It's in Your Mind: Addiction as a Chronic Brain Disease

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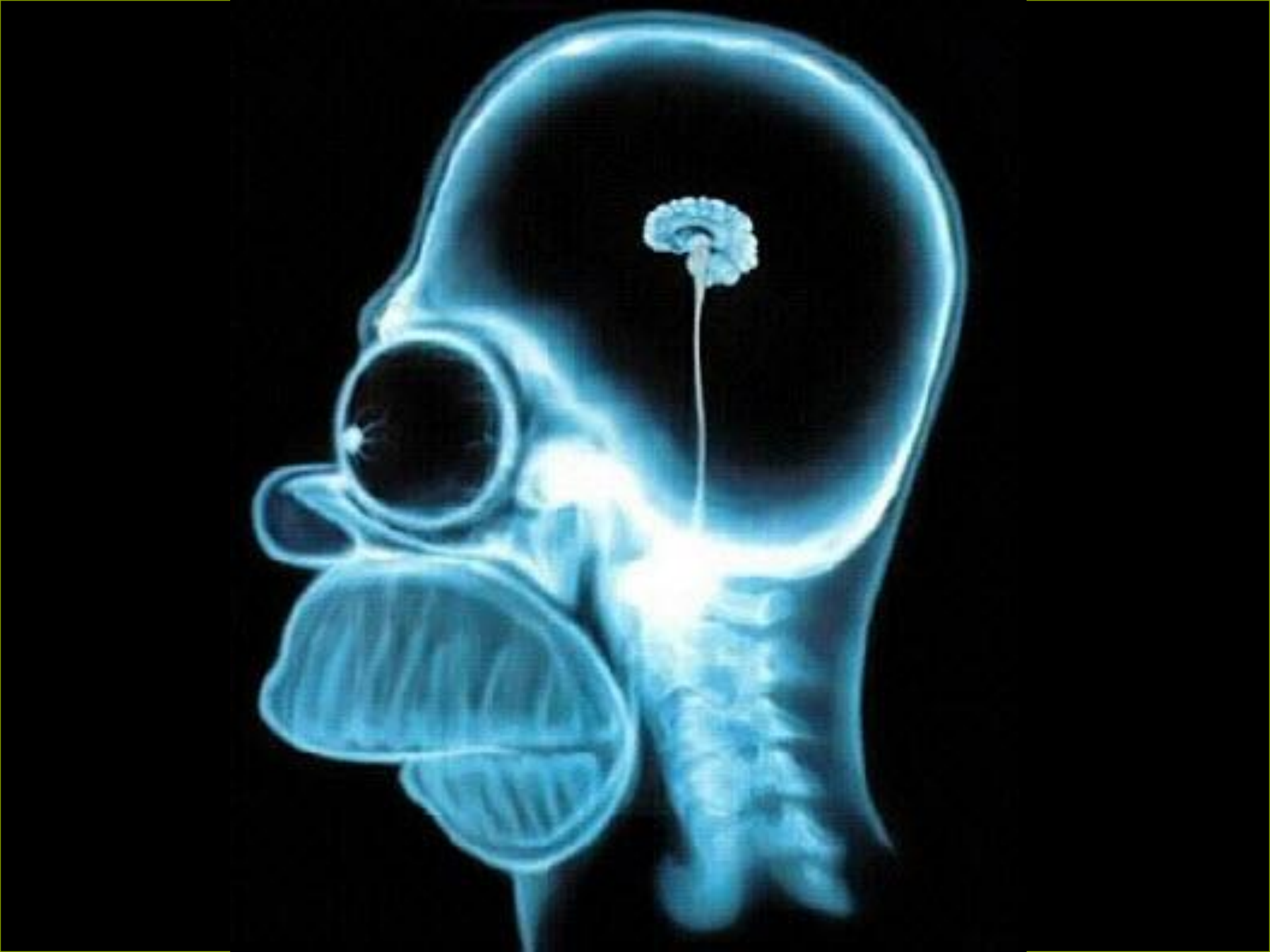
Addiction is Characterized by:

- Compulsion to seek and take the drug
- Loss of control in limiting intake
- Diminished recognition of significant problems
- Emergence of negative emotional state
- Craving
- Chronicity and relapse

Addiction is a Brain Disease

NOT:

- Secondary to another psychiatric illness
- A moral or ethical problem
- A personality disorder
- A choice



Genetic Vulnerability

- Estimated genetic risk 40-60%
- Multiple genes are involved with drug responses
- A few genes have been identified that are protective

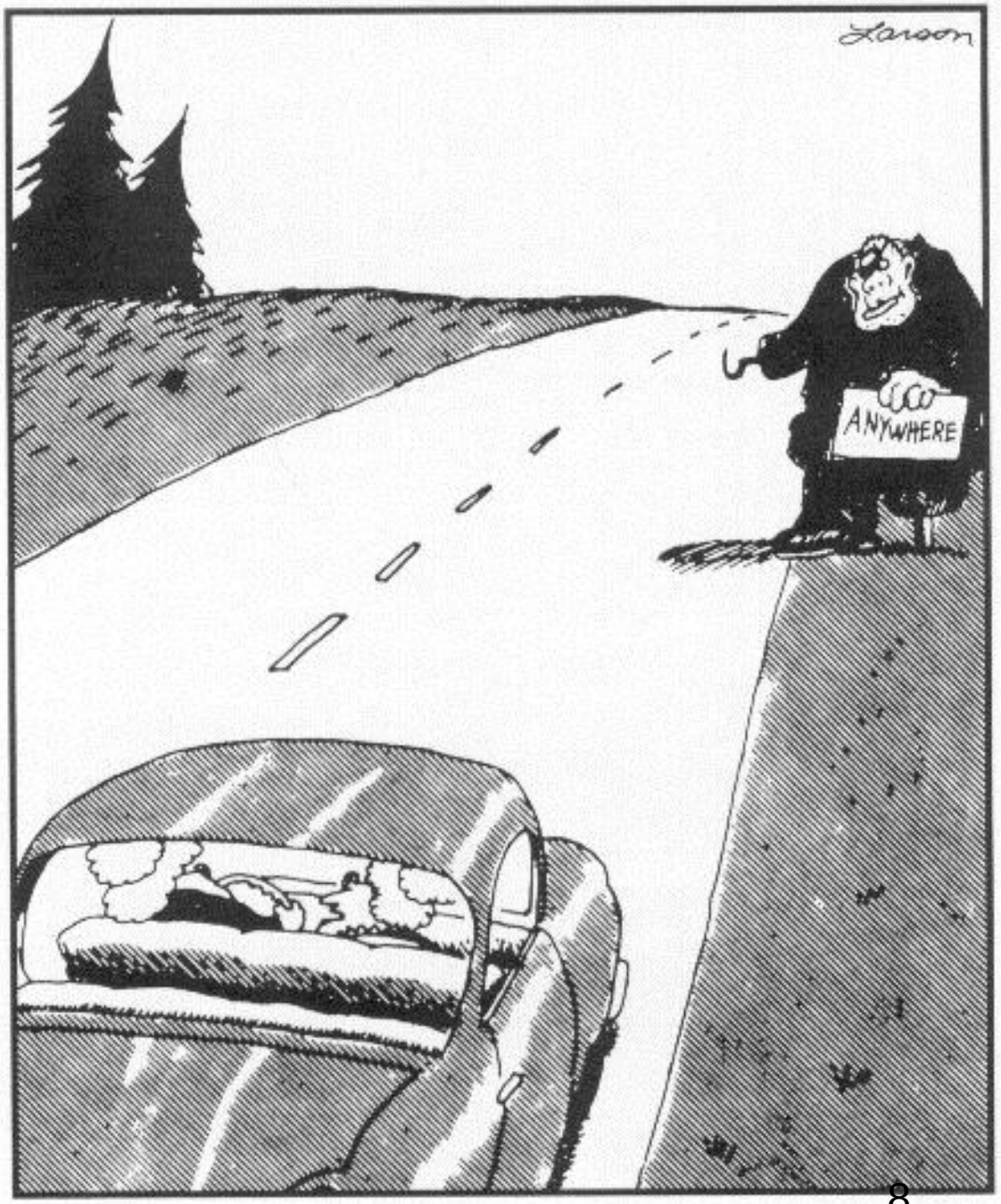
Environmental Risk Factors Consistently Related to Risk of Self Administration

- Low socioeconomic class
- Poor parental support
- Drug availability

Environmental Risk Factors

- **Stress** is a common feature among environmental risk factors, both for initiation of use and relapse.

