The Neurobiology of Substance Use Disorders and Medication Assisted Treatment

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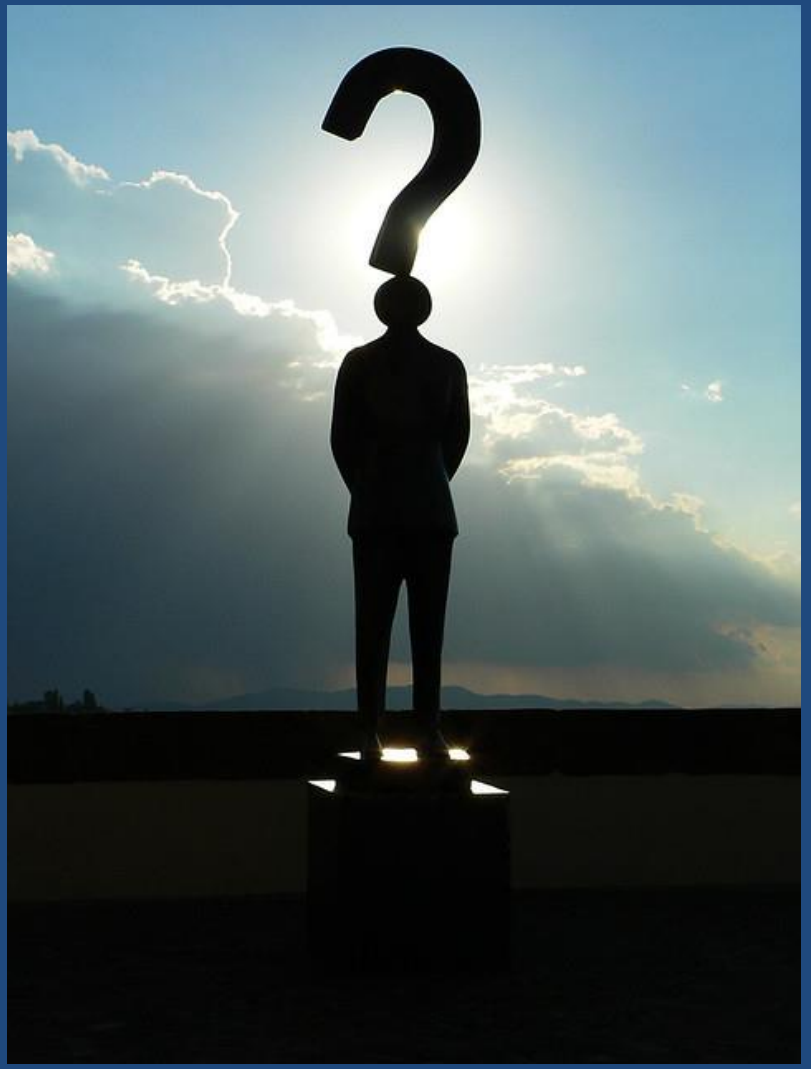
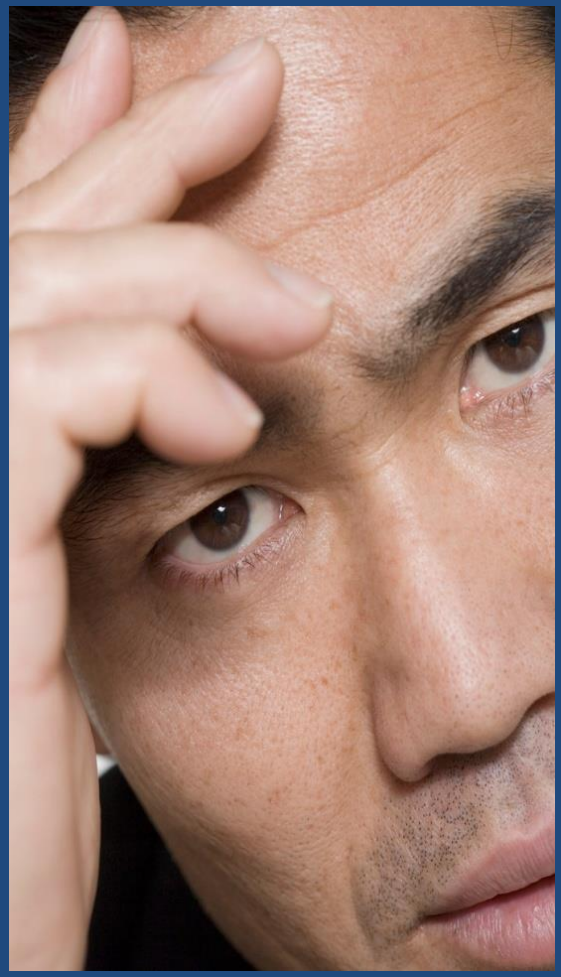
Question

Why do people start using or trying drugs?



Question

Why do they, over time, continue to use drugs?



Drugs Work!

- Cocaine/crack/meth/ice – improves confidence, euphoric mood
- Opiates – reduces both physical and emotional pain
- Tranquilizers – calms you down
- Marijuana – escape through focused attention
- PCP/Special K – anesthesia, dissociation
- Alcohol – anesthesia, calms, confidence

What are the causes?

- Lacking moral principles?
- Lacking will power?
- Poor choices?

Neuroscience Supports Substance Use Disorder = Brain Disease

What's all the fuss about Neuroscience?

- ***Neuroscience*** – definition from dictionary.com - the field of study encompassing the various scientific disciplines dealing with the structure, development, function, chemistry, pharmacology, and pathology of the nervous system that effect the brain.

- Every thought, sensation, emotion, physical movement is accounted for in terms of brain structures and chemistry.
- In other words… nothing happens in human behavior except by the mechanisms of the brain.

Substance Use Disorder

- Illness of the brain.
- Chronic condition that requires life-long management.
- Compared to:
  - Type 2 Diabetes, Chronic hypertensive disease, Asthma, Obesity
  - All have a complex of physiological and behavioral health components
- No one treatment episode will resolve illness.
- Course of dependency is multiple episodes of treatment, recovery activities, relapse periods.

https://newsinhealth.nih.gov/2015/10/biology-addiction

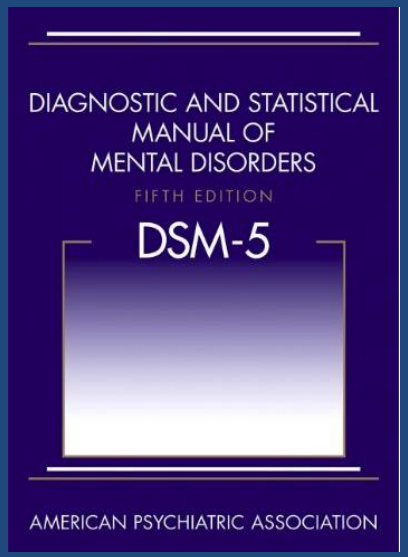
DSM 5 Substance Use Disorder

DSM IV Addiction Diagnosis definition was uncertain and promoted stigma

- 10 Classes of drugs plus gambling
- Impairments of health, disability and failure to meet responsibilities
- Criteria includes craving
- Severity is mild, moderate or severe

DSM 5 – 10 Classes of Drugs

- Alcohol
- Caffeine
- Cannabis
- Hallucinogens
- Inhalants
- Opioids
- Sedatives
- Stimulants
- Tobacco
- Other Substances



Abuse vs. Substance Use Disorder

Carlton Erickson, Ph.D. University of Texas 2009

- Abuse is a problem caused by bad choices, self-anesthetization, celebration, or just wanting to get high
  - Reduced through treatment such as education, positive reinforcement of alternate behaviors, coercion, environmental change, maturation, pressure to stop, life events

- Substance Use Disorder is a brain disease caused by genetic vulnerability, drug use, and environmental influence
  - Reduced through "treatment" to positively affect abnormal brain function to reduce need for drug – Evidence Based Practices

Substance Use Disorder is a complex disease and quitting takes more than a strong will.

Substance Use Disorder is…

- Chronic, relapsing brain disease
- Use and abuse continue regardless of harmful consequences

Therefore…

Understanding how the brain functions during and after drug use, encourages practitioners to use appropriate strategies according to the stage of recovery and consequently impact on program retention.

Three key components in dependency…

- Drug use or exposure to a drug
- Genetic influence or vulnerability
- Environmental influences

Drug Exposure

Who Becomes Dependent?

Estimated lifetime prevalence of risk…

- Nicotine – 32%
- Heroin - 23%
- Crack - 20%
- Cocaine - 17%
- Alcohol – 15%
- Stimulants other than cocaine – 11%
- Cannabis – 9%
- Sedatives – 9%
- Analgesic opioids – 9%
- Psychedelics – 5%
- Inhalants – 4%

US Epidemiological Estimates, 1992-98
Anthony et al,. 1994
Chen & Anthony, 2004
Hughes et al,. 2006

Genetic Vulnerability for Dependence

- Abnormal genes
  - Problems in the pleasure pathway
  - Impaired control over drug use
- Addicting drugs seem to “match” the need in the chemical system that is not normal
- Onset time is variable
- Mild to severe range

