

**cognition**

**motor**

**sensory**

**reward**

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Behavior happens.

Basic Level

Pupillary reflex.

Knee jerk reflex.

Complex Level

Conscious  
movements

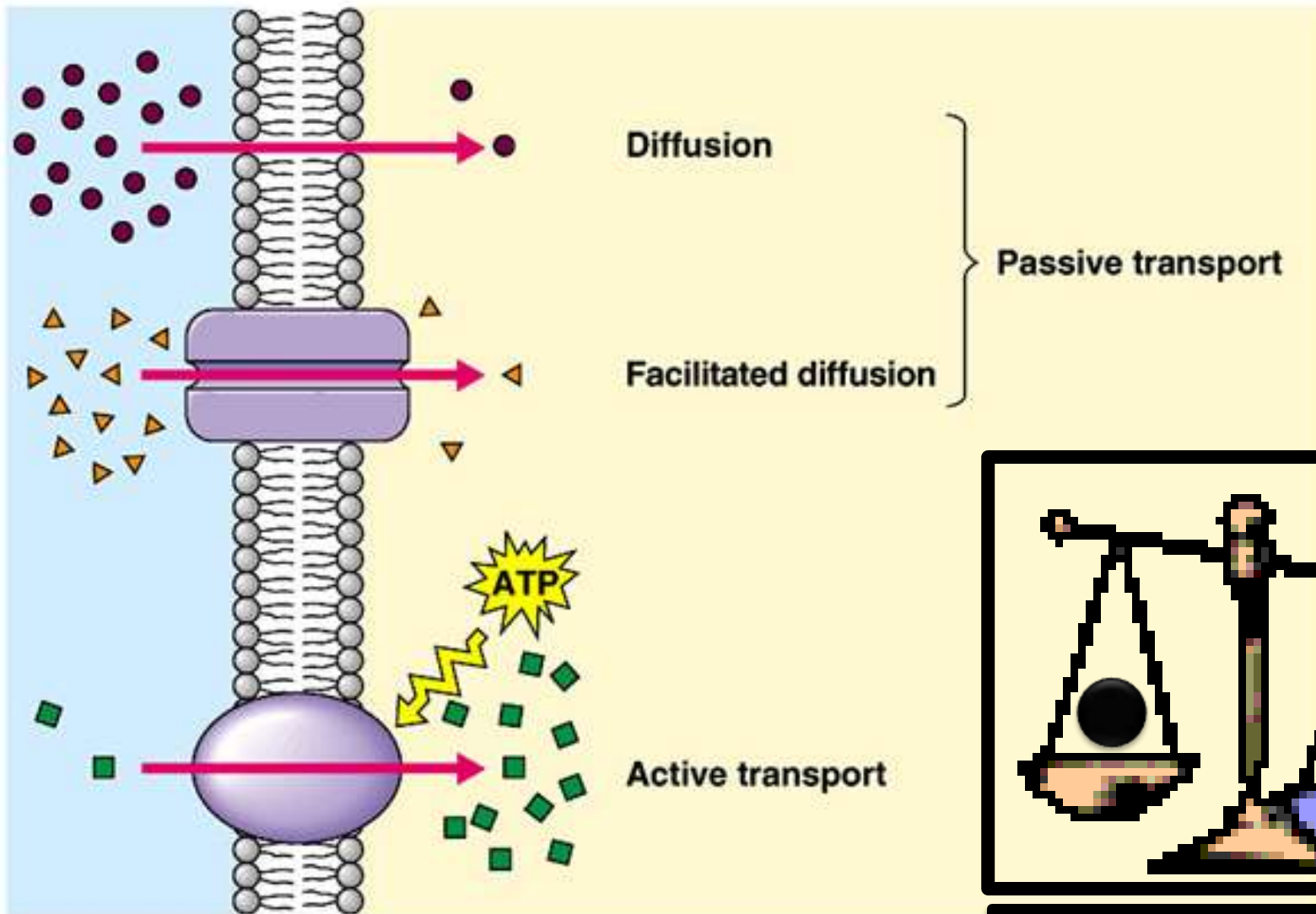
Basic

Motivation

Abstract

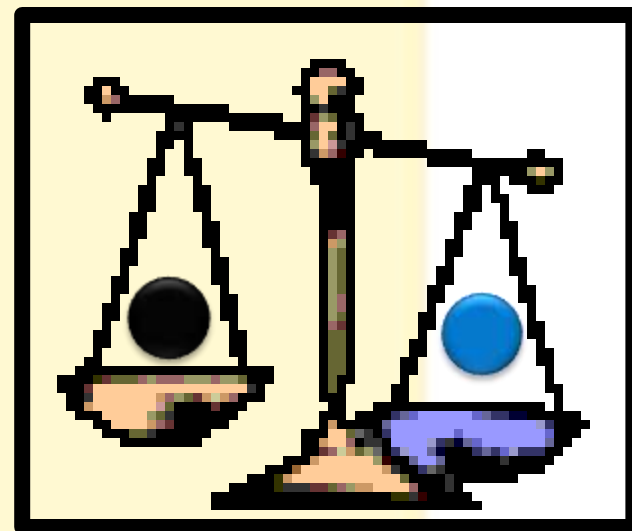
Driving force

s.d. antic



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Driving force for Ions



Driving force  
for Behavior



**Air temperature = 110 °F**

**Driving force for  
Behavior**

**Same Subject  
Same Object  
Same Distance**

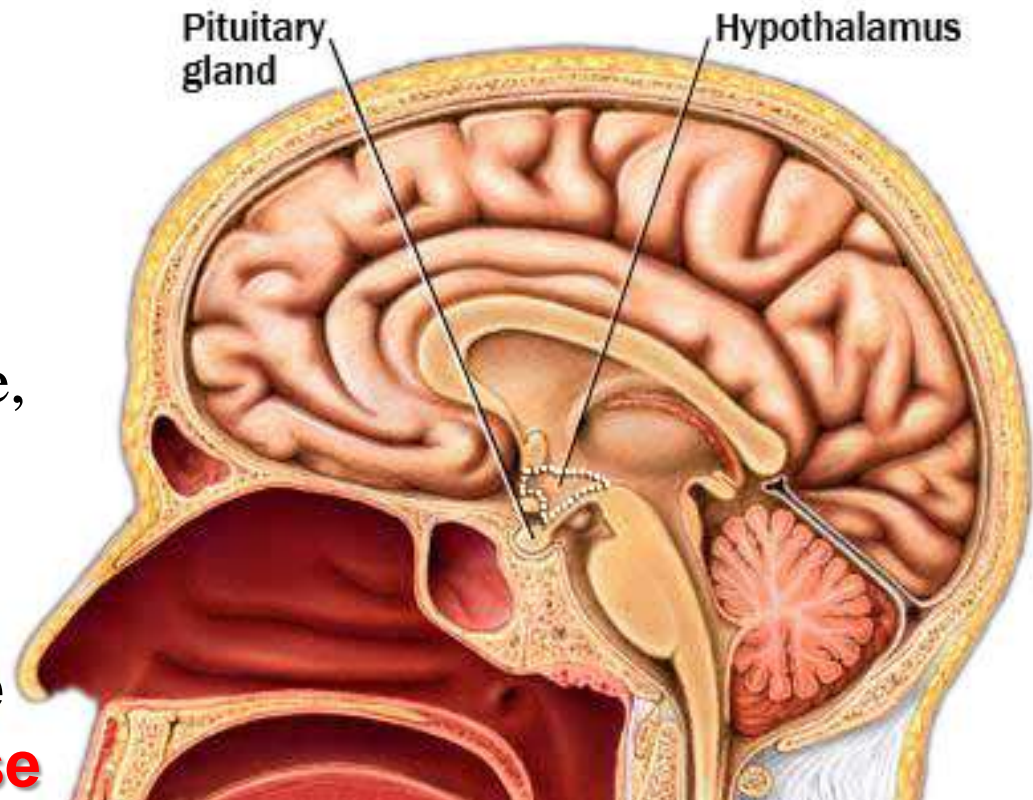
**Motivational states arise from  
the interaction of internal and  
external inputs.**