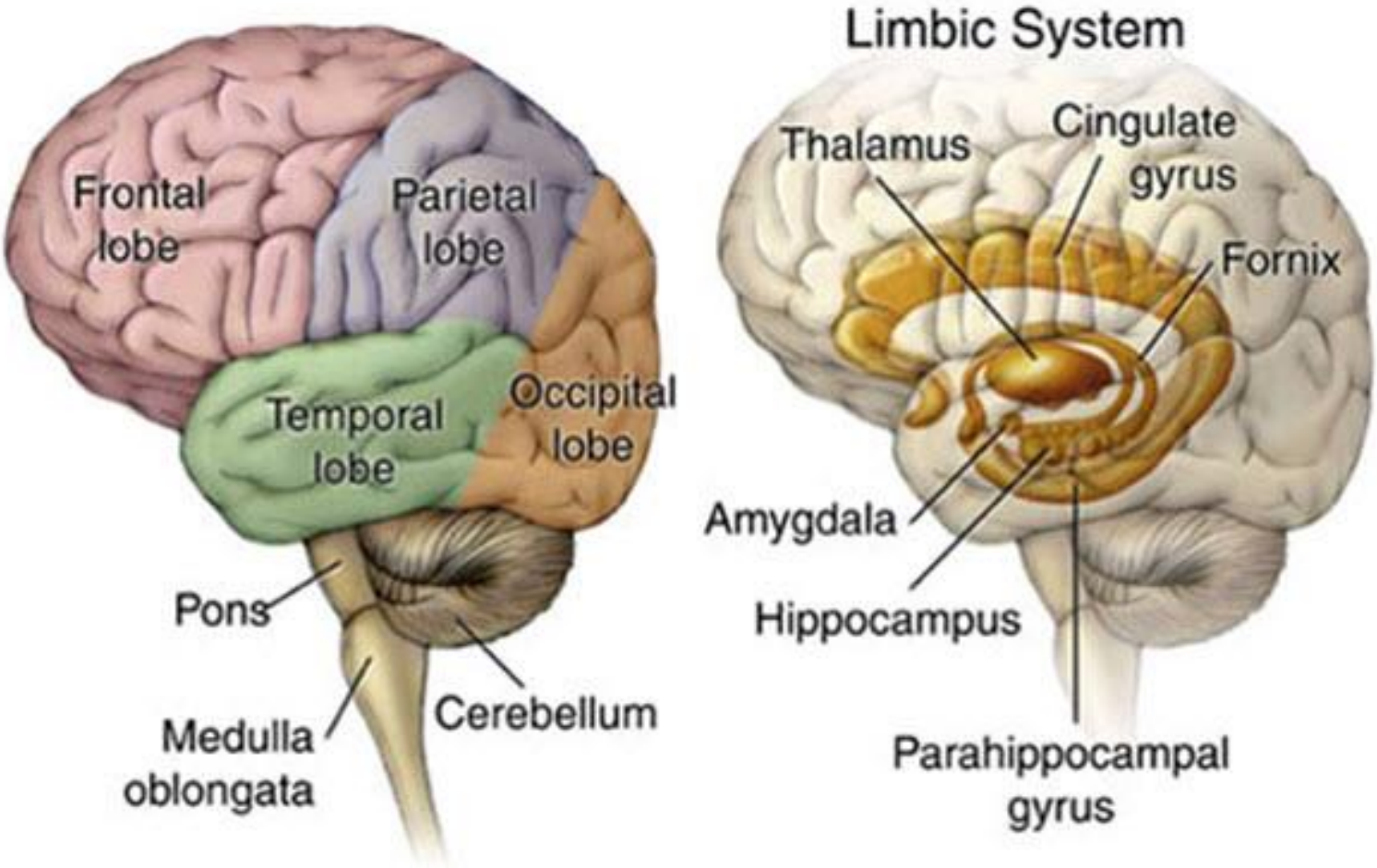
- Co-occurring **psychiatric illness** and a history of **trauma** increase the risk of addiction and of relapse.



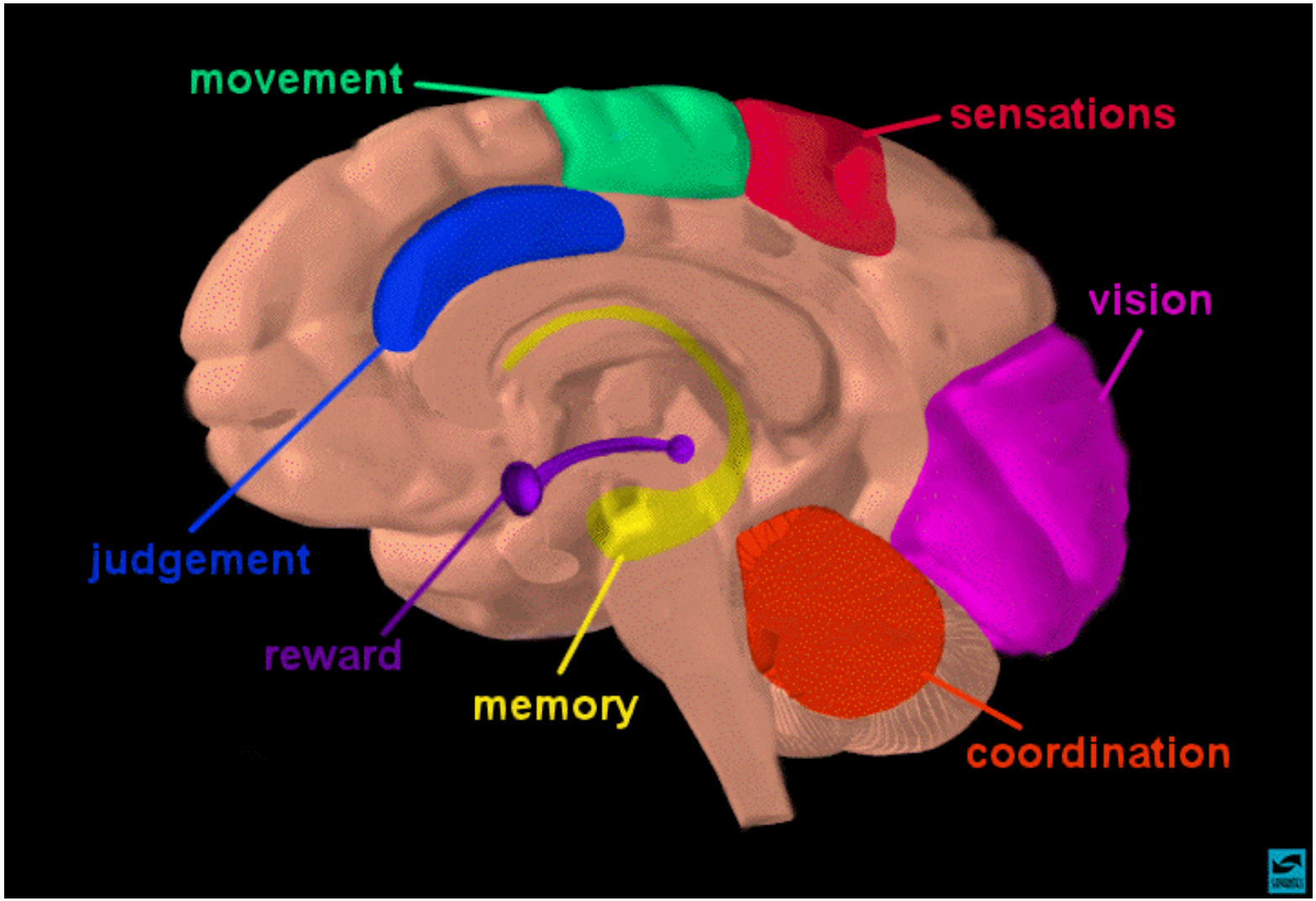
"C'mon, Sylvia ... where's your spirit of adventure?"