Environmental Factors

- Utah Addiction Center at the University of Utah, Dr. Kelly Lundberg, 2012

- Community Domain
- Peer Domain
- Family Domain
- School/Work Domain

Rhesus Monkey Experiment

- Isolated
  - Low dopamine
  - Stressed
  - Subordinate
  - Preferred cocaine

- Grouped
  - High dopamine
  - Non-Stressed
  - Did not prefer cocaine

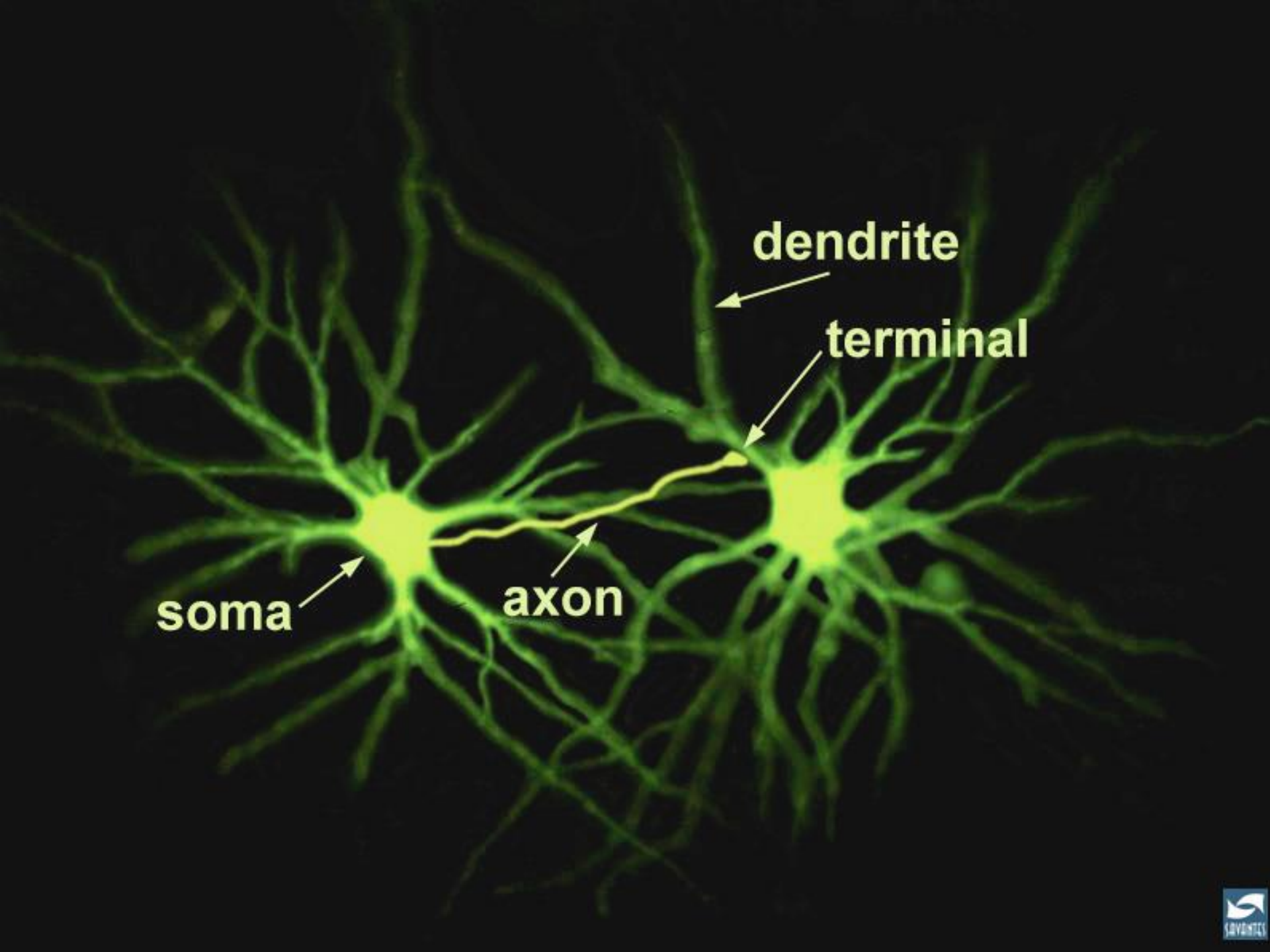
Pandemics

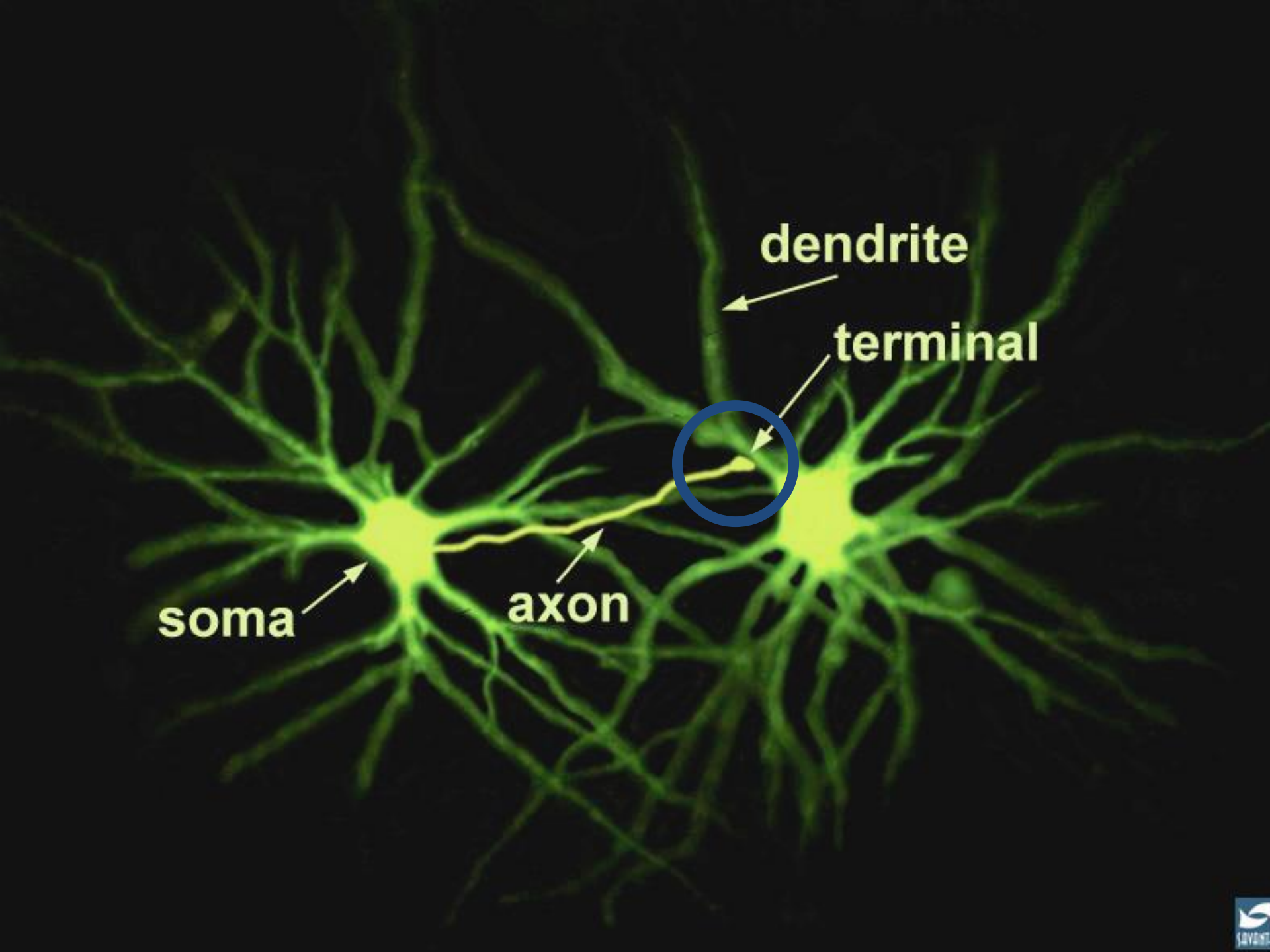
- Cause physical isolation and distancing
- Isolation causes deceases in dopamine
- People tend to become more subordinate and lose feelings of control and empowerment

The Brain

The Players of the Brain

- Neurons - the cells of the brain
  - 100 billion
  - Dendrites, Axons, Cell body with Nucleus
- Neurotransmitters - chemicals that communicate information throughout our brain and body
  - 50+
- Synapse
  - The space between the axon terminal and the receptor dendrite where neurotransmitters flow…
  - 10,000 per neuron


dendrite
terminal
soma
axon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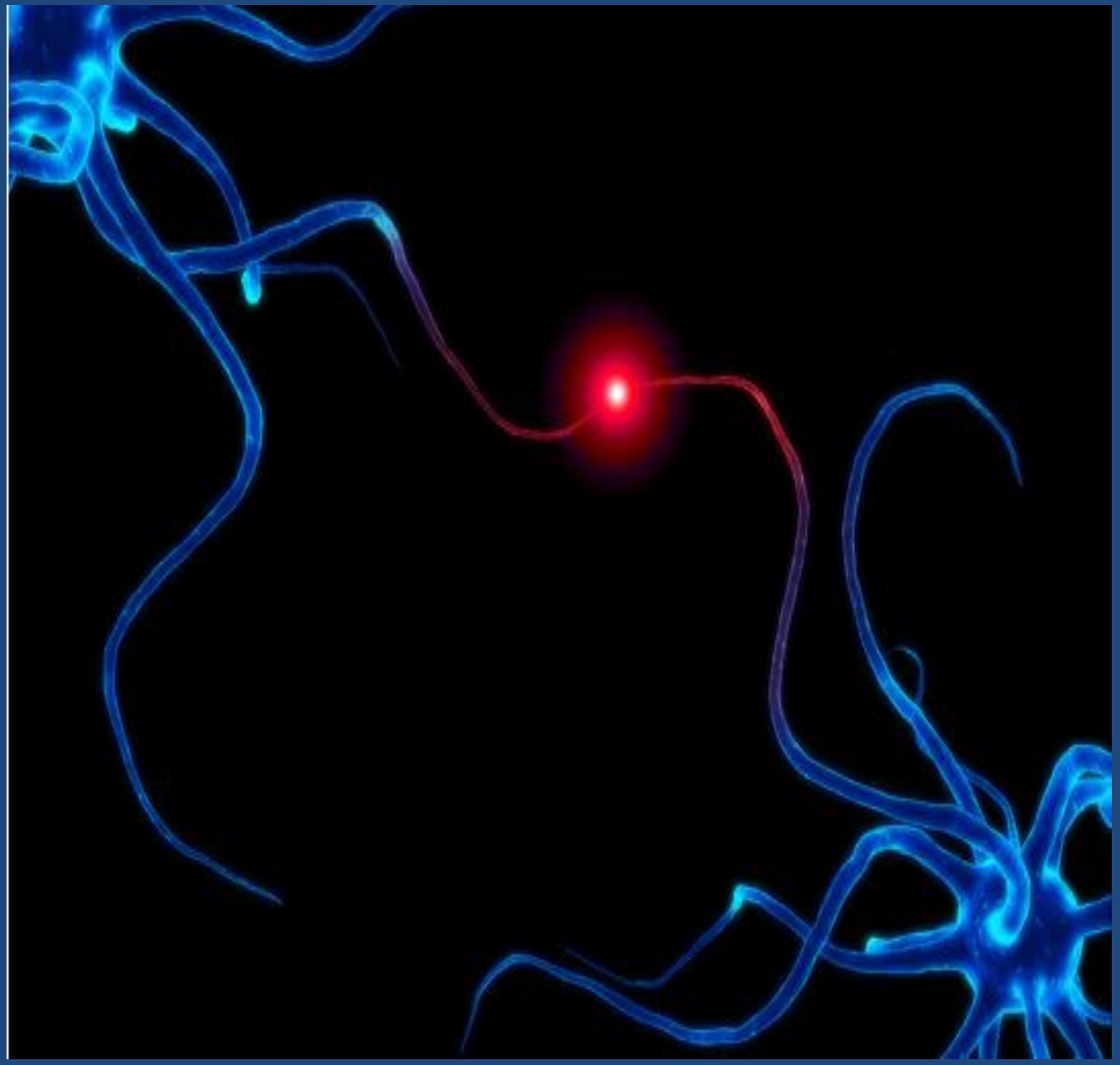


