatum are more relevant to:**
 - Limbic control
 - Arousal states such as craving and “high”
- Highly connected to the mPFC and OFC,

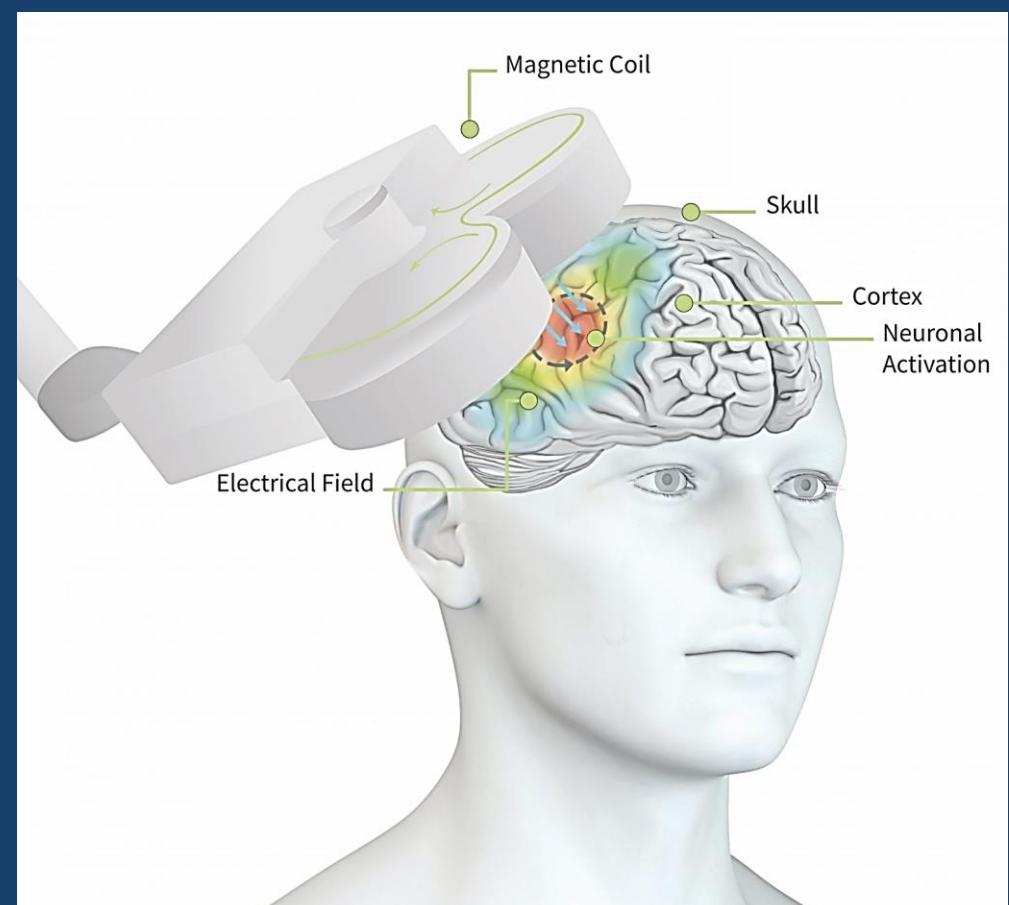
Repetitive Transcranial Magnetic Stimulation for Treatment of Addiction

- A noninvasive approach to alter neuronal activity
- Applied with success to other neuropsychiatric disorders such as depression.
- Is rTMS capable of decreasing craving for, or use of drugs?
- Most studies: high-frequency rTMS (10–20 Hz) in the dlPFC to increase neuronal excitability and cortical activity
- rTMS of dlPFC in addicted individuals is expected to increase cortical activity and improve cognitive/executive control.