The Brain

The Human Brain – A Detailed Examination



Brain Reward Center



Mesolimbic Dopamine System (Median Forebrain Bundle)

NEURONS & NEUROTRANSMISSION

“An Irreproducible System”

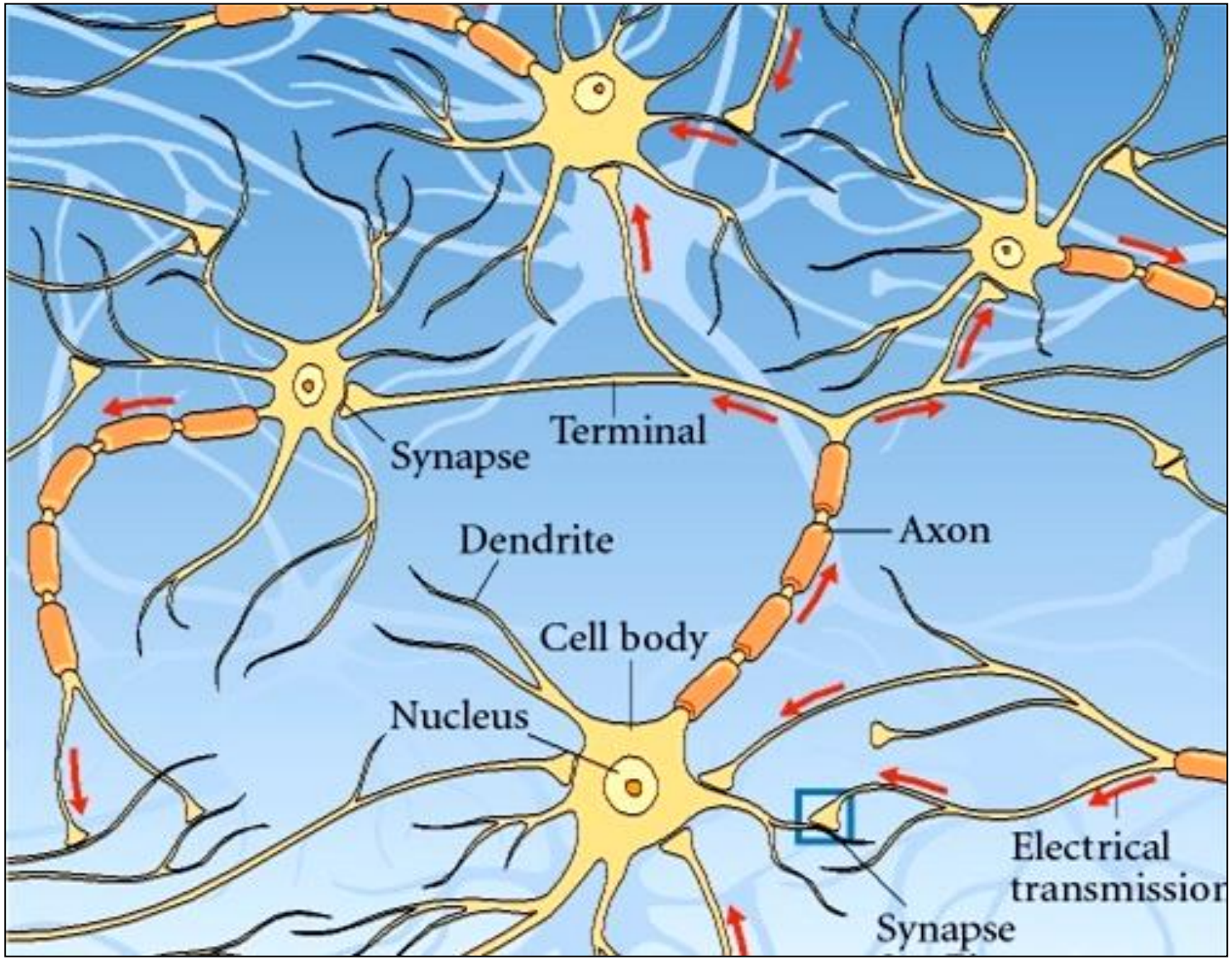
- A human may have 100 billion neurons, with an estimated 100 trillion (100,000,000,000,000) connections

- “*Neuron* and *nerve cell* are synonyms that refer to the major information-conveying cells in the nervous system.”

The Neuron: Its Four Parts

1. Dendrites: “receives signals from other nerve cells and relay them to the cell body”
   - Dendrites can vary from 2 or 3 up to 10,000 in a purkinje cell in the cerebellum, which can have as many as 150,000 connections
2. Cell body: Nucleus with genes of the cell
3. Axon: “carries the message from the cell body”
4. Terminal: “relay the message to the dendrites, cell body, or even terminals of the next cell”

Neurons (Nerve Cells)



Signal Conduction

- Neurons do not touch each other in conducting a signal from one to the other

- A “synapse, synaptic gap” or “synaptic cleft” exists between them

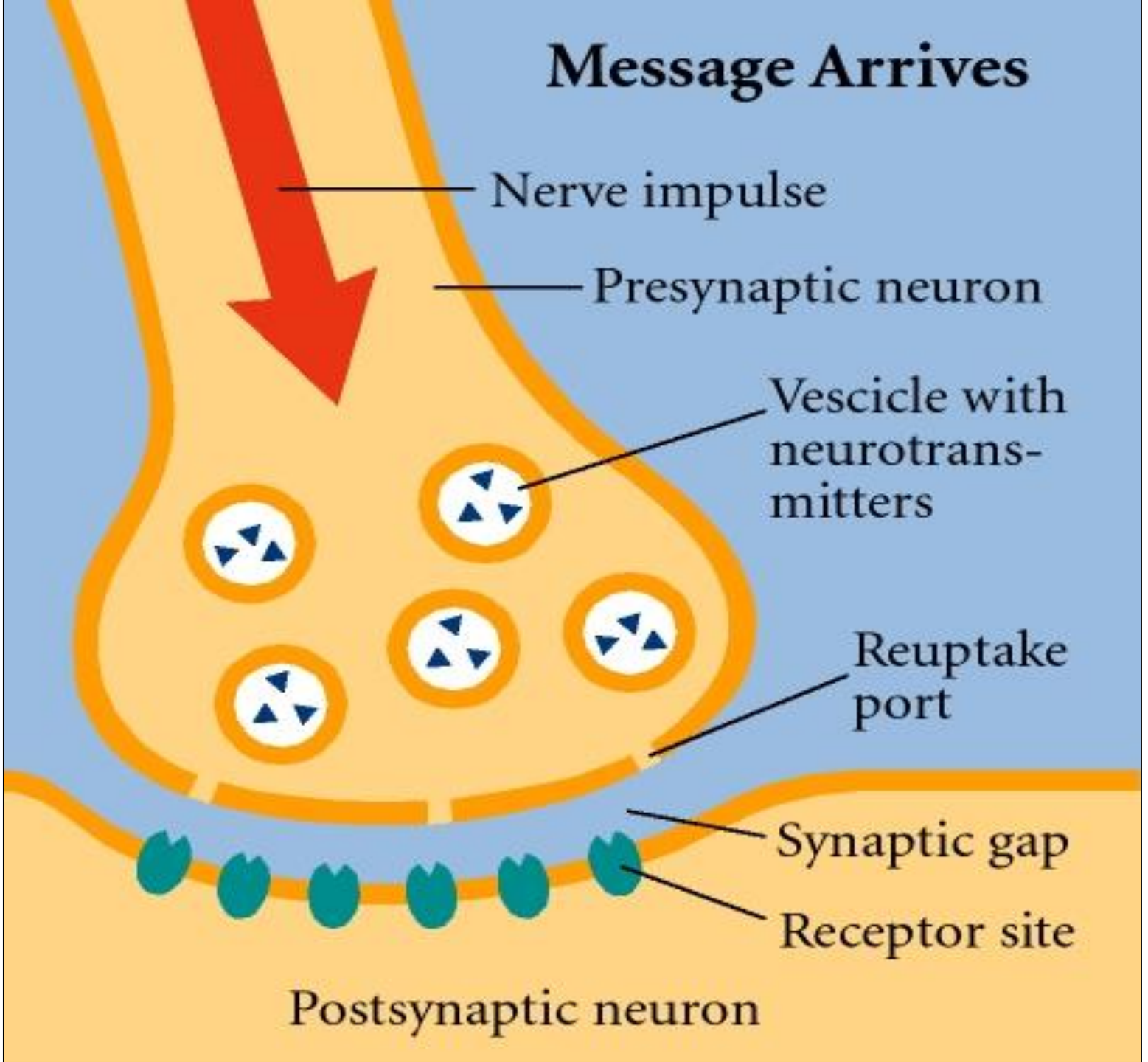
This gap is 15-50 nanometers (nm)
A nanometer is one billionth of a meter
A million synaptic gap widths added together
barely total an inch