Behavior… (including substance use disorder) is related to…

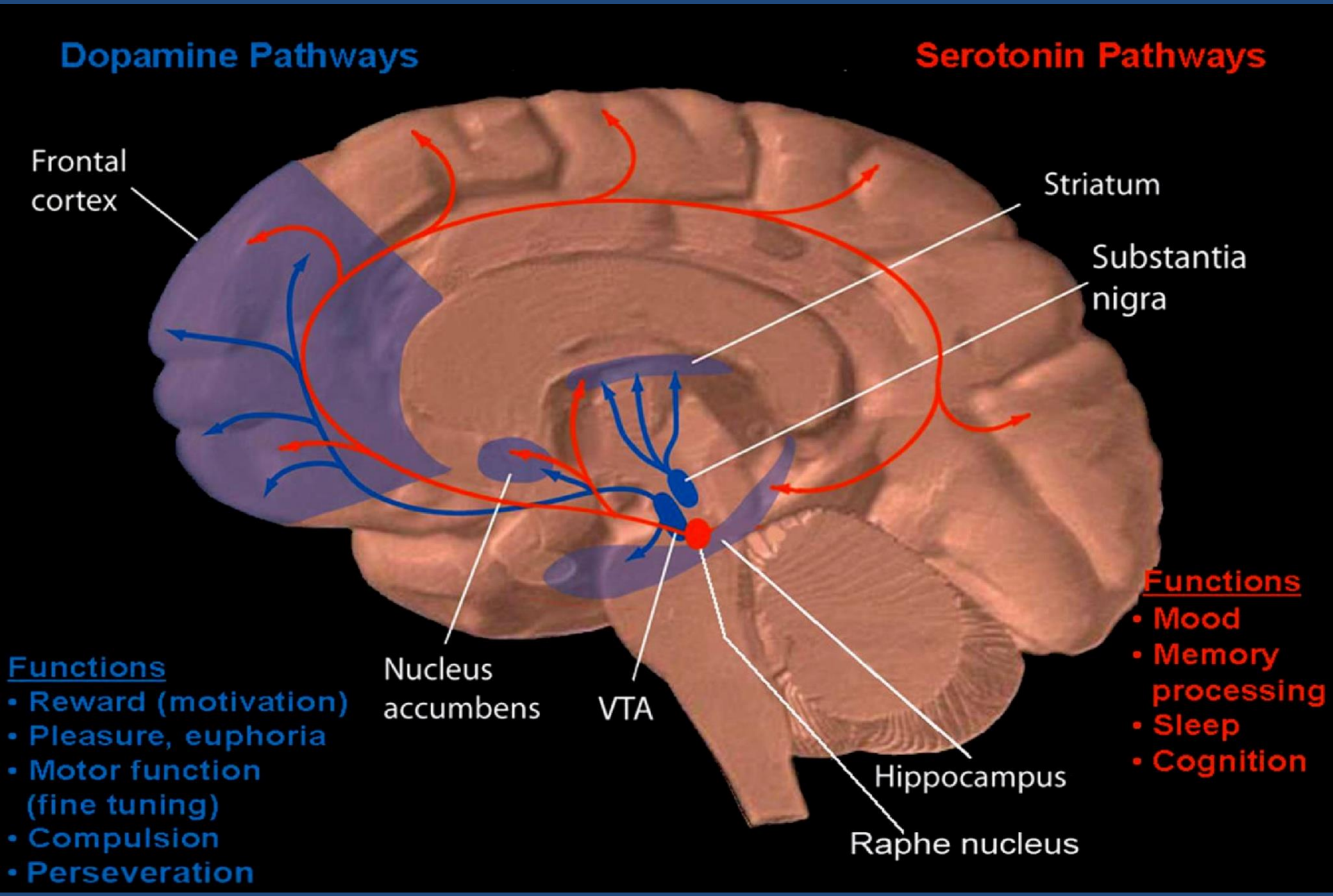
- Characteristics of brain regions
- The functions of neurons, including their connectivity into pathways or circuits
- The neurochemistry that exists between neurons that allows them to interact
- External stimuli

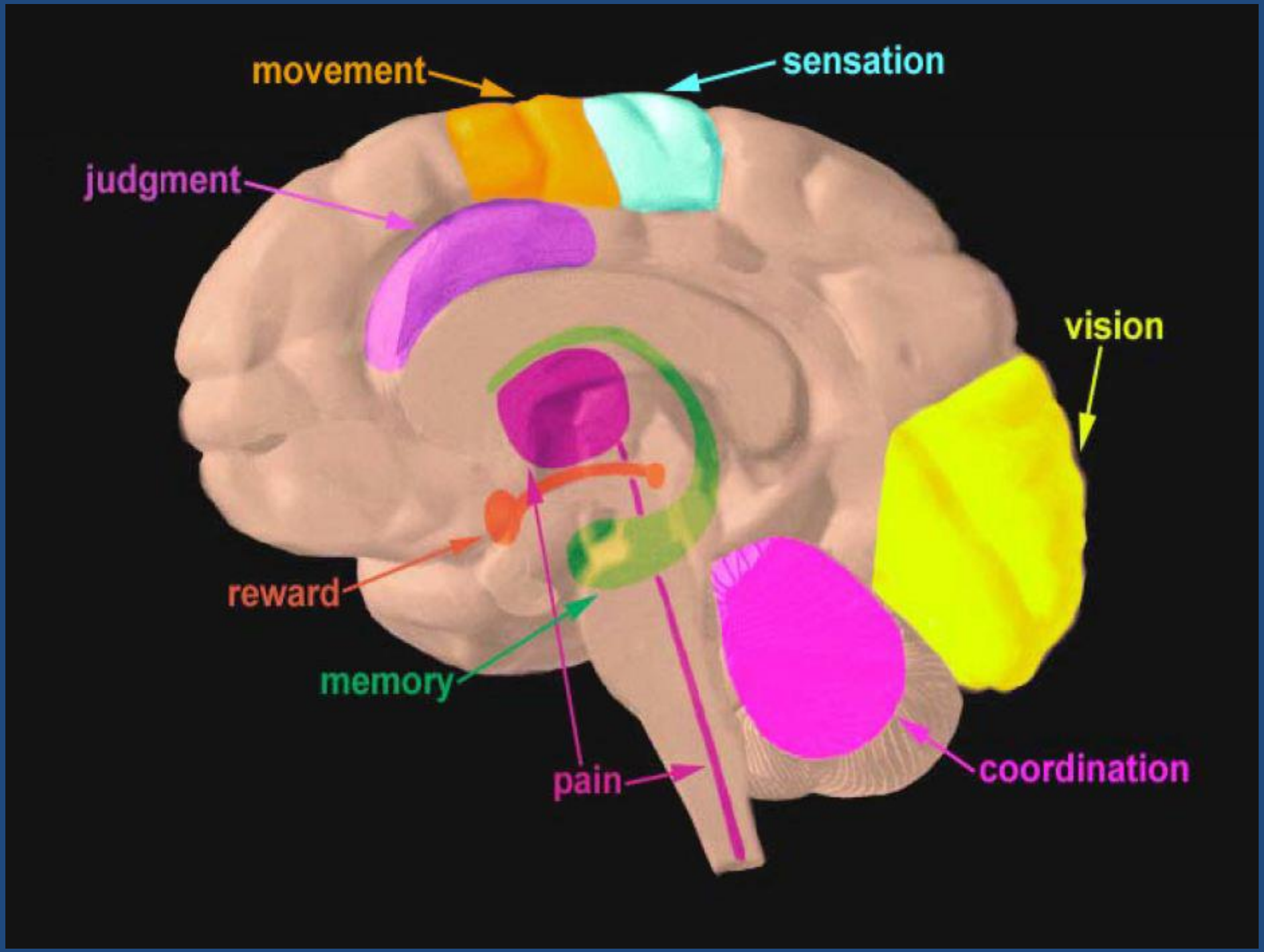
Key parts of the brain – Reward Centers

- Pre-frontal Cortex
  - Voluntary control of skeletal muscle
  - Personality
  - Higher intellectual processes (prefrontal cortex takes up the majority of the frontal lobe – executive suite)
    - Concentration, planning, decision making
  - "On second thought… "
  - Matures last (ages 25-26 for full maturity)
  - Modulated by Dopamine…

Why are adolescents more prone to chemical dependency?