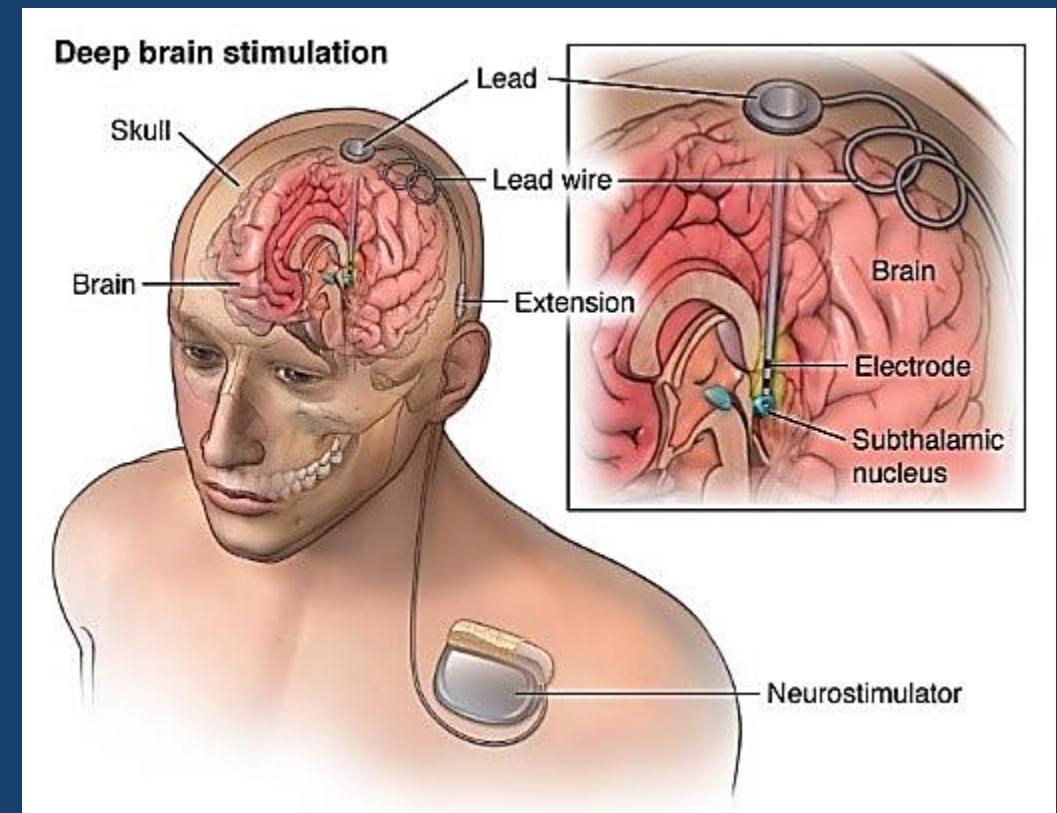
Repetitive Transcranial Magnetic Stimulation for Treatment of Addiction

- The results are promising, rTMS can be safely used in cocaine-addicted patients.
- ***Issues that could ultimately limit its effectiveness in the treatment of addiction:***
 - Constraints on the specificity of stimulation target region
 - Frequency of treatments necessary
 - Long-term persistence of any beneficial effects.



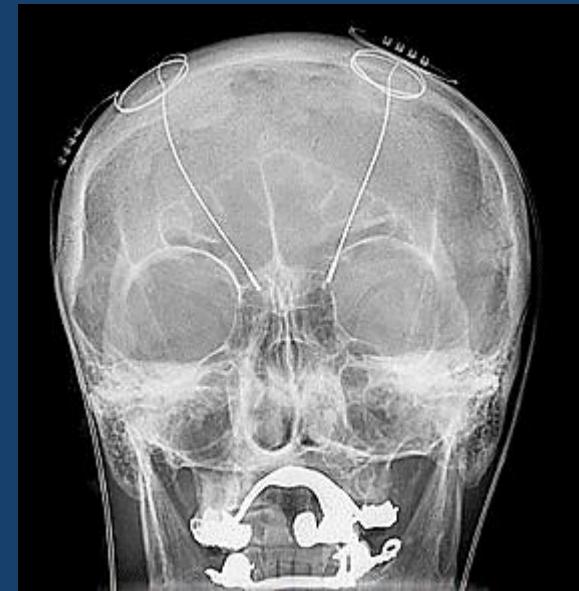
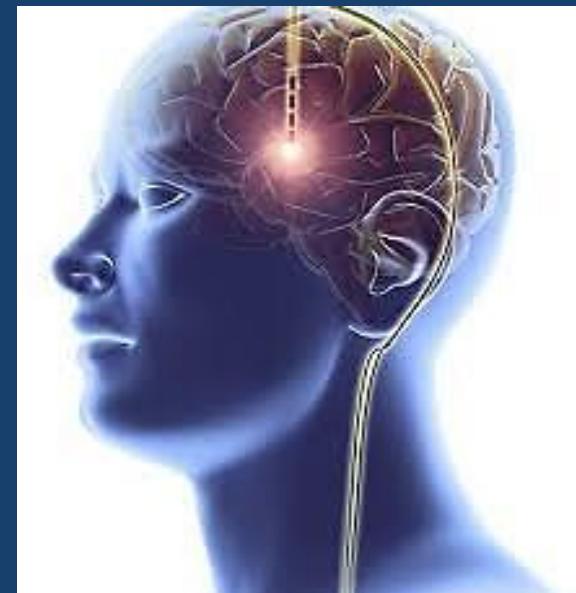
Deep Brain Stimulation for Treatment of Addiction

- Electrical stimulation of brain regions through surgical implantation of current passing electrodes.
- Pioneered for the treatment of Parkinson's disease
- More recently in the treatment of psychiatric disorders such as depression.



Deep Brain Stimulation for Treatment of Addiction

- A stimulation protocol to reverse cocaine-induced changes in neuroplasticity.
- Combined with administration of D1 receptor antagonist to block competing effects of the stimulation on DA release
- Both reverse the cocaine-induced changes in synaptic plasticity and cocaine locomotor sensitization.





Thank you for your attention