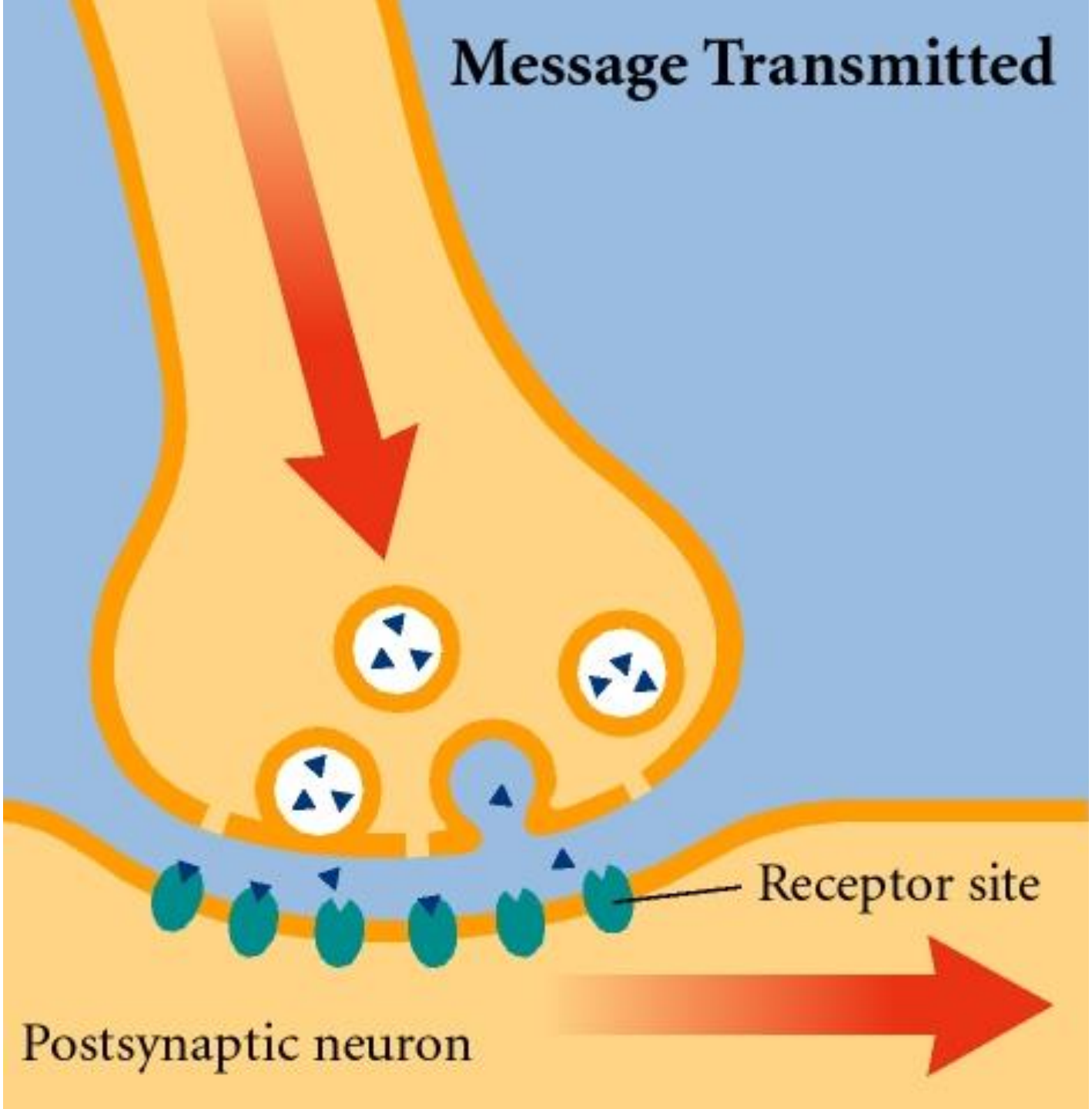
Signal Conduction

- Signals are transmitted electrically within the neuron
- But once the signal reaches the synapse, it stops, so a microscopic chemical called a neurotransmitter crosses the synapse
- Neurotransmitters are produced in the neuron, stored in sacs called “vesicles”

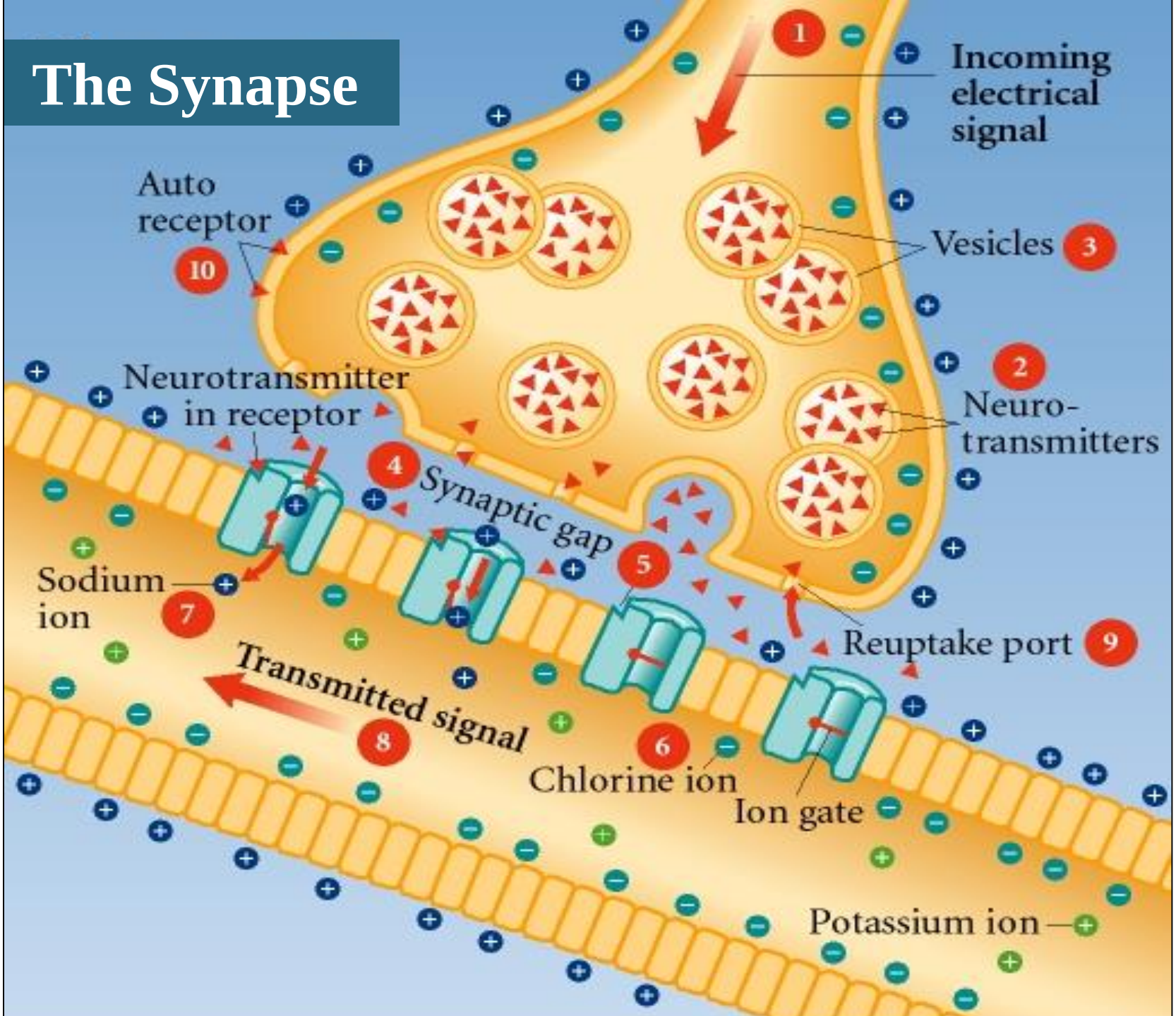
The Most common Neurtransmitters

- Acetylcholine
- Norepinephrine
- Epinephrine
- **Dopamine**
- Endorphin
- Enkephalin
- Serotonin
- GABA
- Substance “P”
- Anandamide
- Glycine
- Histamine
- Nitric oxide
- Glutamic acid
- Cortisone