- Frontal cortex is not developed
- Decisions are made in the amygdala
- Amygdala controls
  - Emotions
  - Motivation
  - Memory and fear


Dopamine Pathways
Serotonin Pathways
Frontal cortex
Striatum
Substantia nigra
Nucleus accumbens
VTA
Hippocampus
Raphe nucleus
Functions
• Reward (motivation)
• Pleasure, euphoria
• Motor function (fine tuning)
• Compulsion
• Perseveration
Functions
• Mood
• Memory processing
• Sleep
• Cognition


movement
sensation
judgment
vision
reward
memory
pain
coordination

Neurotransmitters

NEUROHORMONES

Glycine

ATP

GABA

Serotonin

Dopamine

TRH

Glutamate

GTP

Histamine

Norepinephrine

Substance P

Acetylcholine

Neurotransmitters

NEUROHORMONES

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Glutamate

GTP

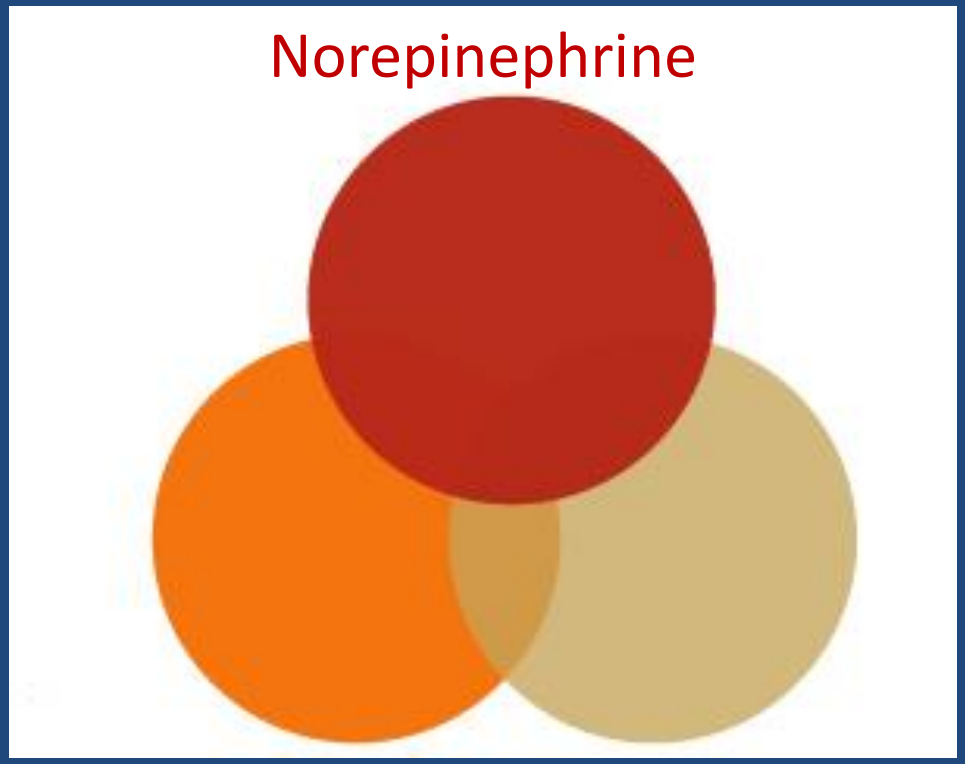
Histamine

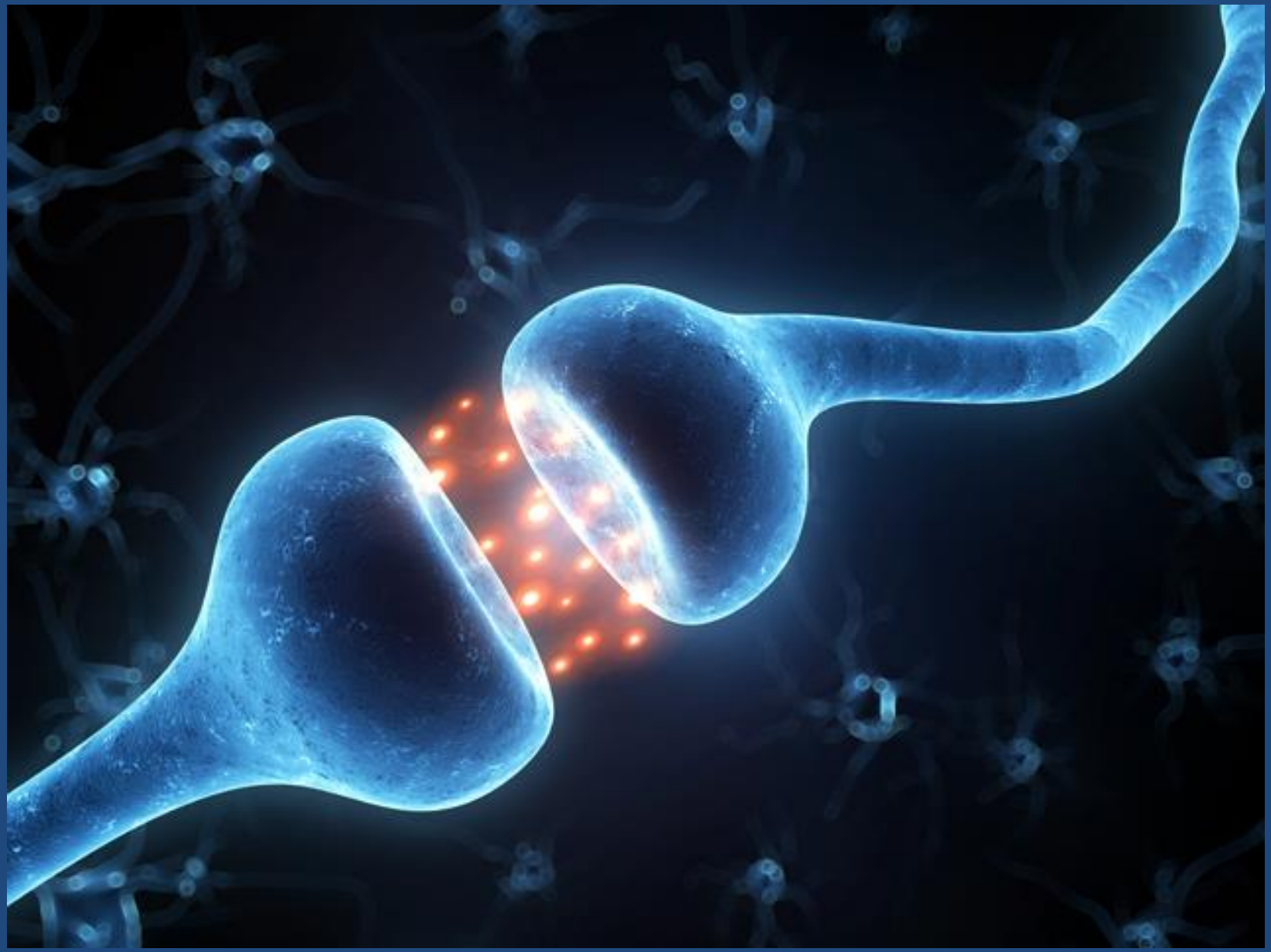
Norepinephrine

Substance P

Acetylcholine

The Monoamines

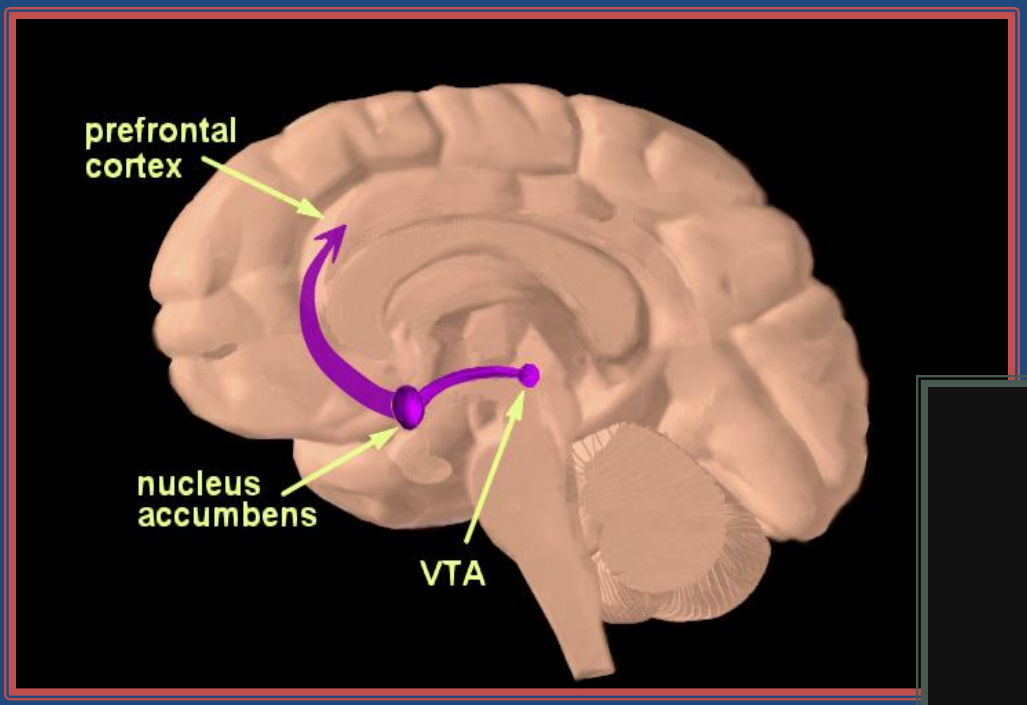




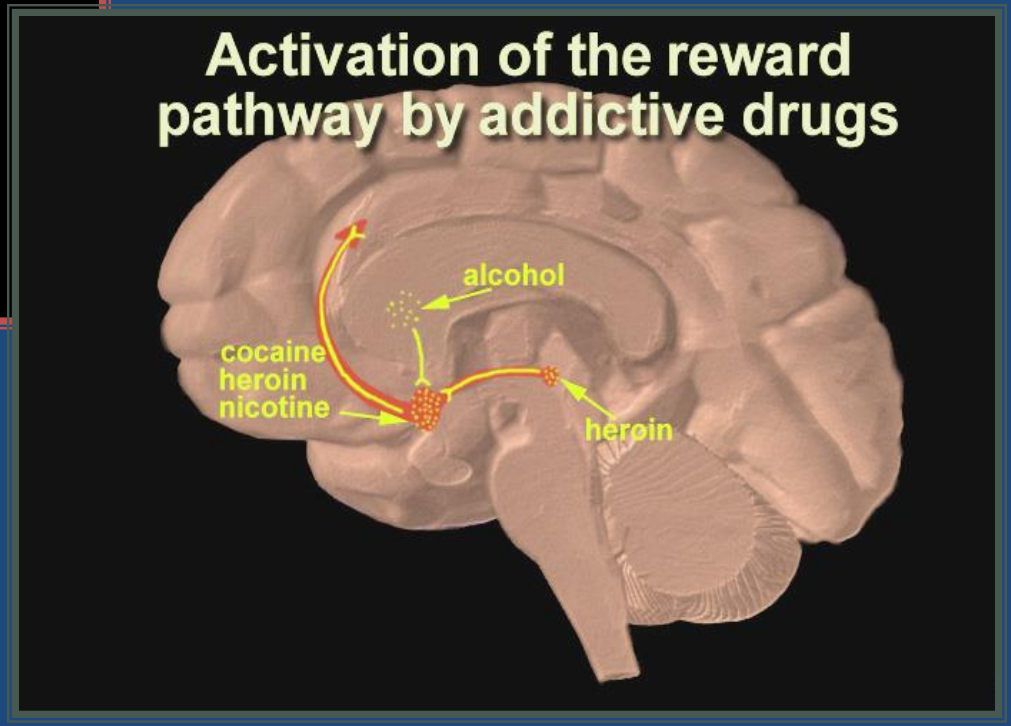
The monoamines control our psychological and substance use disorder destiny.