# Driving force for Behavior

## Hypothalamus

regulation of body temperature,  
fluid, and energy balance

- 1] Humoral response
- 2] Visceromotor response
- 3] **Somatic motor response**



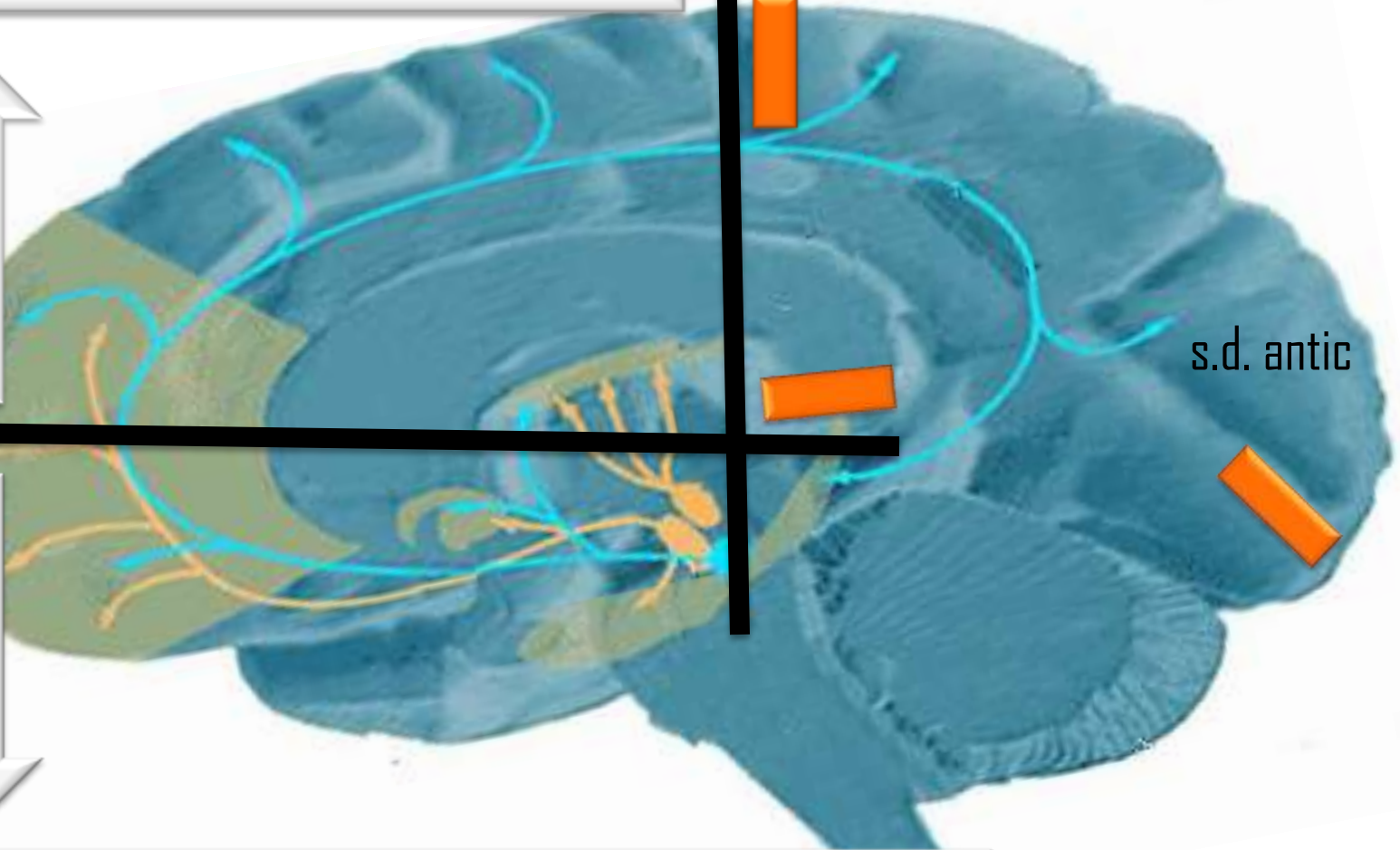
You are cold, dehydrated, and depleted of energy. The appropriate humoral and visceromotor responses kick in automatically. You shiver, blood is shunted away from the body surface, urine production is inhibited, body fat reserves are mobilized, and so on. **But the fastest and most effective way to correct these disturbances is to actively seek or generate warmth by moving, to find and drink water, and to find and eat food.**