Message Arrives
Nerve impulse
Presynaptic neuron
Vescicle with neurotrans-mitters
Reuptake port
Synaptic gap
Receptor site
Postsynaptic neuron


Message Transmitted
Receptor site
Postsynaptic neuron

The Synapse


1
Incoming electrical signal
Auto receptor
10
Vesicles
3
2
Neuro-transmitters
Neurotransmitter in receptor
4
Synaptic gap
5
Sodium ion
7
Reuptake port
9
Transmitted signal
8
6
Chlorine ion
Ion gate
Potassium ion

Two Types of Neurotransmitters

- “Excitatory” neurotransmitters: augment the potential for signal propagation in the post-synaptic neurons; they increase the likelihood of an electric signal
- “Inhibitory” neurotransmitters, prevent the propagation of the action potential; they decrease the likelihood of an electric signal
- The specificity of a particular neurotransmitter (whether it acts in an excitatory or inhibitory fashion) is normally an inherent property of the neurotransmitter itself.

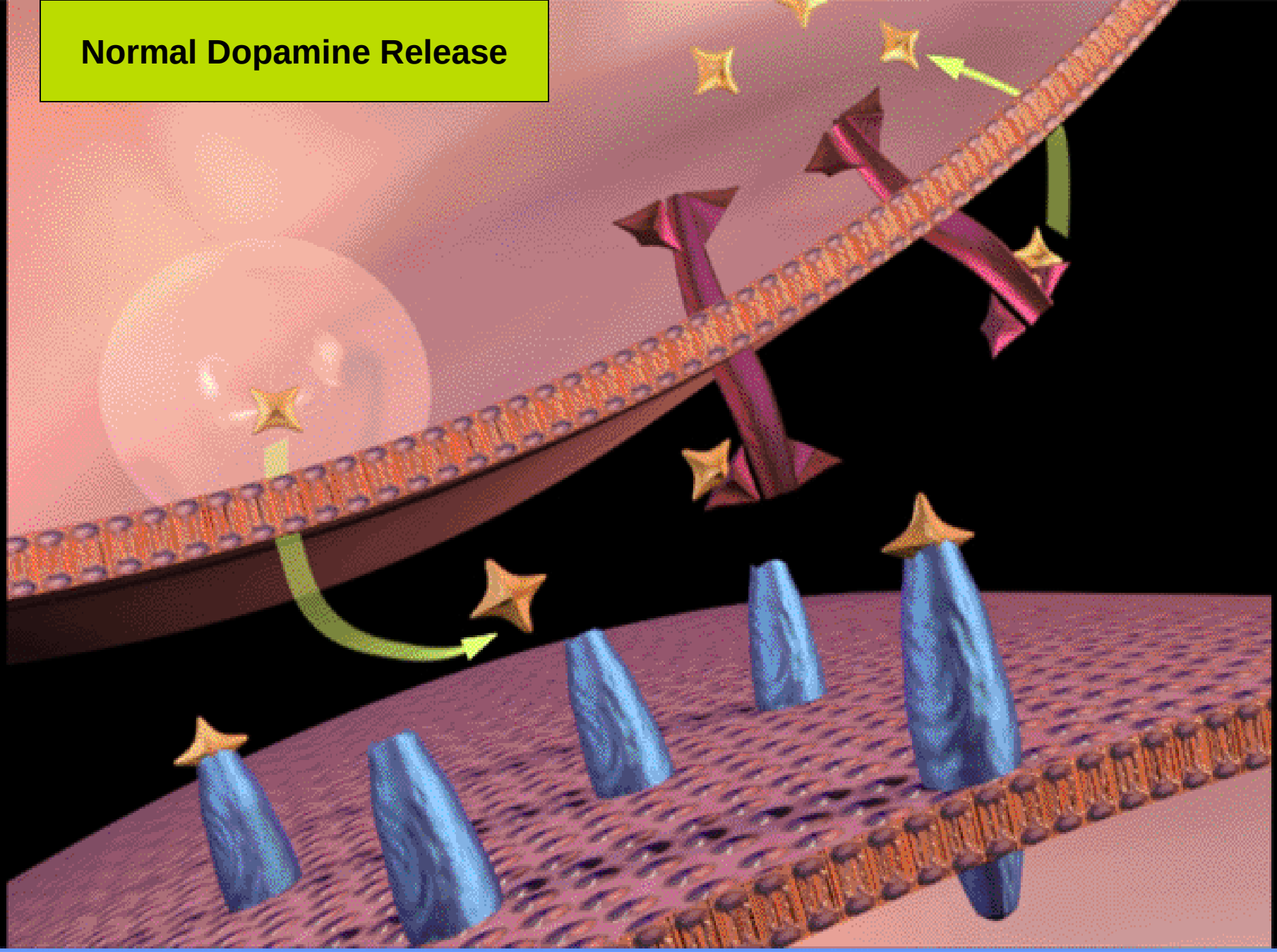
Dogs and alcohol: the tragic untold story

THE NEUROTRANSMITTERS ROLE IN ADDICTION

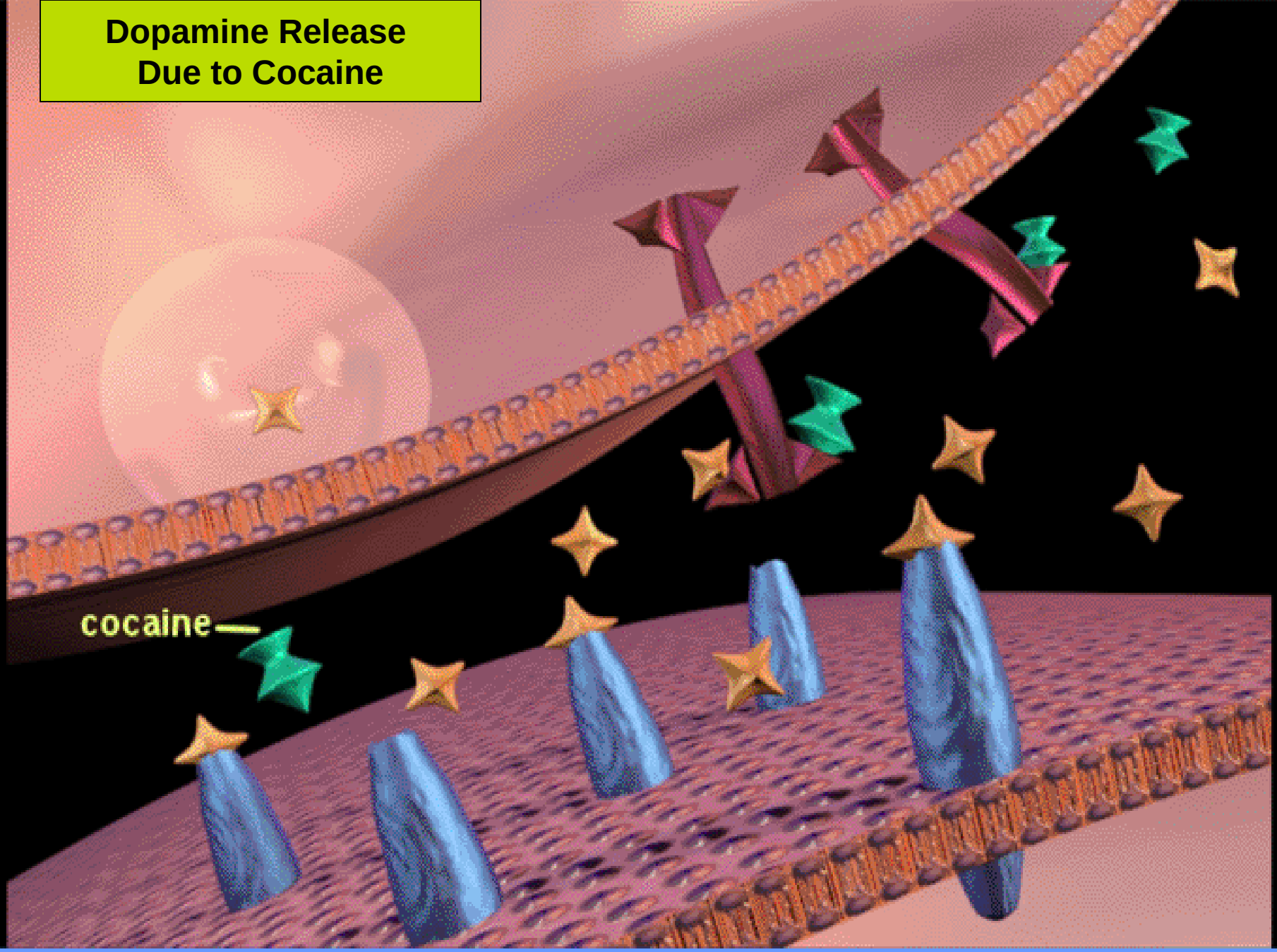
Addictive Drugs Are Associated With Specific Neurotransmitters