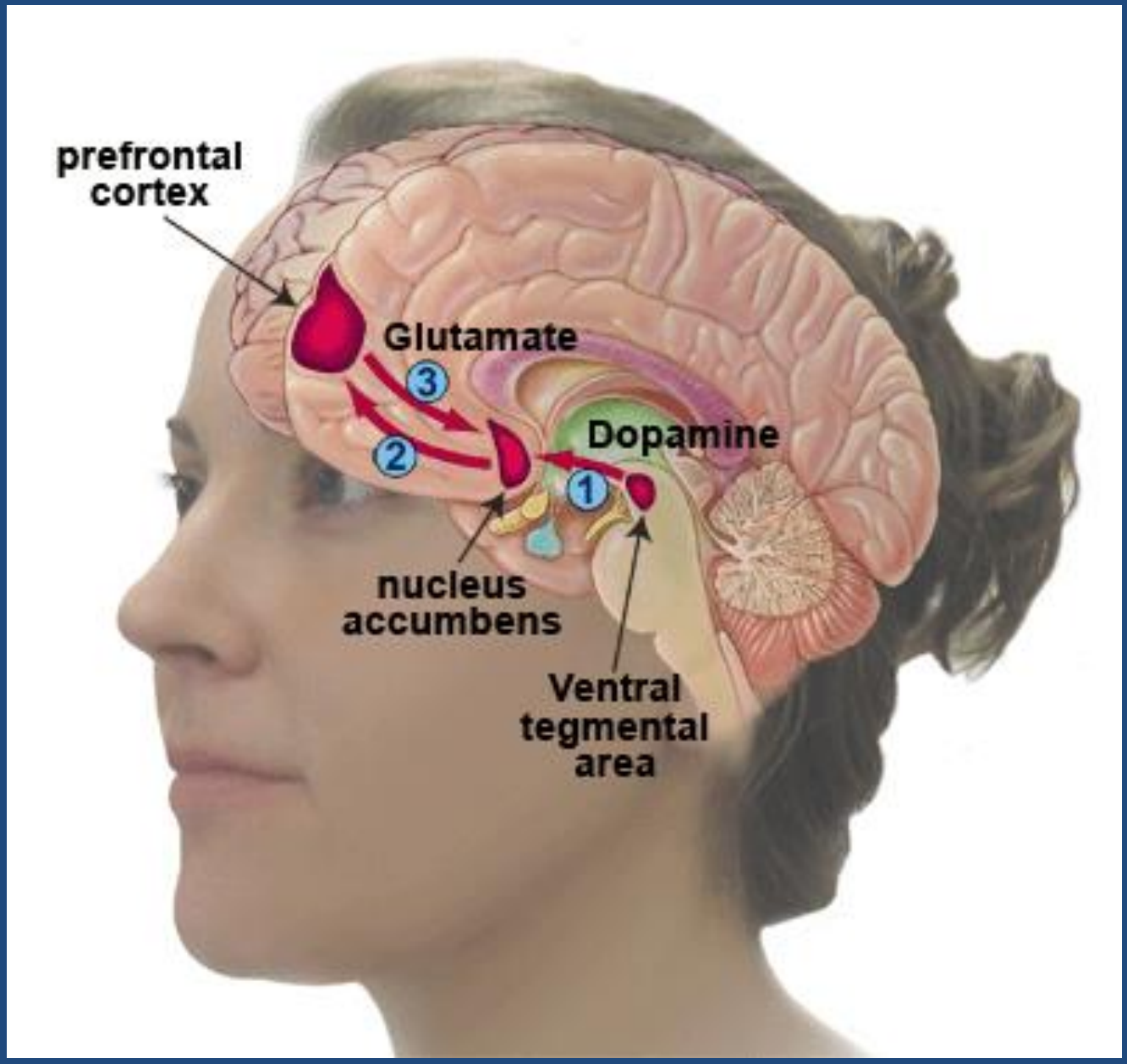
How do addictive substances affect the reward pathway?

Pathway for Understanding Chemical Dependence
Effects of Drugs on the Brain & Behavior



Reward Pathway




prefrontal cortex
Glutamate
3
2
Dopamine
1
nucleus accumbens
Ventral tegmental area

DOPAMINE AND GLUTAMATE VIDEO

Drugs Cause Chemical Disruption in the Brain

- Imitate the brain's chemistry

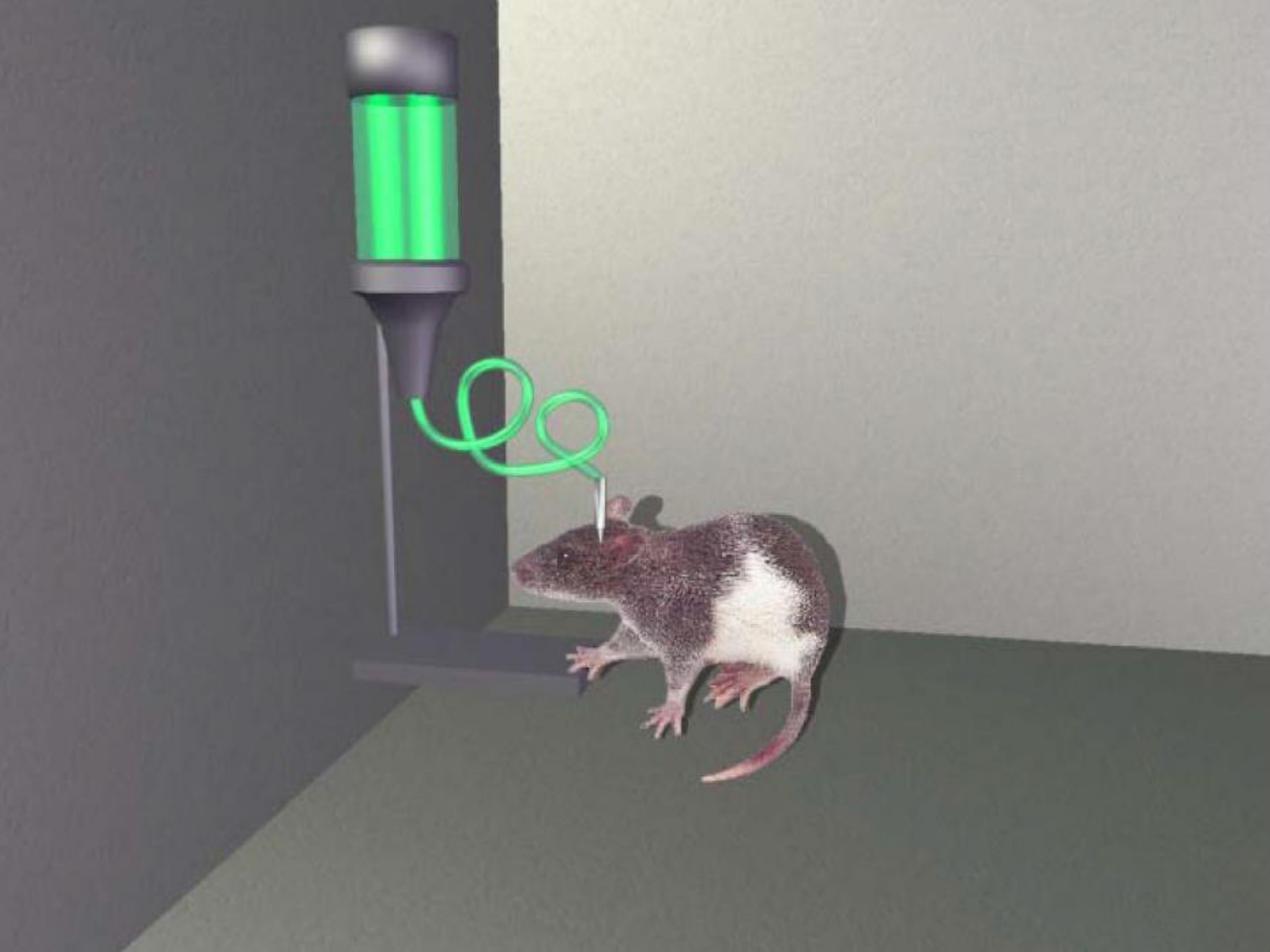
  Marijuana & heroin can "fool" the brain's receptors sending abnormal messages