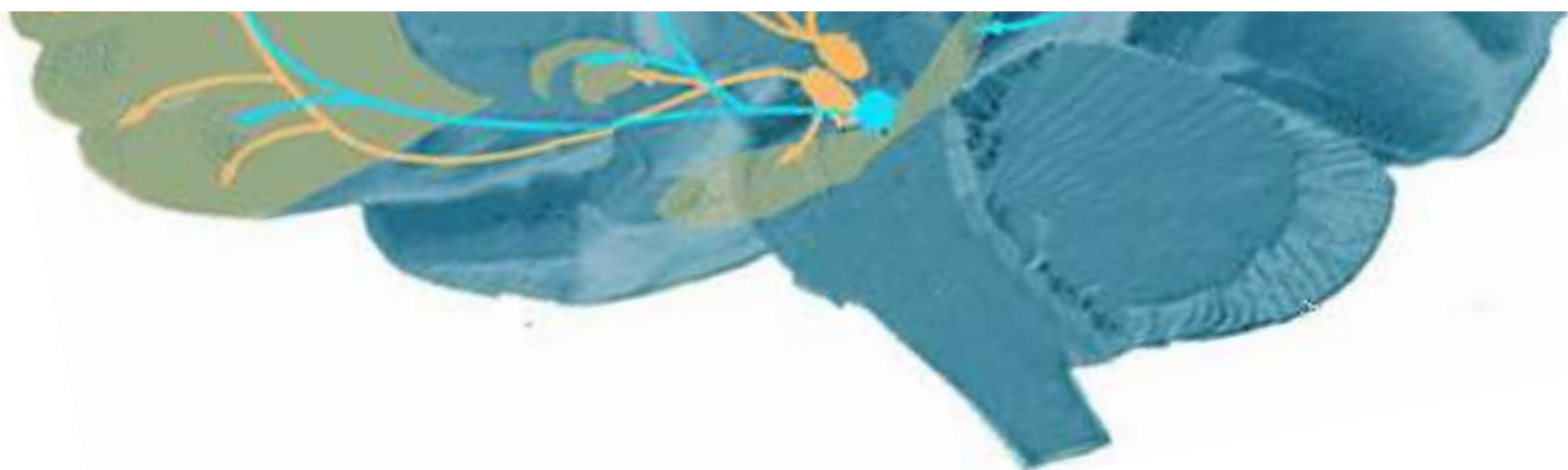
COGNITION, CALCULATION



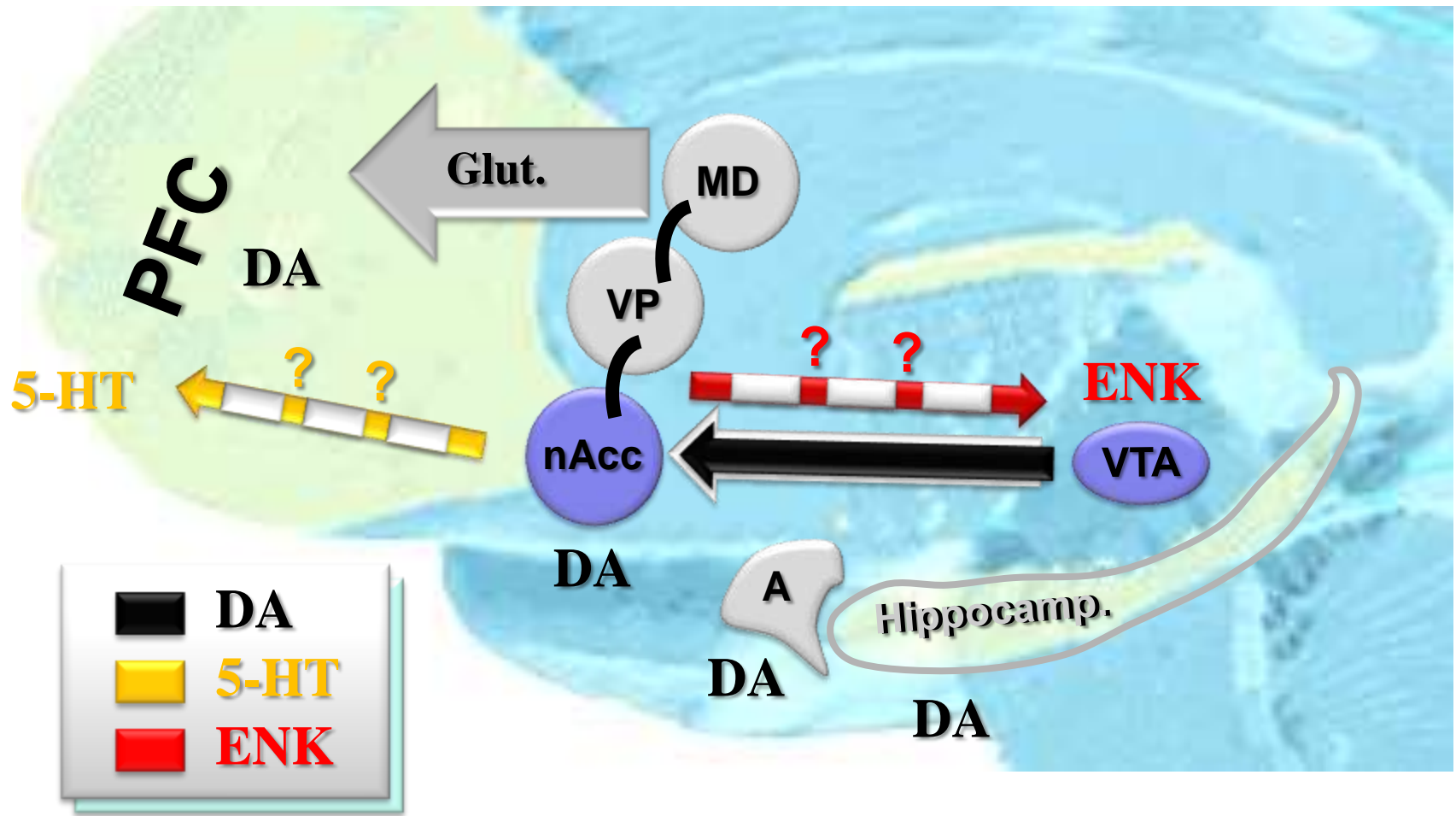
MOTIVATION, REWARD, COMPULSION



s.d. antic

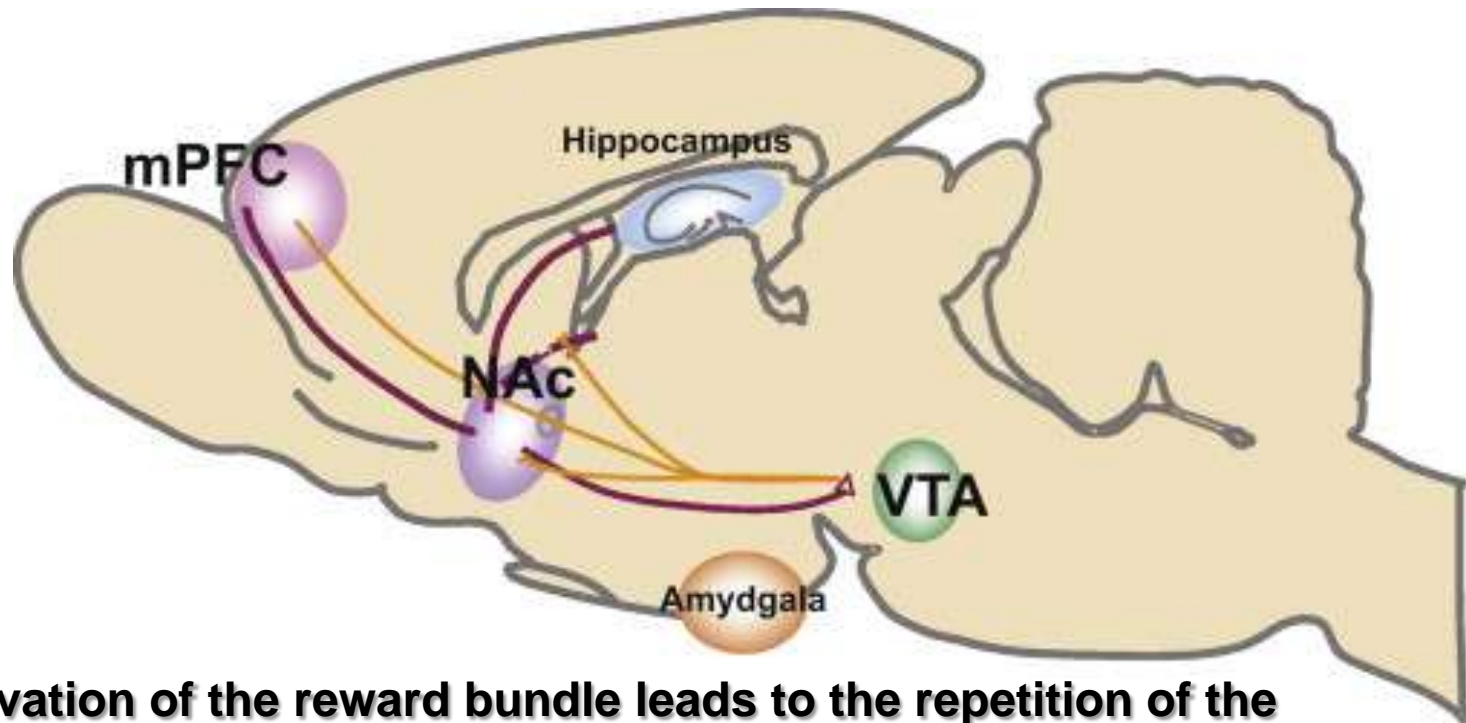


# The pleasure or reward bundle





# The Pleasure or Reward bundle



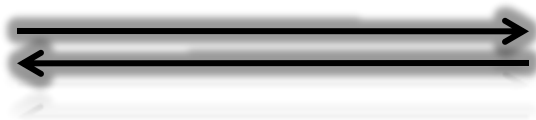
**Activation of the reward bundle leads to the repetition of the gratifying action to strengthen the associated pathways in the brain.**

When the cortex has received and processed a sensory stimulus indicating a reward, it sends a signal announcing this reward to the VTA – whose activity then increases. The VTA then releases dopamine not only into the nucleus accumbens, but also into the septum, the amygdala, and the prefrontal cortex. The nucleus accumbens then activates the individual's motor functions, while the prefrontal cortex focuses his or her attention.

The pleasure or reward bundle has its own anatomical name

## Medial Forebrain Bundle (MFB)

Activation leads to the repetition of the gratifying action to strengthen the associated pathways in the brain



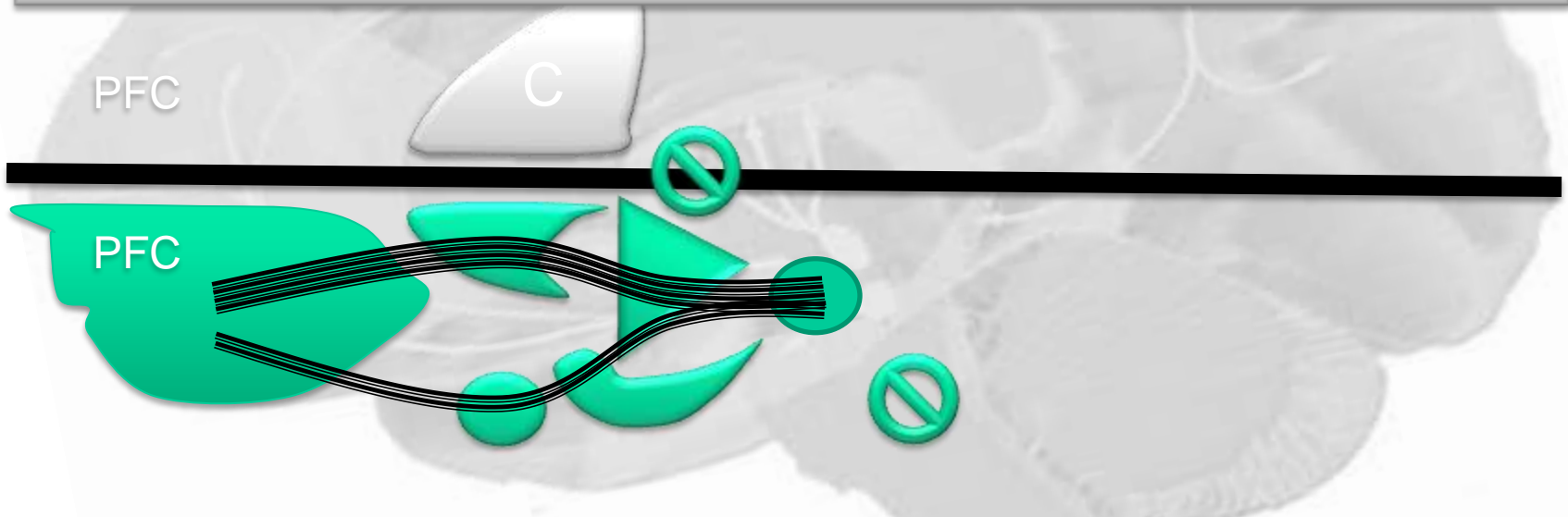
Bidirectional communication between

Ventral tegmental area (VTA) and the lateral hypothalamus

VTA and Nucleus Accumbens

VTA and the amygdala, septum, and prefrontal cortex

## Medial Forebrain Bundle (MFB)



The MFB projections from VTA, Nuc Accumbens and Amygdala to the prefrontal cortex allow the most primitive parts of the brain to exert strong influence on our behaviors. This leaves the neocortex with the embarrassing task of having to justify our behavior in words!