Drugs	Neurotransmitter System Action
Alcohol	Facilitates GABA receptor function Inhibits NMDA (Glutamate) receptor function
Marijuana	Agonist at CB_1 and CB_2 cannabinoid receptors
Cocaine	Indirect agonist of dopamine receptors by inhibiting dopamine transporters
Amphetamine	Indirect agonist of dopamine receptors by stimulating dopamine release
Opiates	Agonist at MU, delta and kappa receptors
Nicotine	Agonist at nicotinic acetylcholine receptors

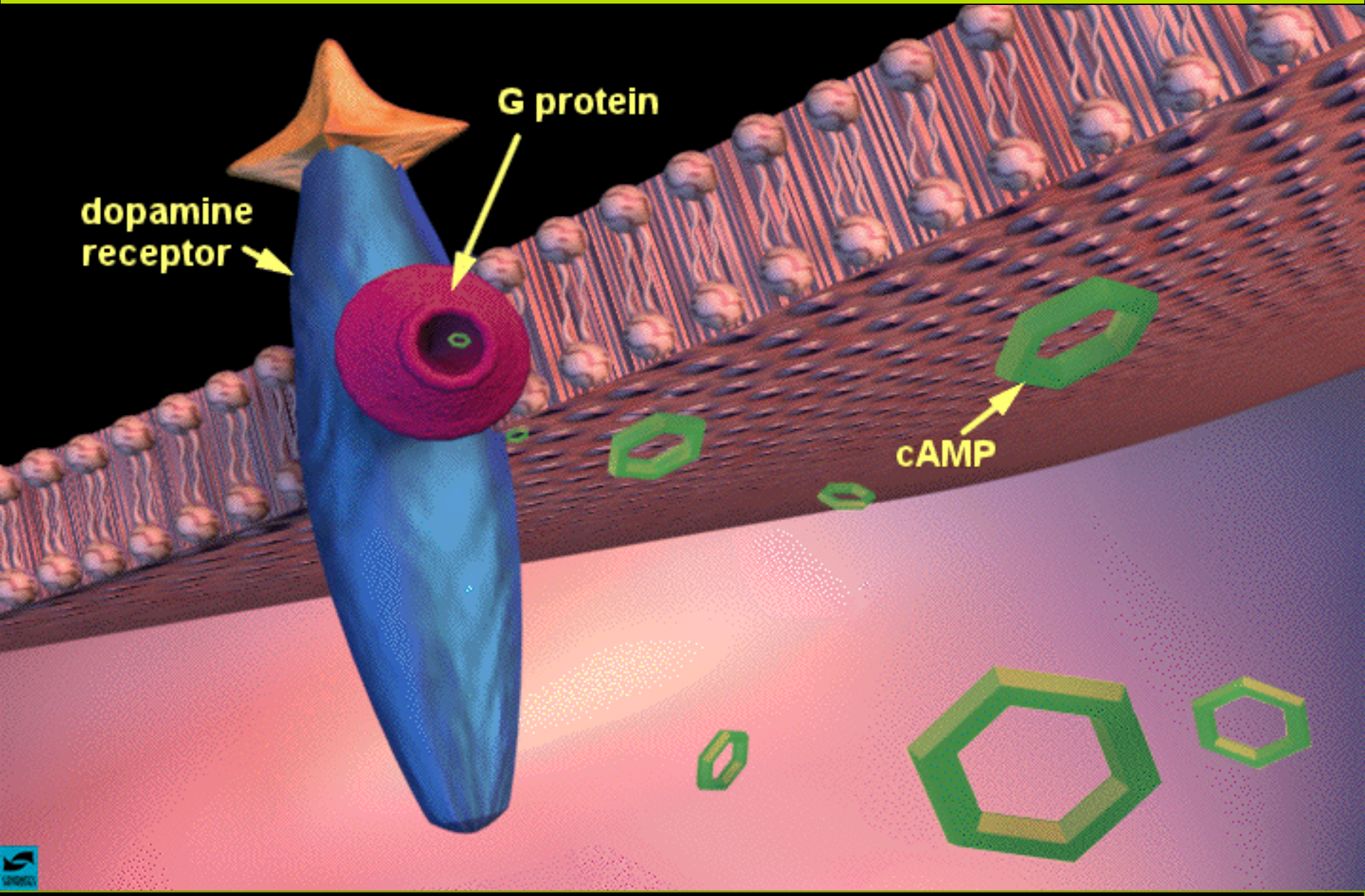
Normal Dopamine Release



Dopamine Release Due to Cocaine



Normal Receptor Function



Alcohol and Neurotransmitters

GABA

- Primary inhibitory neurotransmitter
- Decreases with chronic use

Glutamate:

- Primary excitatory neurotransmitter
- Increases with chronic use

Opioids:

- Alcohol stimulates endorphin release

Dopamine:

- Alcohol stimulates release, directly and via endorphins

Neuroadaptation (Neuroplasticity)