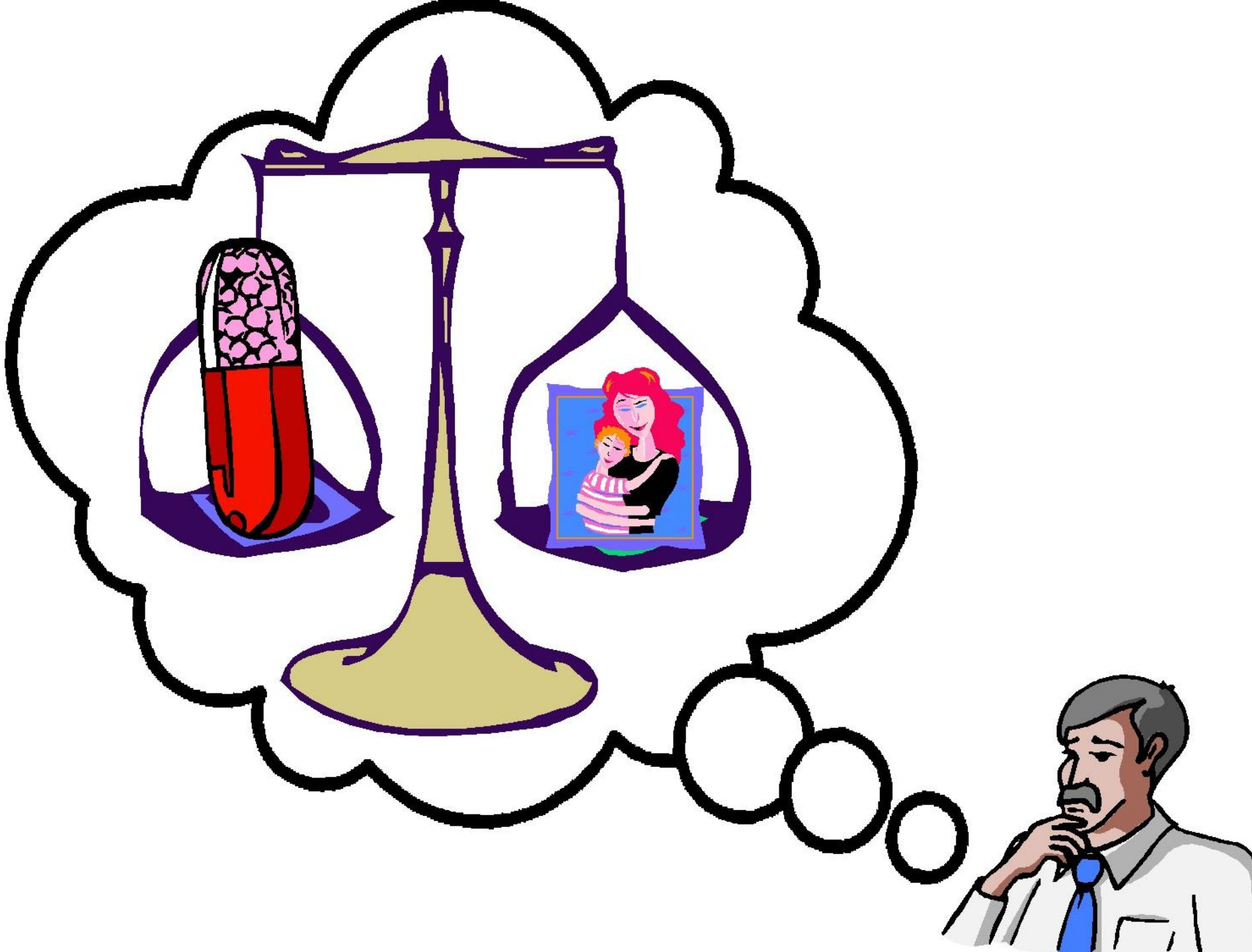
- Over-stimulating the reward circuit

  Cocaine & meth cause nerve cells to release abnormal amounts of neurotransmitters (dopamine)

Dopamine Overstimulates the Reward System

- Produces a euphoric effect
- Reinforces a pattern that “teaches” people to repeat the behavior of using drugs
- Brain stops making dopamine or reduces the number of receptors
- The person uses more (tolerance)



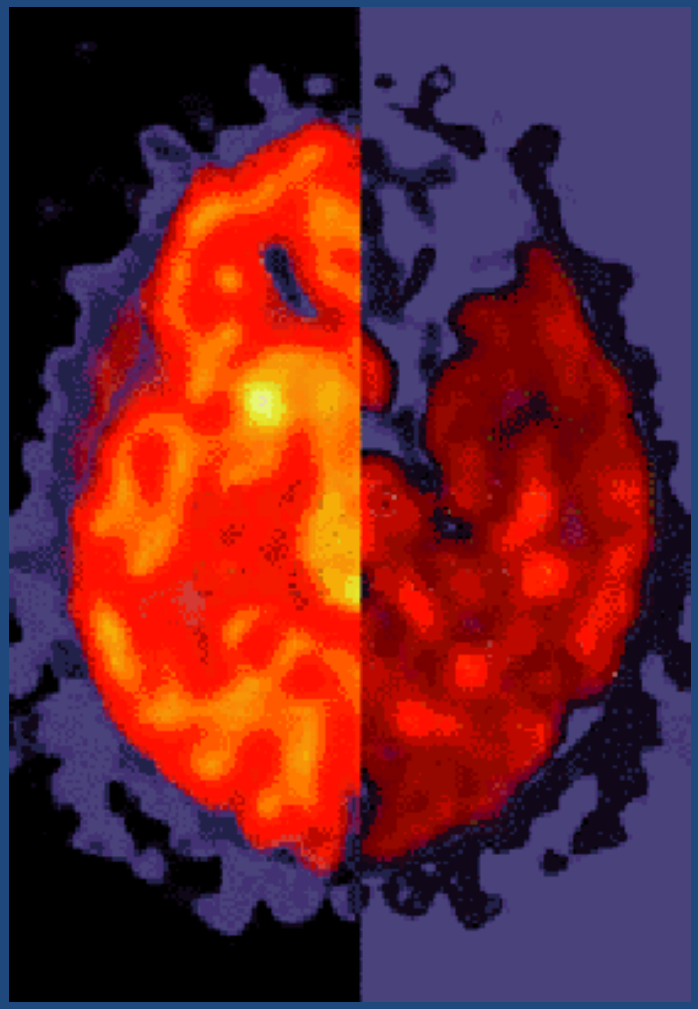



Activation of the reward pathway by addictive drugs
alcohol
cocaine
heroin
nicotine
heroin
Reward Center

Brain changed in PET Scans

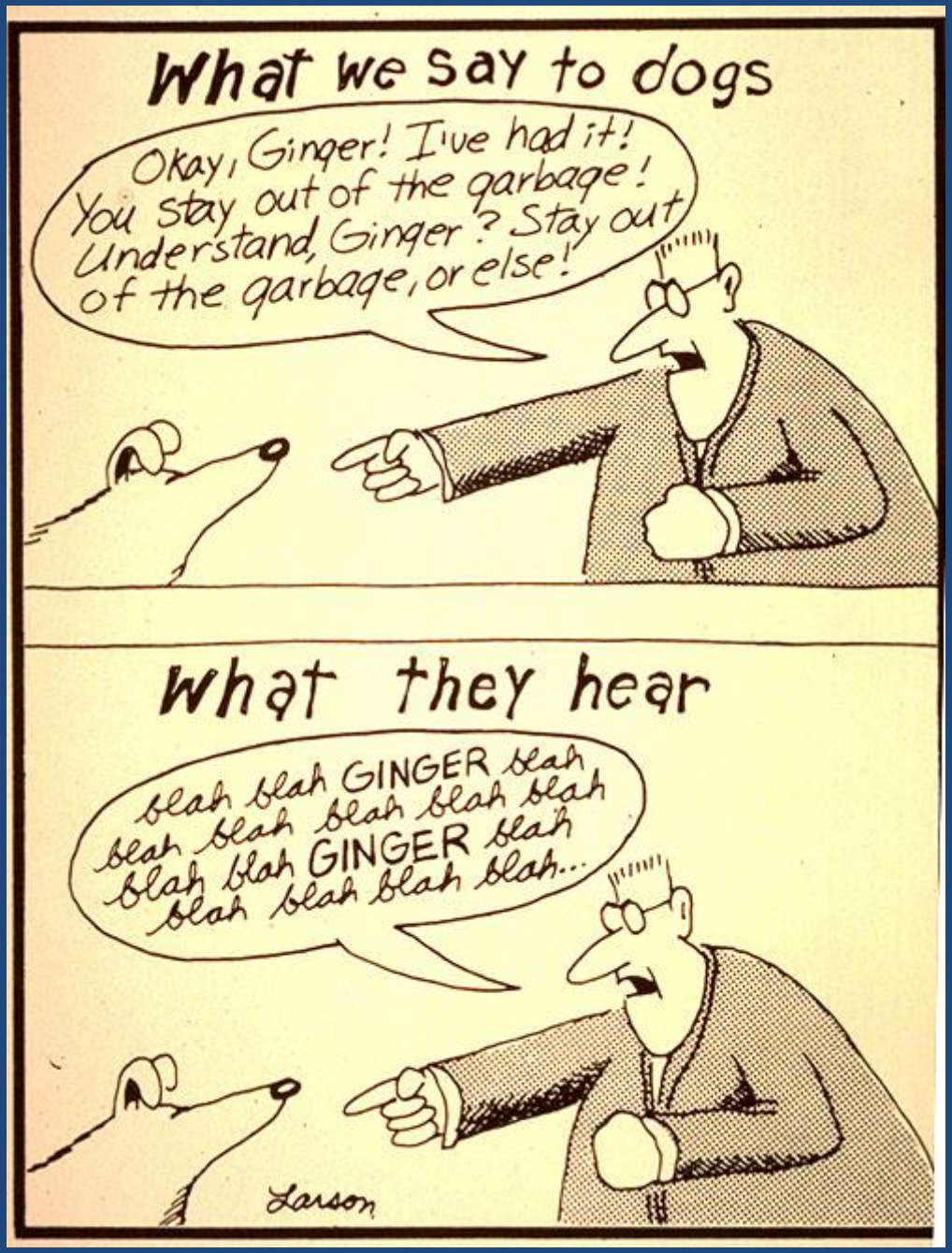
- Drug users have far less dopamine activity (*right*), as is indicated by the depletion (dark red shows disruption), compared to the controls *(left)*

  Studies show that this difference contributes to dependence and a diseased brain




metabolism
normal subject
cocaine addict

Drugs like cocaine mute visual and auditory centers required for normal social functioning. All brain resources are redirected to acquiring the drug.


What we say to dogs
Okay, Ginger! I've had it! You stay out of the garbage! Understand, Ginger? Stay out of the garbage, or else!
What they hear
blah blah GINGER blah blah blah blah blah blah GINGER blah blah blah blah blah...
Larson

If I see you smoking crack, I'll arrest you!