# Medial Forebrain Bundle (MFB)

The MFB projections originate in the reticular formation, they cross the ventral tegmental area, pass through the lateral hypothalamus, and continue into the nucleus accumbens, as well as the amygdala, the septum, and the prefrontal cortex.

**Reticular formation**

**VTA**

**Lat Hypothalamus**

**Nuc. Accumbens**

**Amygdala**

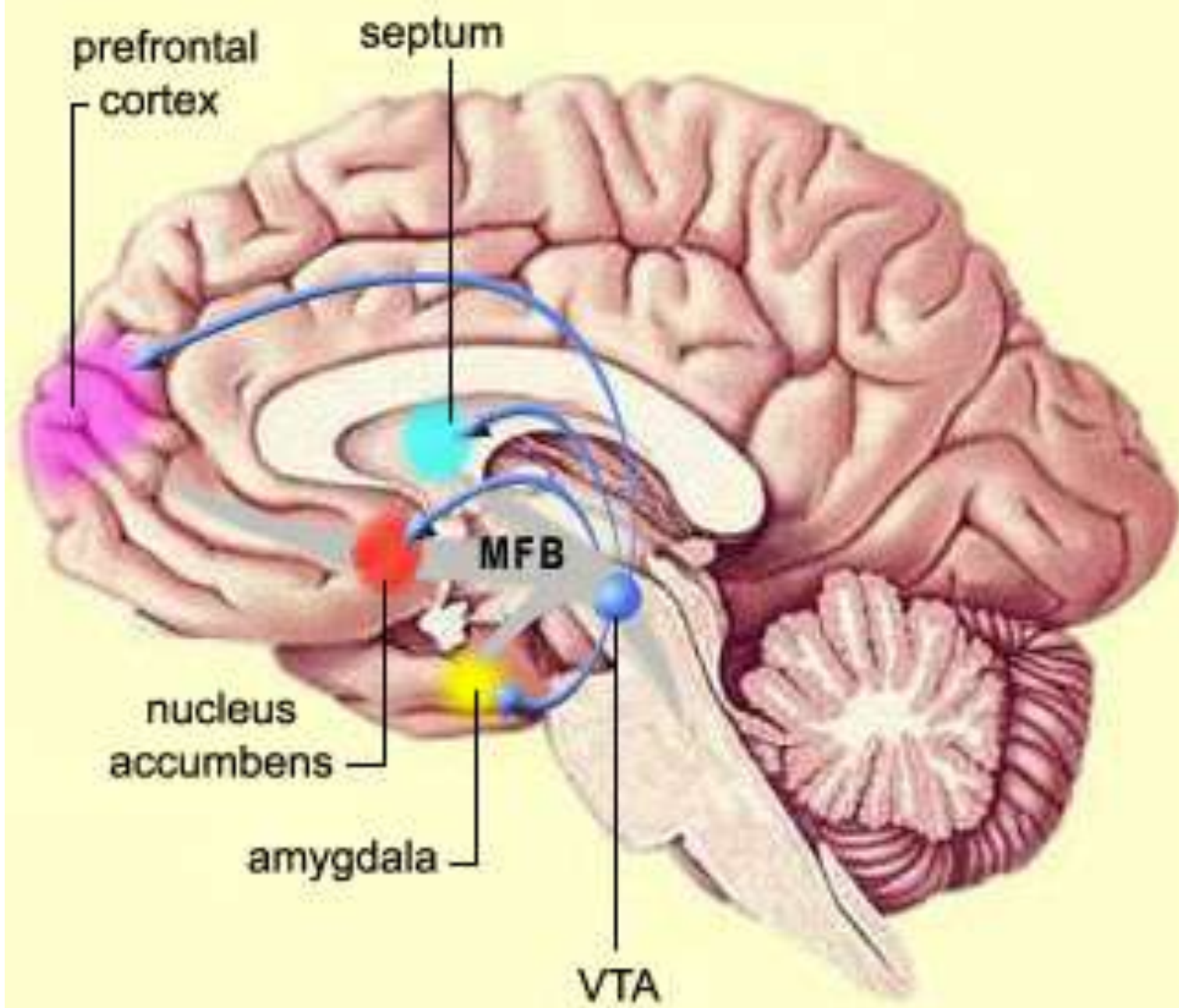
**Septum**

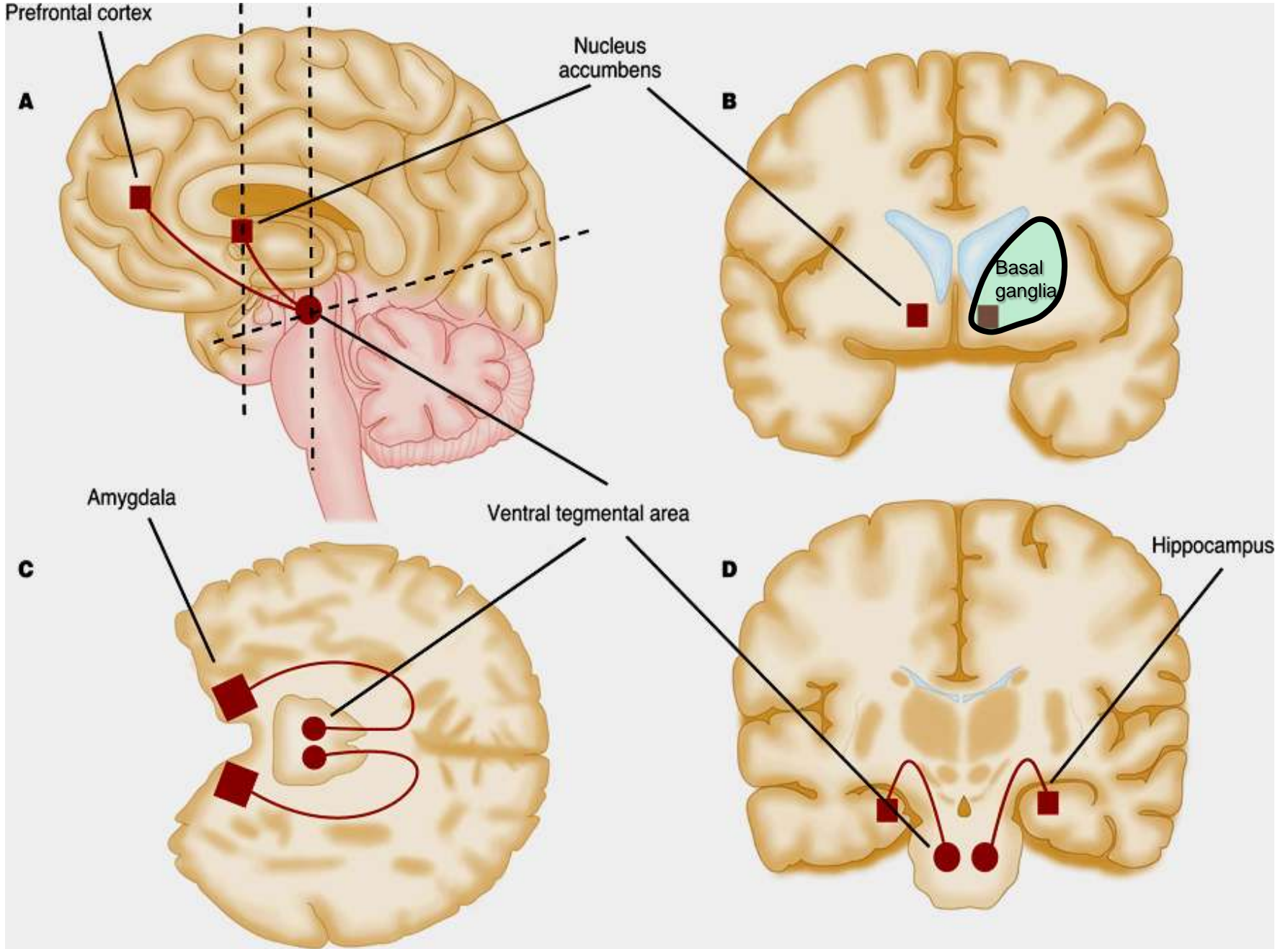
**Hippocampus**

**PFC**

PFC









# HUMAN - Medial Forebrain Bundle (MFB)

## Self-Stimulation of the Human Brain

Two patients of Robert Heath, Tulane Univ. 1960s.