Repeated exposure

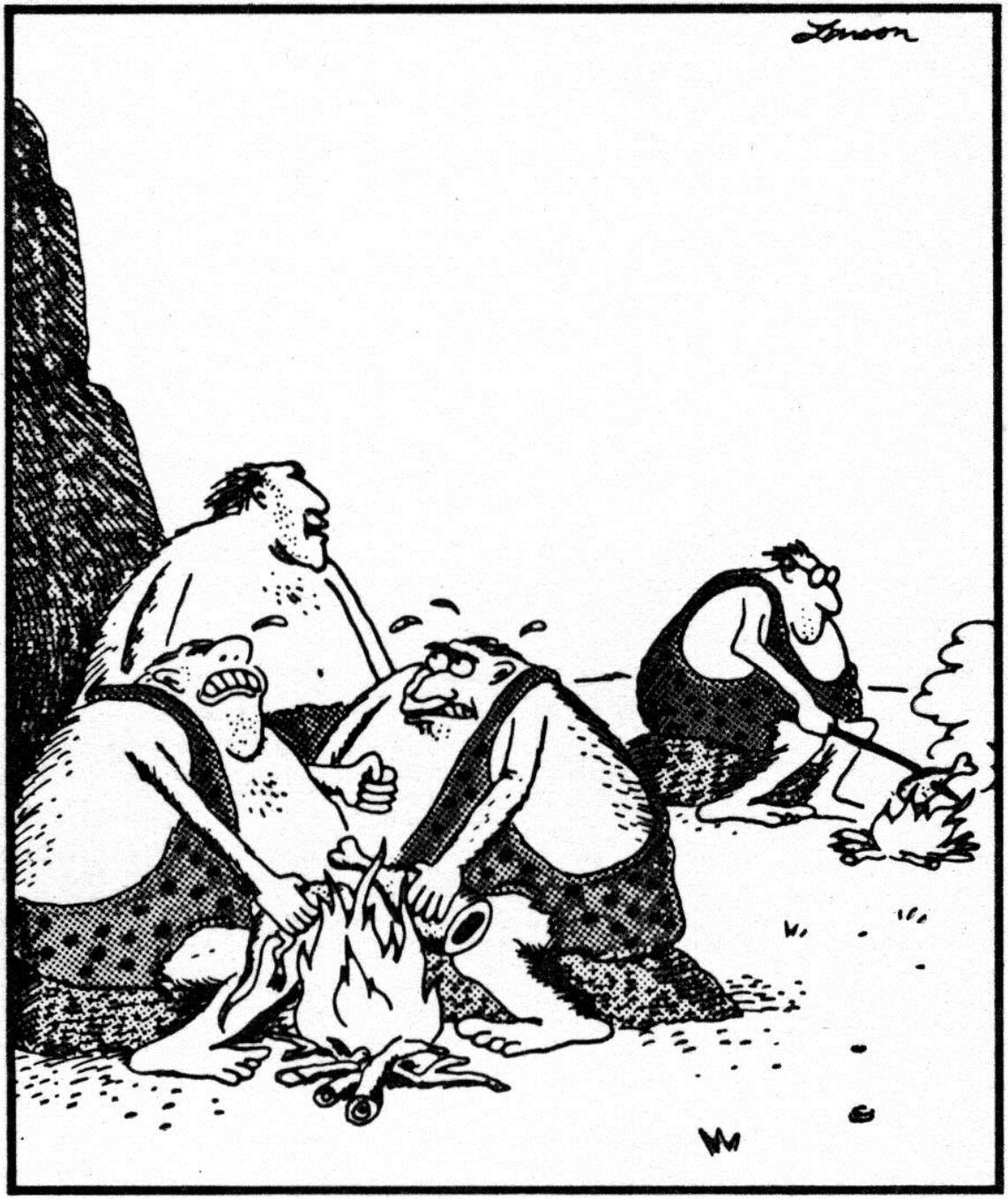
Changes in nuclear function

Altered transcription of target genes
(abnormal proteins or receptors)

Altered activity of the neuron
(neurotransmitter dysregulation)

Altered reward curcuitry

Altered behavior (Loss of control)



"Hey! Look what Zog do!"

ADDICTION: A BRAIN DISEASE

Addiction is a Disorder of…

- Incentive salience
- Reward deficit
- Stress surfeit
- Executive function

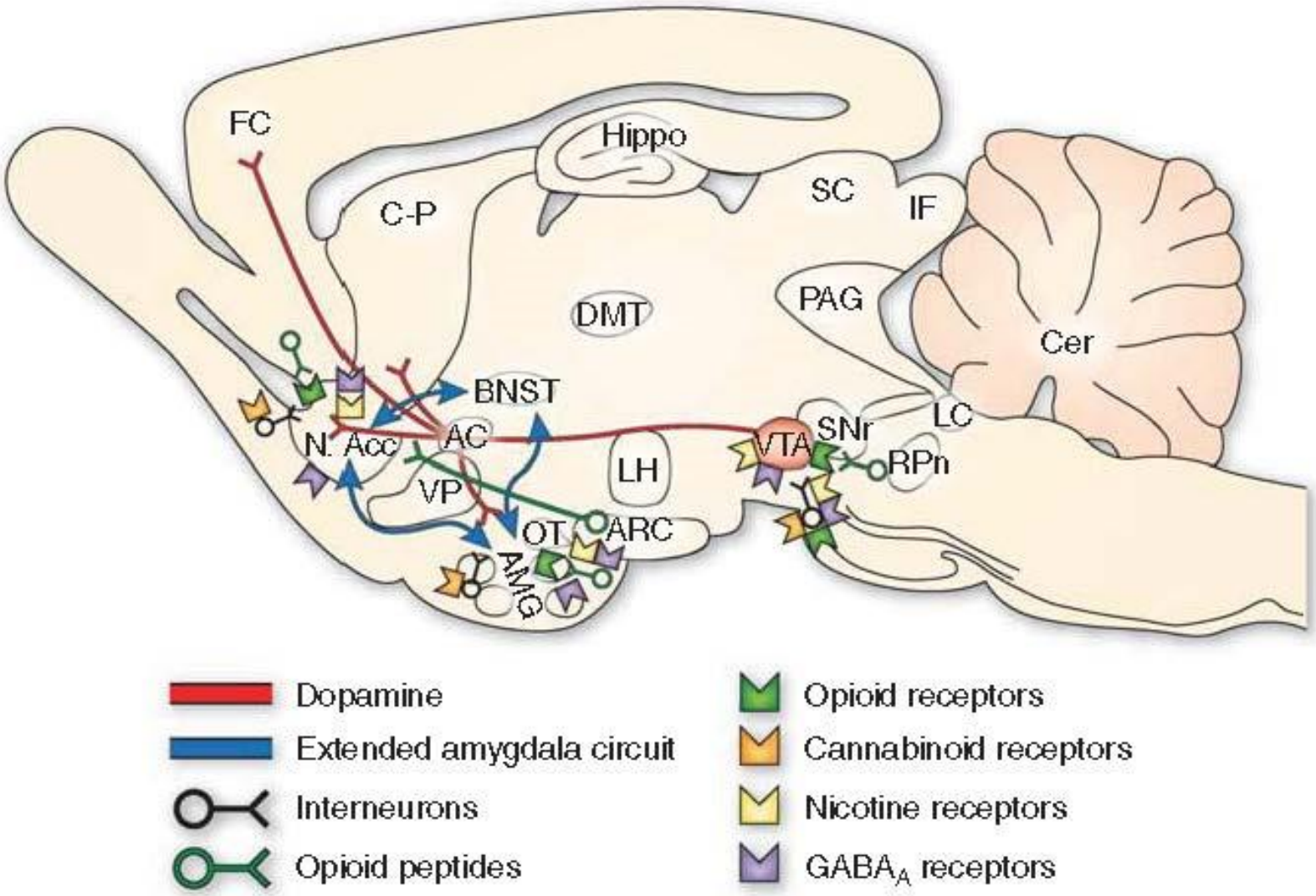
Addiction ≠ Casual Use

- Compulsion to seek and take the drug
- Loss of control in limiting intake
- Diminished recognition of significant problems
- Emergence of negative emotional state
- Craving
- Chronicity and relapse

Acute Intoxication: Primarily Reward Circuitry

- A Hedonic activity
- Positive reinforcement
- All drugs of abuse enhance dopamine release
- Mesolimbic dopamine system

Neurochemical Circuits in Drug Reward (Acute)



Drug	Action	Where
Cocaine/ Amphetamine	Release dopamine by direct action on dopamine terminals	Nucleus Accumbens Amygdala
Opioids	Activate opioid receptors	VTA, Nucleus Accumbens Amygdala
	Facilitate dopamine release	VTA, Nucleus Accumbens
Alcohol	Actives GABA receptors or GABA release	VTA, Nucleus Accumbens Amygdala
	Facilitates release of opioid peptides	VTA, Nucleus Accumbens Amygdala
	Facilitates release of dopamine	Nucleus Accumbens
Nicotine	Actives nicotine acetylcholine receptors	VTA, Nucleus Accumbens Amygdala
Cannabinoids	Actives cannabinoid CB_1 receptors	VTA, Nucleus Accumbens Amygdala
	Facilitates release of dopamine	Nucleus Accumbens

Establishment of the Addictive Cycle

- Positive Reinforcement from the drug diminished
- Negative Reinforcement from the drug increases
- Motivational withdrawal syndrome established
- Incentive salience narrows the individuals focus