Blah, blah blah
CRACK blah,
blah blah

Gray Matter

The brain tissue that serves to process information

Gray Matter Loss in These Three Areas Occurs With

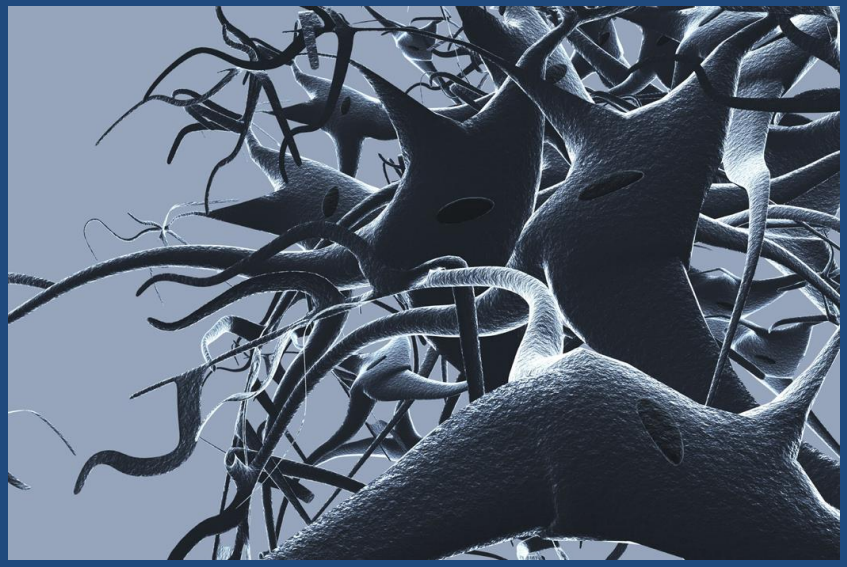
- Schizophrenia
- Bipolar Disorder
- Major Depression
- Obsessive Compulsive Disorder
- Anxiety Disorder
- Substance Use Disorder

https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2108651

All these disorders share common brain architecture.

Three Stages of Chemical Dependence

- Binge and intoxication
- Withdrawal
- Preoccupation and anticipation (Craving)



Behavioral Responses

- Loss of control
- Continued compulsive use despite harmful consequences
- Multiple relapses preceding stable recovery

STRESS AND ADDICTION VIDEO

Relapse Increases During the Pandemic

- Increase contact—through remote means—with participants
- Encourage self-reporting of new drug use
- Offer support and resources
- Limiting the use of sanctions

Risk Factors

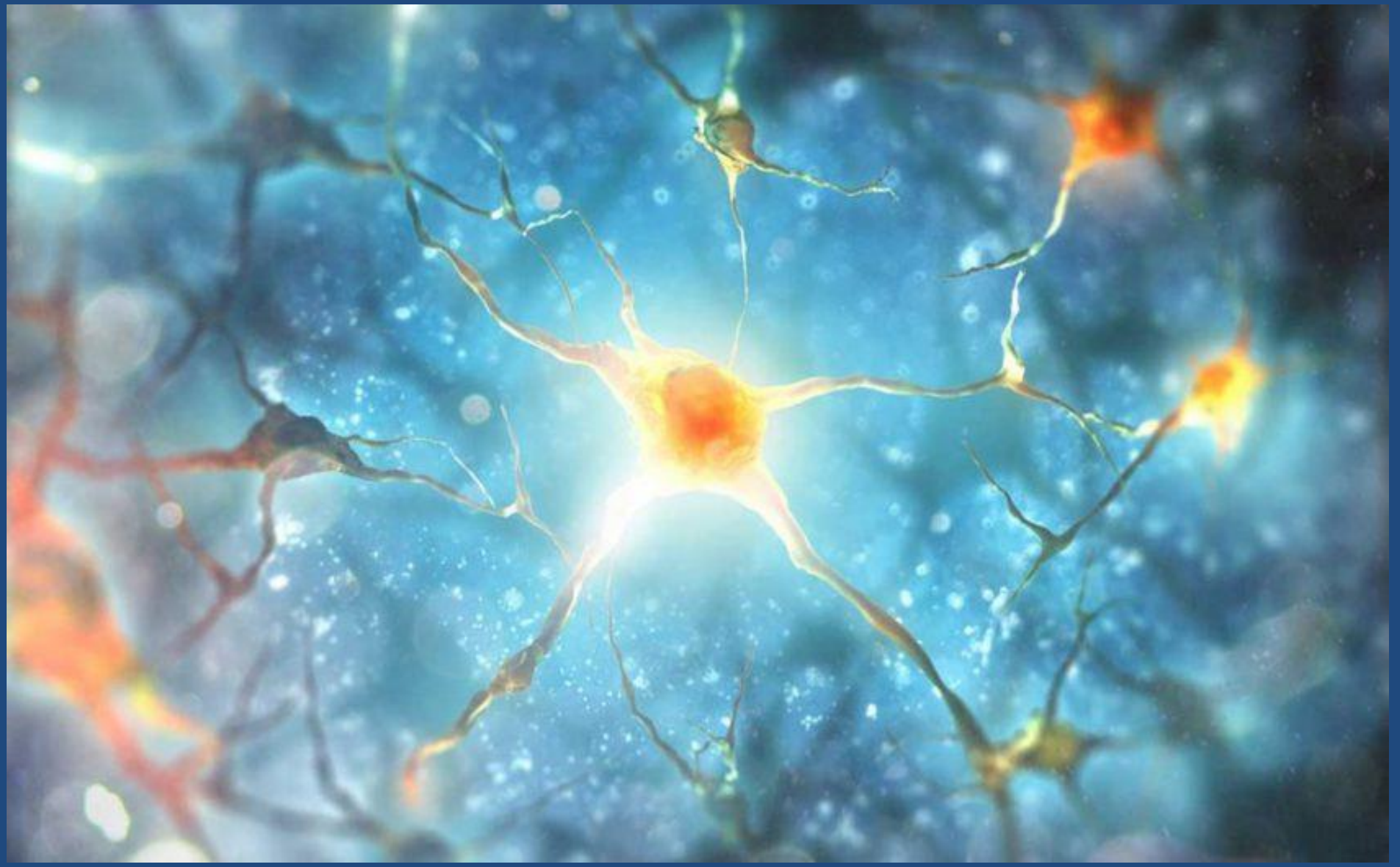
- Biology accounts for half of the vulnerability
- Gender, ethnicity and mental disorders
- Environment
  - Support system
  - Socioeconomic status
  - Peer pressure
  - Trauma & abuse
- Development – age use begins

https://newsinhealth.nih.gov/2015/10/biology-addiction

Neuroscience Supports Substance Use Disorder = Brain Disease

Neuroplasticity

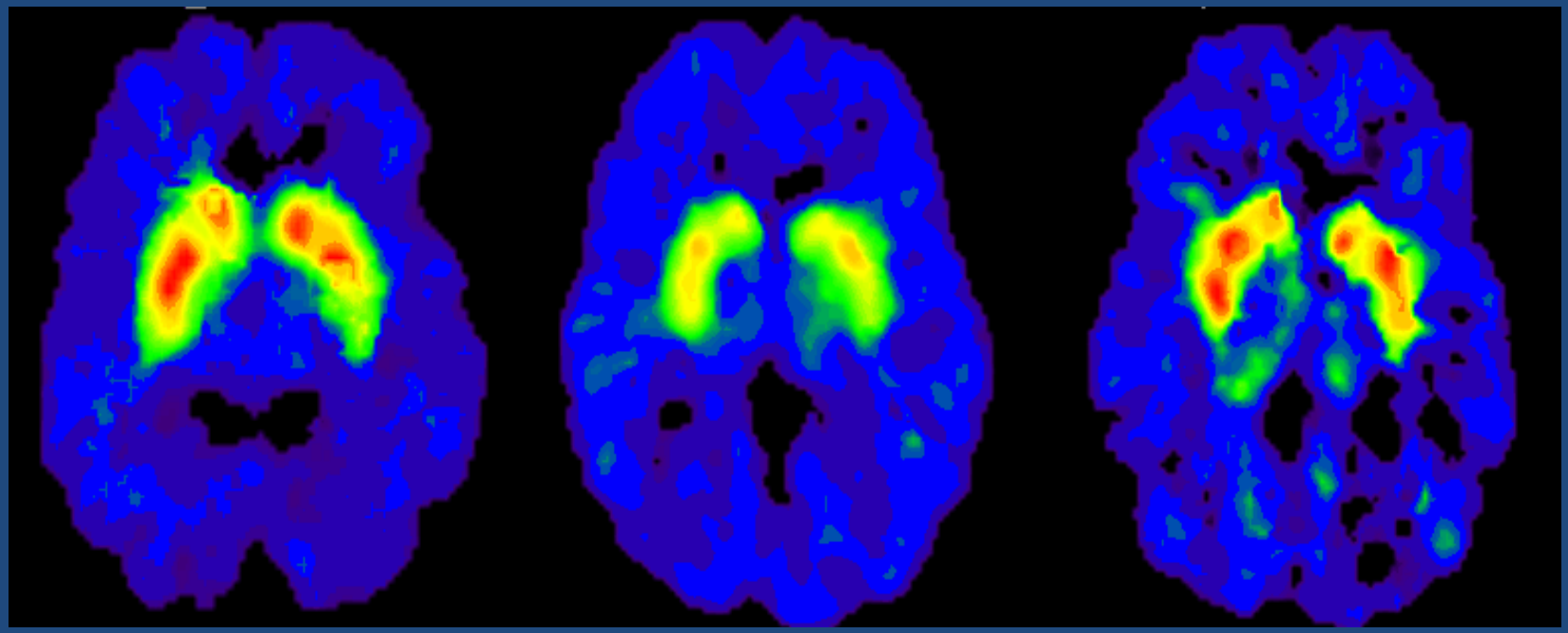
- The ability of the neurons to change their function, chemical profile (amount and type of neurotransmitters) or structure
- The plastic changes in neurons can occur
  - Physiologically according to activity or skills
  - Pathologically due to injury or disease



“

NEUROPLASTICITY PROVIDES US WITH A BRAIN THAT CAN ADAPT NOT ONLY TO CHANGES INFLICTED BY DAMAGE, BUT **ALLOWS ADAPTATION** TO ANY AND ALL EXPERIENCES AND CHANGES WE MAY ENCOUNTER...