### Patient 1

Severe narcolepsy. Fitted with 14 electrodes in different brain areas in the hope of finding a self-stimulation that might keep him awake and alert.

Hippocampus – Mild pleasure.

Midbrain tegmentum - alert but unpleasant.

He chose septal area of the forebrain. Stimulating the septal area made him more alert and gave him a good feeling, which he described as building up to orgasm. He reported that he would sometimes push the button over and over, trying to unsuccessfully to achieve orgasm, ultimately ending in frustration. Frustration.

# HUMAN - Medial Forebrain Bundle (MFB)

Patient 2

Severe epilepsy. 17 electrodes.

Septal area – pleasure and sexual feelings

Midbrain tegmentum – pleasure, happy drunk

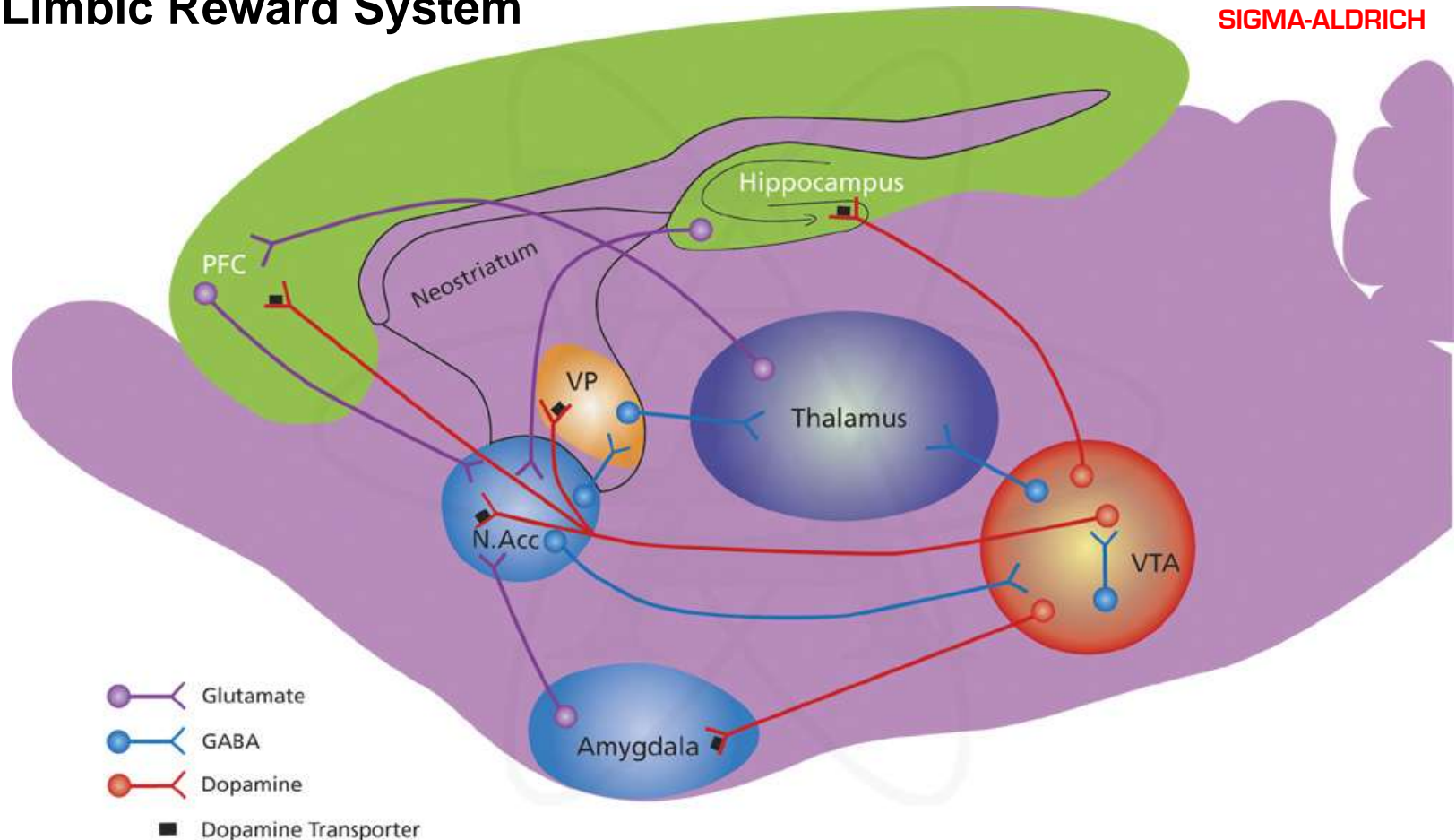
Amygdala – mildly positive feelings

Caudate nuc. - mildly positive feelings

Most frequently stimulated site of his choice was in the medial thalamus, even though a stimulation here produced an irritable feeling, one that was less pleasurable than stimulation in other sites. The reason – it gave him a feeling he was about to recall a memory. Frustration.

# Limbic Reward System

SIGMA-ALDRICH



**Sagittal section of the rat brain. Highlighted are the nuclei representing the limbic structures of the basal forebrain including the amygdala, hippocampus, prefrontal cortex (PFC), nucleus accumbens (N. Acc.), ventral pallidum (VP) and ventral tegmental area (VTA). Dopaminergic neurons in the VTA modulate information flow through the limbic circuit via projections to the nucleus accumbens, amygdala, hippocampus, PFC and VP. Increased dopaminergic transmission in limbic nuclei, particularly the nucleus accumbens, underlies the reinforcing effect of virtually every abused drug. Note that psychostimulants increase dopaminergic transmission in areas receiving projections from the VTA via interactions with dopamine transporters.**



# Limbic Reward System

## **Ventral Tegmental Area (VTA)**

Part of the Natural Reward Circuitry. Cognition, Motivation, Drug addiction. Intense emotions relating to love. Novel stimuli, unexpected rewards, and reward predictive sensory cues.

## **Hypothalamus**

Humoral, Visceral Motor and Somatic Motor, Homeostasis, Rage, Motivation, Behavioral Driver.

## **Nuc. Accumbens (nAcc.)**

Activates the individual's motor functions (like all basal ganglia do). But ventral and anterior position – Activation of mental processes (Mental focus, Motivation). Pleasure and reward.

## **Ventral Pallidum (VP)**

Reward and incentive Motivation, Emotions, Emotional regulation of behavior, Addiction. It collects inputs from the temporal lobes, and the hippocampus via the ventral striatum (Nuc. Accumbens). Ventral Pallidum sends OUTputs to THALAMUS (MD nucleus VA nucleus) – similar to the hypothalamic outflow (mammillothalamic pathway).

# Limbic Reward System

## **Amygdala**

Euphoric Recall, Fear, Memory of Fear, Anxiety, Affect – Subcortical emotional reaction. Motor expression of fear and other emotions. Initiation of the physical contact and sexual behavior.

## **Septum**

Pleasure zone. Inhibition of fear. Reward and reinforcement. Expression of pleasurable responses. A relay center for the Hippocampal contents to get into VTA. Link reward signals with the context in which they occur. Suspicious proximity to the primary olfactory cortex. Pleasurable odors. Erotic odors. Erotic arousal. Sexual pleasure. Regarding the inhibition of fear, the inhibitory signals sent by the septal area modulate sexual responses of amygdala and hypothalamus, and promote more intimate contact, bonding with a sexual partner, bonding with other people. Love and long-lasting friendship. Bipolar disorder, schizophrenia and Major depressive disorder have something in common. Lack of proper emotions, especially towards other people. Interestingly, these three conditions are associated with pathoanatomical changes in the septal area manifested by loss of cells.

## **Hippocampus**

Consolidation of memories. Emotional Responses to sounds and odors. Navigation through a maze. Spatial Orientation.

## **PFC**

# ADDICTION

## ***NIDA – National Institute of Drug Abuse***

Drug abuse and addiction are now recognized as a chronic relapsing brain disease expressed in the form of **compulsive behaviors**.

**Decades of research have revealed addiction to be a disease that alters the brain.** We now know that while the initial decision to use drugs is voluntary, drug addiction is a disease of the brain that compels a person to become singularly obsessed with obtaining and abusing drugs despite their many adverse health and life consequences.