The Addictive Cycle

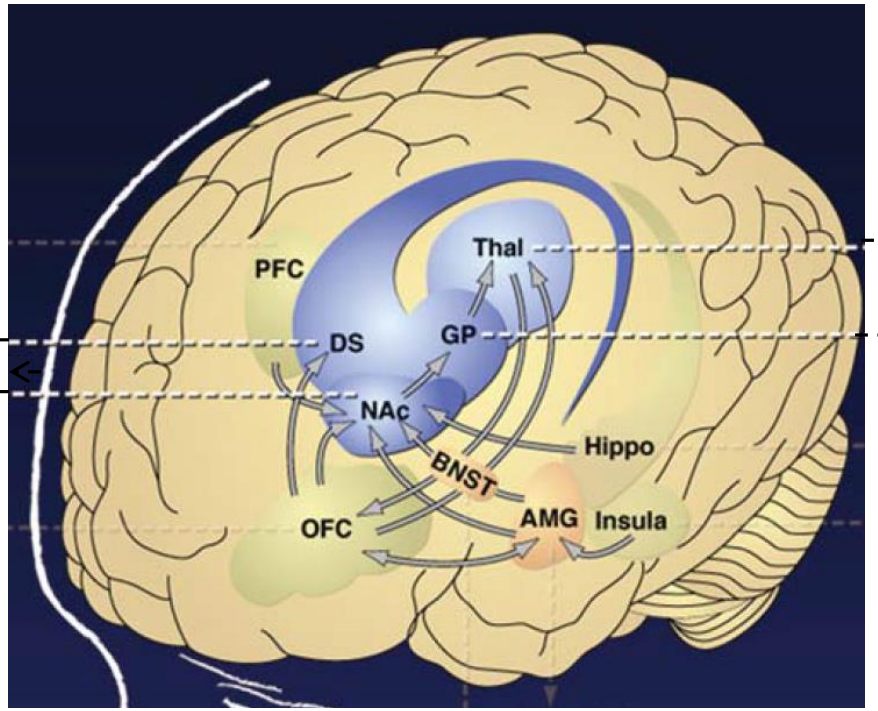
Three Stages

The transition to addiction from casual drug use involves the brain areas associated with these three stages

- Binge / Intoxication
- Withdrawal / Negative Affect
- Preoccupation / Anticipation (craving)

Neural Circuits of the Binge/Intoxication Stage

Koob GF. Volkow ND.
Neuropsychopharmacol Rev, 2010, 35:217-238.



Thalamus

Doral Striatum

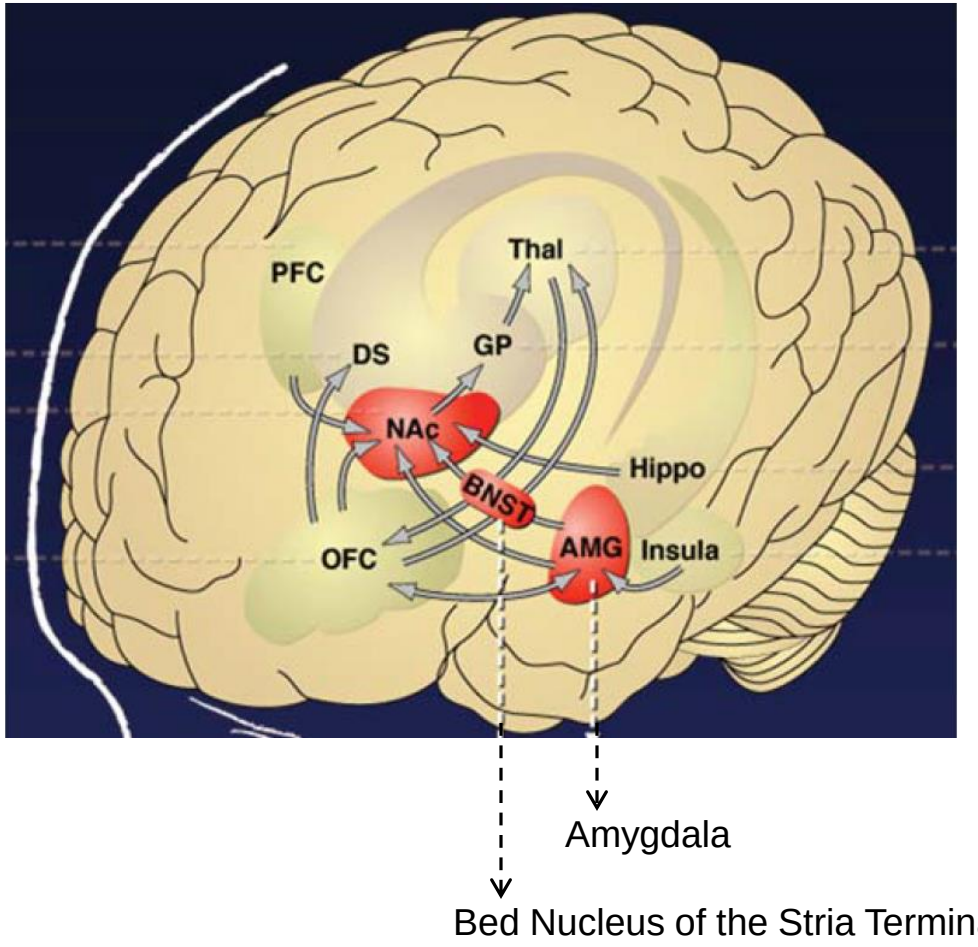
Globus Pallidus

Nucleus accumbens

Incentive Salience

- euphoria
- intoxication
- cue learning
- habits

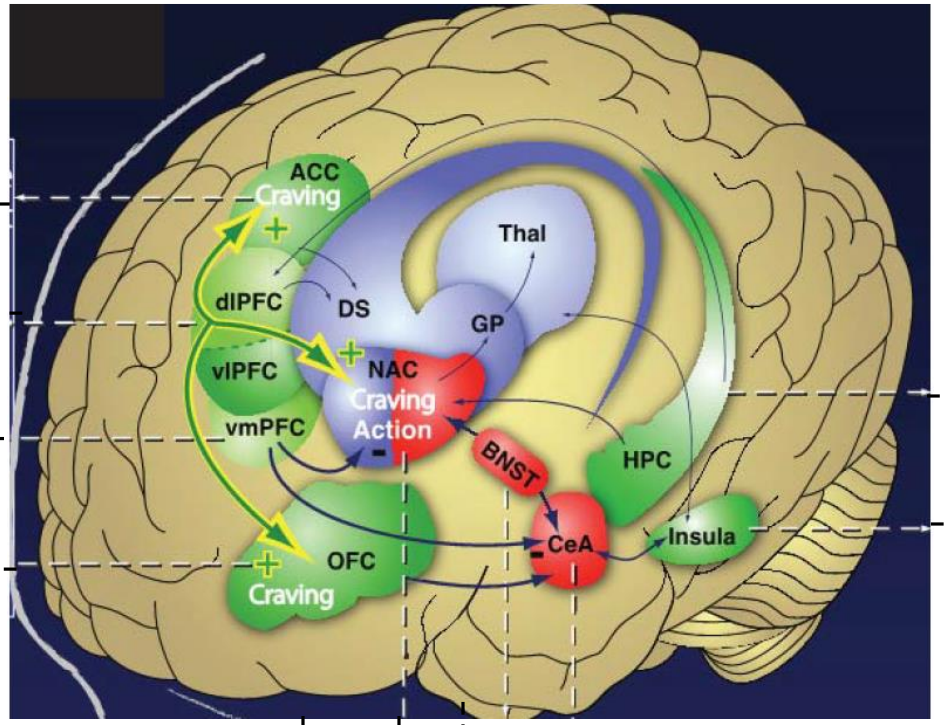
Neural Circuits of the Withdrawal/Negative Affect Stage



Negative Affect

- dysphoria
- anxiety
- irritability
- malaise

Neural Circuits of the Preoccupation/Anticipation "Craving" Stage



Stimulus value Action Value/cost

Anticipation/Availability Context

Action inhibition Emotion control

Outcome valuation Drub subjective value

External context

Internal context

Stress

Affective state

Incentive to action

Executive Dysfunction

- impulsivity
- compulsivity
- sleep disturbances
- impaired decision making

Summary

Addiction is a chronic brain disease and the manifestations that we find so puzzling are best understood by examining the neurobiological underpinnings. We can come to understand the behaviors associated with addiction by understanding the brain pathology.

Resources

- Neurocircuitry of Addiction
  Koob, Volkow: Neuropsychopharmacol Reviews (2010) 35, 217-238

- Dynamics of Neuronal Circuits in Addiction
  Koob Pharmacopsychiatry 2009; 42 (Suppl 1): S32

- Neuropathology of Substance Use Disorders
  Cadet, Bisagno, Milray Acta Neuropathol (2014) 127; 91-107