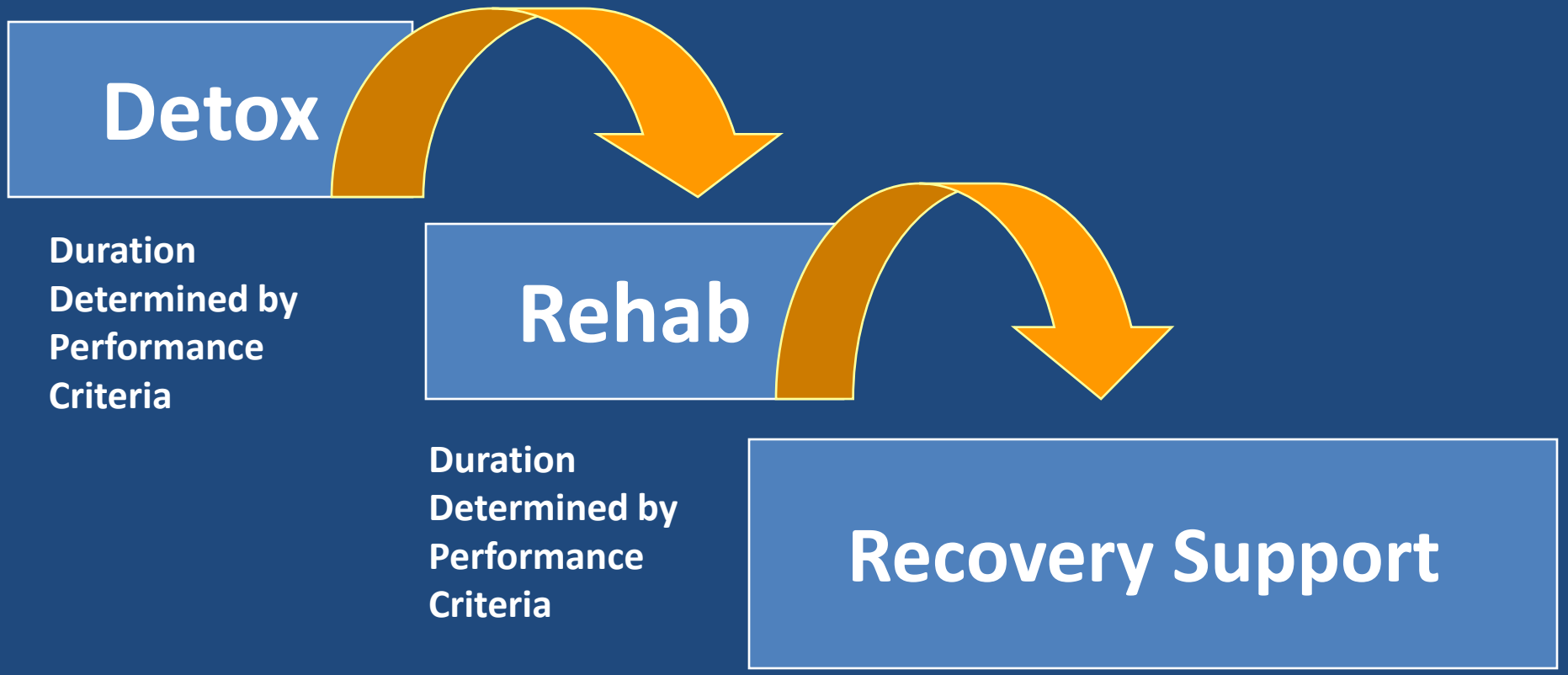
Why is Continued Treatment Critical?



Normal Control | **Meth user (1 month abstinent)** | **Meth user (36 months abstinent)**

Partial Recovery of Dopamine Transporters After Prolonged Abstinence

Treatment Model



Lessons Learned from Treatment

- Behavior change is necessary for sustained benefit
- Treatment effects do not last very long after treatment stops
- Patients not in some form of treatment or monitoring are at greater risk for relapse
- Retention is critical
- Monitoring is essential

Evidence-Based Practices

- Cognitive Behavioral Therapy
- Motivational Interviewing
- Recovery Support

https://www.mentalhealth.va.gov/providers/sud/selfhelp/docs/4_moos_timko_chapter.pdf
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3753023/

Other Best Practices

- 12 Step and Other Self Help Groups

Why Medication-Assisted Treatment?

- Improves survival
- Increases retention in treatment
- Decreases illicit opiate use
- Decreases hepatitis and HIV
- Decreases criminal activities
- Increases employment
- Improves birth outcomes

MEDICATIONS FOR TREATMENT OF ALCOHOL USE DISORDER

Antabuse – Disulfiram

Aversive therapy

- Dose: 500mg 4 x day x 10 days; then 250mg 4 x day
- Side effects: Hypotension, drowsiness, headache, metallic taste, decreased libido/potency
- Prescription for Antabuse reaction: Benadryl 50mg IM or IV

MEDICATIONS FOR TREATMENT OF ALCOHOL USE DISORDER

ReVia, Traxan – Naltrexone

- Approved in 2006
- Reduces alcohol craving and relapse
- Dose: 50mg 4 x day with meals
- Side effects: nausea & headache
- Best with compliant younger patients
- Requires counseling (CBT)
- XR-injectable

MEDICATIONS FOR TREATMENT OF ALCOHOL USE DISORDER

Campral – Acamprosate

Alters GABA & NMDA systems

- Dose: 666 mg 3 x day
- Diarrhea, Dizziness, Dry mouth, Headache, Nausea
- Excreted by kidneys, not liver metabolized
- Reduces alcohol craving
- No tolerance, withdrawal or sedation

Topamax – Topiramate (not FDA approved)

- Promotes abstinence
- Effective for persons who are still drinking
- Lessens anxiety and mood instability
- Reduces dopamine and craving

MEDICATIONS FOR TREATMENT OF OPIOID USE DISORDER

Definitions

- Opiate agonists (Full Agonist)
  Medications that activate opiate receptors in the brain (e.g., Heroin, Methadone)
- Opiate antagonists
  Medications that bind to opiate receptors but do not active them (e.g., Naltrexone and Naloxone)
- Opiate partial agonists
  Medications that bind and activate opiate receptors but NOT to the same degree as opiate agonists
  (e.g., Suboxone)

OPIATES

- MORPHINE – a naturally occurring opiate
- HEROIN – a semi-synthetic opiate

Morphine is isolated from the crude opium and then reacted with acetic anhydride, a chemical also used in the production of aspirin. The purity of the extracted morphine determines in large part the quality of the resulting heroin. Most black-market heroin is highly impure due to contaminants left after refinement of opium into morphine when then remain in the final product.

Medications for Opioid Treatment

Methadone: (full agonist)
- Regulations require one-year dependence history
- Average 60-120mg a day
- Best for dependents with large habits

Buprenorphine: (partial agonist)
- Requires criteria for dependence for one year
- Rapid stabilization in 2-3 days
- Range 12-24mg a day
- Best for younger, motivated, smaller dependents

Naltrexone (antagonist)
- Oral Naltrexone: 50mg by mouth 4 x day
- Works with very motivated and stable patients
- Injectable Naltrexone (requires less initial patient motivation)

RATIONALE FOR OPIOID AGONIST MEDICATIONS

- OPIOID AGONIST TREATMENT
  - The most effective treatment for opioid dependence
  - Controlled studies have shown significant
    - Decreases in illicit opioid use
    - Decreases in other drug use
    - Decreases in criminal activity
    - Decreases in needle sharing
    - Improvements in prosocial activities
    - Improvements in mental health

BUPRENORPHINE

- Butrans, Buprenex, Subutex
- Partial Opiod Agonist
  - At low dose behaves as an agonist
  - At high doses as either an agonist or antagonist
  - Will displace Morphine, Methadone from the receptor
  - If given to someone maintained on Methadone or using opiates, it can cause significant withdrawal
  - Semisynthetic derivative of thebaine (from opium)

Buprenorphine Benefits

- Blocks craving
- Blocks opiate withdrawal
- Does not produce a ‘high’
- Blocks the effects of abused opioids
- No cognitive impairment
- No organ toxicity
- Use in pregnancy
- Less physical dependence than methadone and therefore easier withdrawal

Buprenorphine Risks

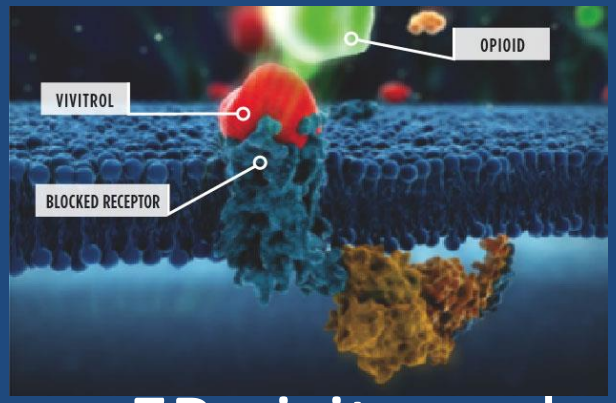
- Is abused when injected
- Risk of overdose when combined with other drugs and injected
- Is abused by non opioid dependent individuals
- Has street value and is diverted
- Relatively low abuse potential compared to other opioids - slower onset of action, less of a ‘high’

Vivitrol - XR Injectable Naltrexone

- Opioid antagonist
- Not a controlled substance
- Good safety profile
- No abuse potential
- Danger of overdose after treatment
- Seems to have more acceptance (and less stigma) in the general public and the courts

Vivitrol - XR Injectable Naltrexone

- Can be prescribed by any health care provider
- Use requires the patient be opioid free at beginning of treatment
- Requires a monthly injection
- Higher pharmacy cost
- May reduce inpatient admissions, ER visits and other health system costs, increases treatment retention



OPIATE OVERDOSE TREATMENT

- Narcan - Naloxone
  - Injected fastest action.
  - Acts after about two minutes and its effects may last about 20 - 45 minutes.
  - Distributed as part of emergency kits to heroin addicts and has been shown to reduce death rates from overdose.
  - The Narcan effect is short lived and may have to be repeated or the patient will lapse back into overdose symptoms.

Questions