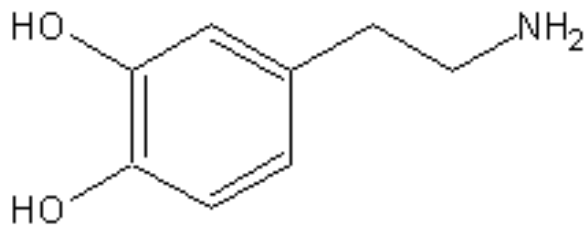
## **Why Do People Take Drugs in The First Place?**

**To feel good.** To have novel feelings, sensations, experiences and to share them.  
**To feel better.** To lessen: anxiety, worries, fears, depression and hopelessness.



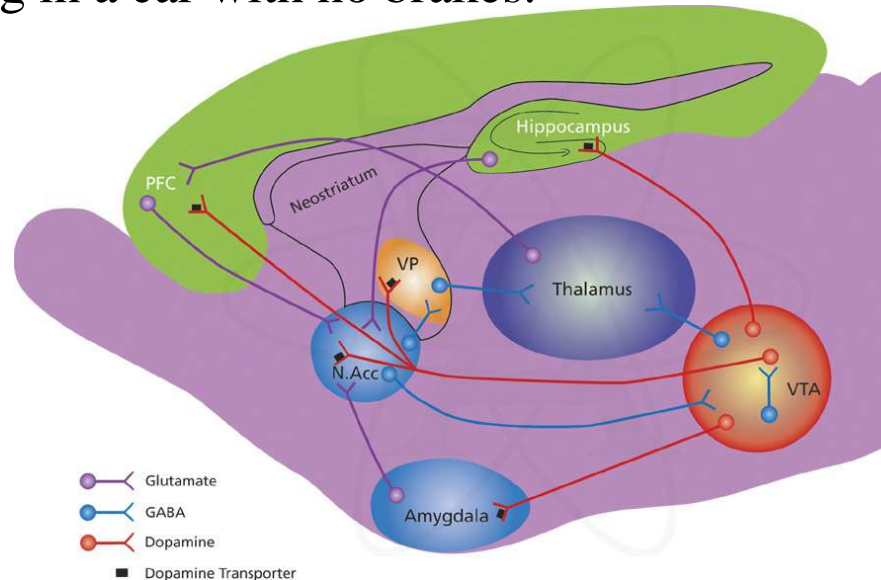
Brain circuits involved in reward, motivation, memory, and inhibitory control are altered by drugs. And when these neuronal circuits are altered, so is a person's capacity to freely choose *not* to use drugs, even when it means losing everything they used to value. In fact, the inability to stop is the essence of addiction, like riding in a car with no brakes.

**Dopamine** is involved in motivation, reward, movement and addiction. Nearly all drugs of abuse directly or indirectly increase dopamine.



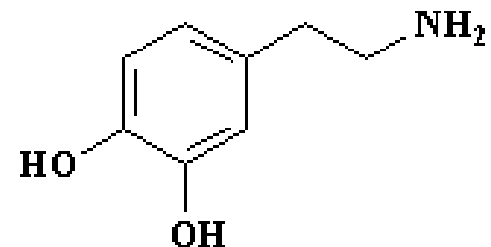
Dopamine

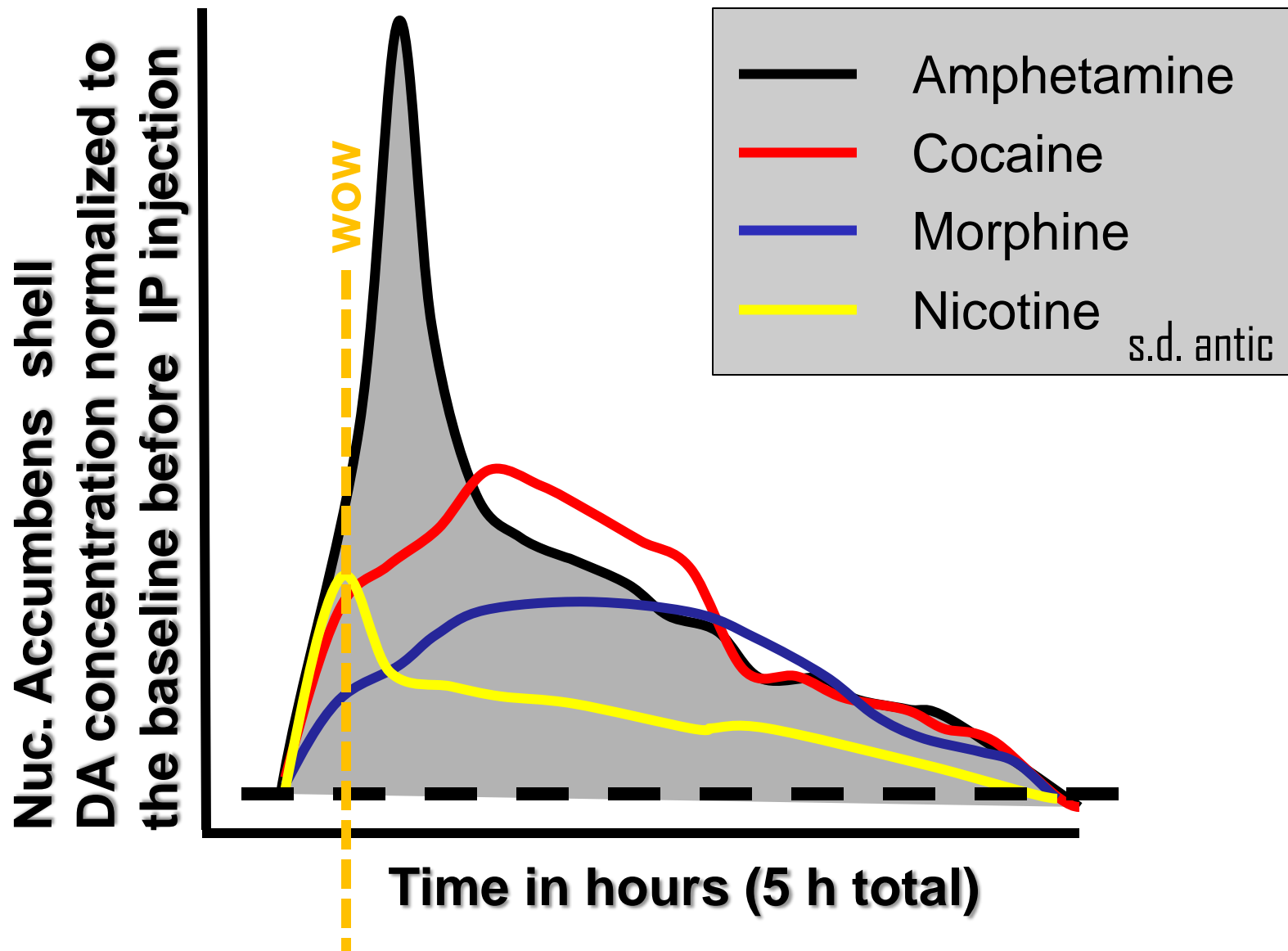
4-(2-aminoethyl)-1,2-benzenediol



**Dopamine**

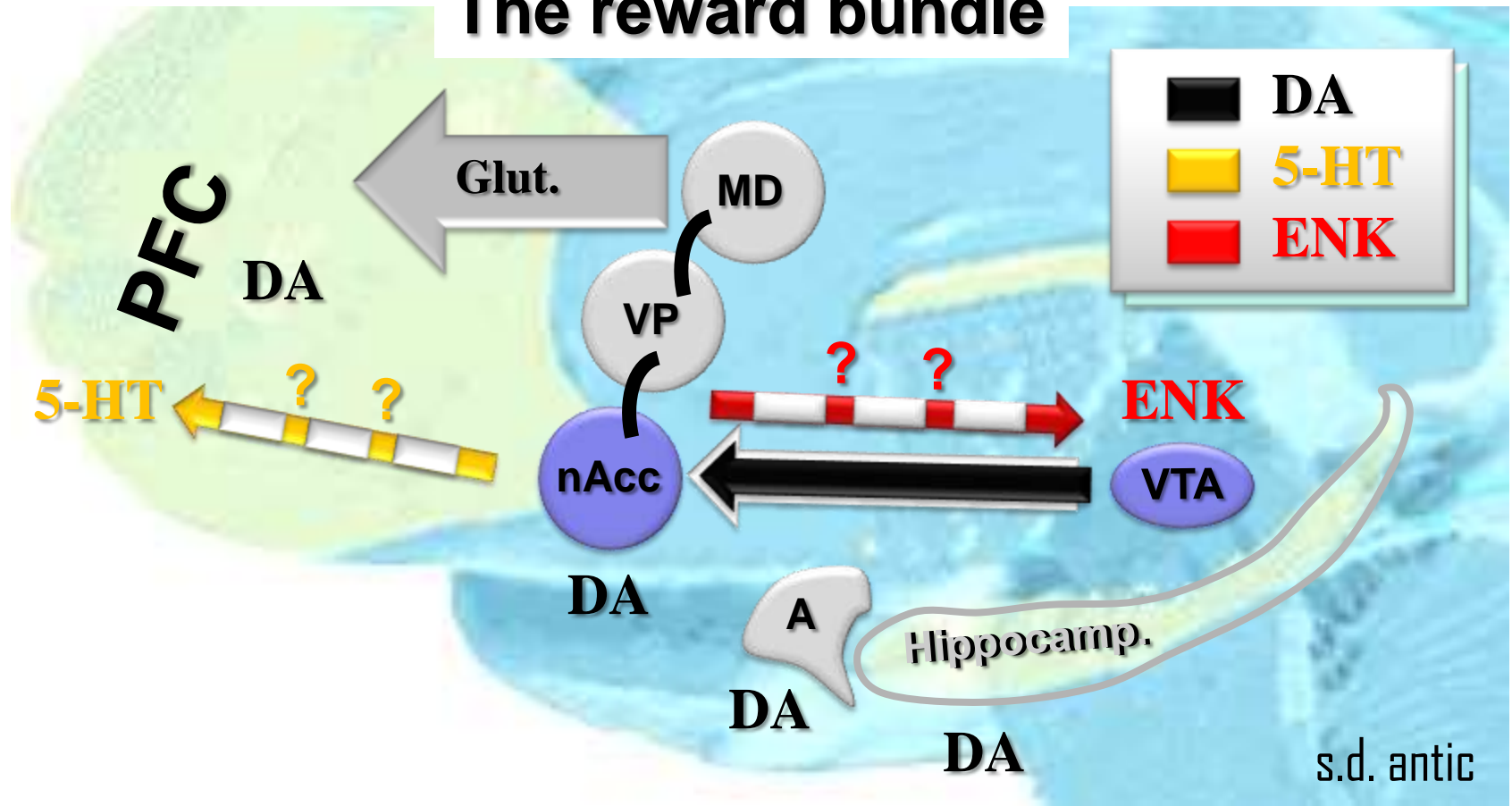
$C_8H_{11}NO_2$





*Di Chiara and Imperato, PNAS, 1988*

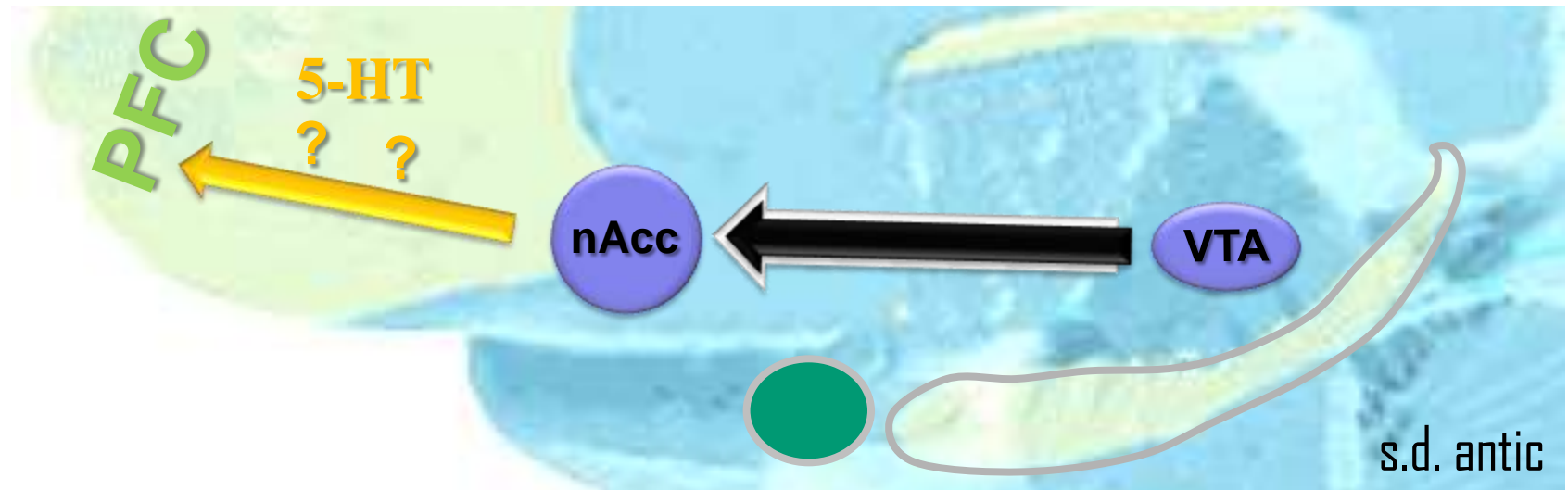
# The reward bundle



When there is enough of DA in the nuc. Acc., then there is enough of everything in my life. I do not need anything else.

When there is enough of 5HT in PFC then I am really well, I am accomplished, content, I am approved and satisfied. Worry-free.

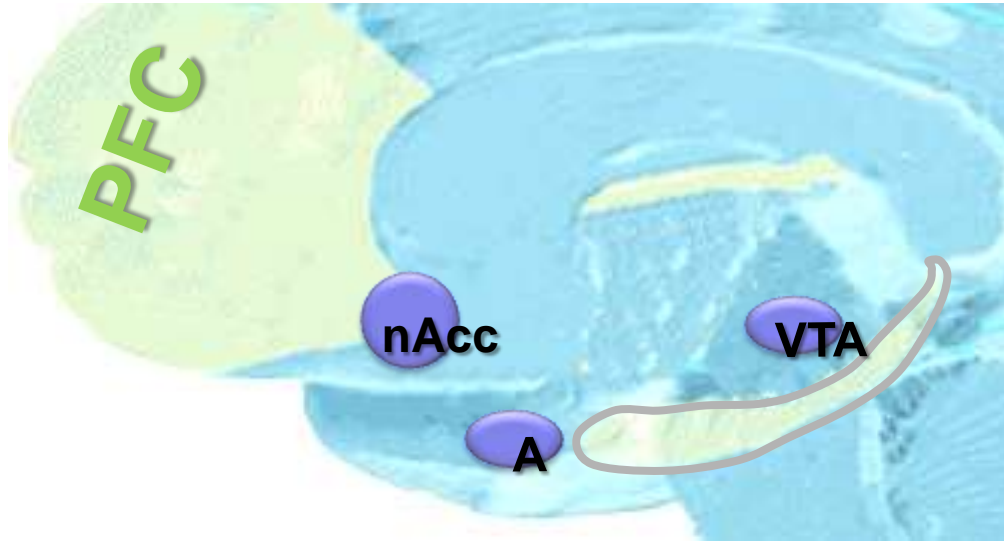
# Compulsive Circuit



**Wow! This gave me a great pleasure (VTA).**  
**Pleasure gave me a sense of wellbeing (PFC).**  
**I will remember the object that gave me pleasure (Amygdala).**  
**I will remember actions that led me to this object (Hippocampus).**  
**I will engage my basal ganglia to repeat these actions, because this is a great path to attaining pleasure and my wellbeing (Nuc. Accumbens).**  
**I will inhibit all distracters coming from my PFC. They just distract me from repeating the pursuit of my object of pleasure (Concerted action of Nuc. Accumbens, Ventral Pallidum and VTA).**  
**The “object” is no longer giving me any real pleasure, but this will not stop me from pursuing the object (Nuc. Accumbens).**



# Triggers of the Compulsive Circuit



**Methamphetamine.**

Hand washing.  
Locking the doors.  
Jogging.  
Working in the lab.

Video gaming.  
Eating.  
Playing a lead guitar.  
Cannabis sativa.

Smoking.  
Drinking.

Cocaine.  
Heroin.  
Morphine.  
Amphetamine.

Antihistamines.  
Benzodiazepines.

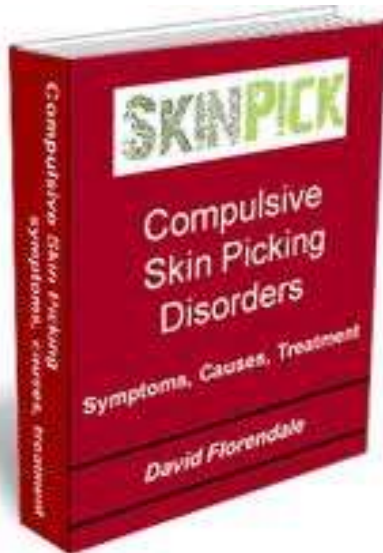
**Methamphetamine.**



**Compulsive hoarding**



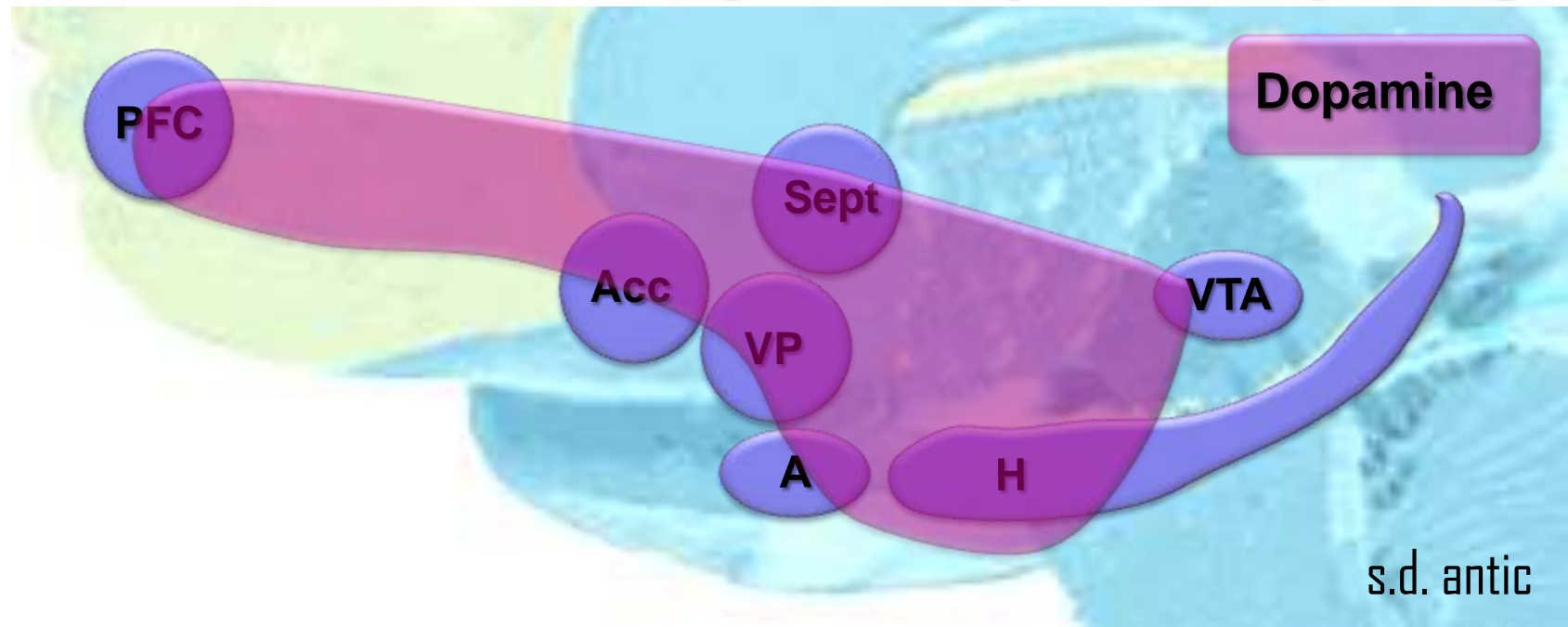
Something that gave me pleasure in the past (“the object”) is no longer giving me any real pleasure today. But this will not stop me from relentlessly pursuing the same object over and over again.



Although, it is no longer giving me great pleasure, I must take it in order to stay alive and function somehow. Without it, I am just a pile of pain and misery. My misery goes away only, and for a brief period of time, when I take the drug (or the object of my compulsion).

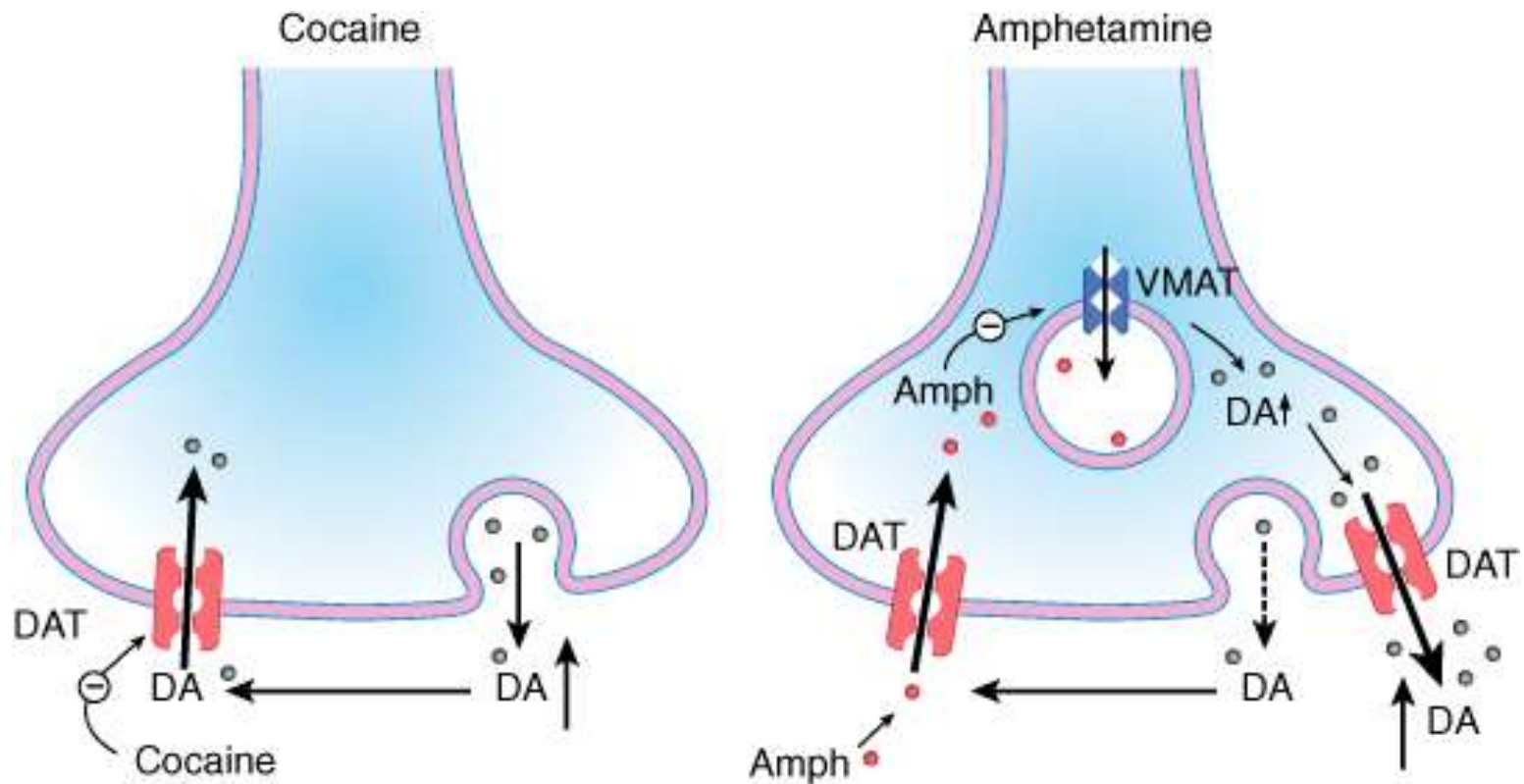
**I must somehow bring dopamine back in my Nuc. Accumbens.**

# Addiction = Reward System Hijacked by Drugs



Under physiologic conditions the mesolimbic dopamine signal could represent a learning signal responsible for reinforcing constructive behavioral adaptation (eg, learning to press a lever for food). Addictive drugs, by directly increasing dopamine, would generate a strong but inappropriate learning signal, thus hijacking the reward system and leading to pathologic reinforcement. As a consequence, behavior becomes compulsive; that is decisions are no longer planned and under control, but automatic, which is the hallmark of addiction.

**The Dopamine Hypothesis of Addiction**



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: <http://www.accessmedicine.com>

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### **Cocaine and amphetamine effects on synaptic terminals of dopamine (DA) neurons.**

**Left:** Cocaine inhibits the dopamine transporter (DAT), decreasing DA clearance from the synaptic cleft and causing an increase in extracellular DA concentration. **Right:** Amphetamine (Amph) is a substrate of the DAT. It competitively inhibits DA transport. In addition, once in the cell, amphetamine interferes with the vesicular monoamine transporter (VMAT) and impedes the filling of synaptic vesicles. As a consequence, vesicles are depleted and cytoplasmic DA increases. This leads to a reversal of DAT direction, strongly increasing nonvesicular release of DA, and further increasing extracellular DA concentrations.