Neurobiology of Addiction (Short Version)

(yes we have groups after this…)

Roy E. Smith, MD

Addiction Medicine

Primary Neurologic Disorder

- Example-Parkinson's Disease –

  Michael J. Fox is spokesperson
- Both addiction and Parkinson's are diseases of dopamine deficiency

Take Home Message

- Addiction is a PRIMARY Neurologic Disease

  Neurologic=Brain and spinal cord

  PRIMARY=not due to something else (anxiety, depression, ADD/ADHD, Bipolar Disorder)

  Sometimes difficult to differentiate Primary vs. Substance induced (secondary) Psychiatric disorder

How Common are Substance Disorders?

- 85-90% of adult US population uses alcohol or other mood altering chemicals at any one time
- What percent have a substance use disorder?

  10-12%
- What makes these 10-12% different (why me)?

Genetics

FAMILY STUDIES

- Children of Alcoholics are 3- 4 times more likely to be alcoholic than the general population

Genetics

ADOPTION STUDIES

- Biological children of alcoholics have a much higher risk of alcoholism REGARDLESS of WHO PARENTS THEM

- Studies involved monozygotic twins separated at birth- same results by age 30

Genetics

MESSAGE from Adoption Studies

- **YOU CAN'T "OUTPARENT" A GENETIC ALCOHOLIC**

- Bad parenting does not cause alcoholism/addiction and good/great parenting can't fix it.

Genetic Predisposition

- Accounts for 50-60% of vulnerability for addiction
- Higher vulnerability than other family related illnesses
- DM II
- Hypertension
- Breast cancer

Pre-Morbid Differences

- Euphoria - First time drinkers report of intensity of euphoria

- FHP report MUCH greater euphoria with alcohol exposure than FHN (family history negative)

Pre-Morbid Differences

- First time drinkers report of negative effects of acute alcohol exposure
- FHP report less negative effects than FHN

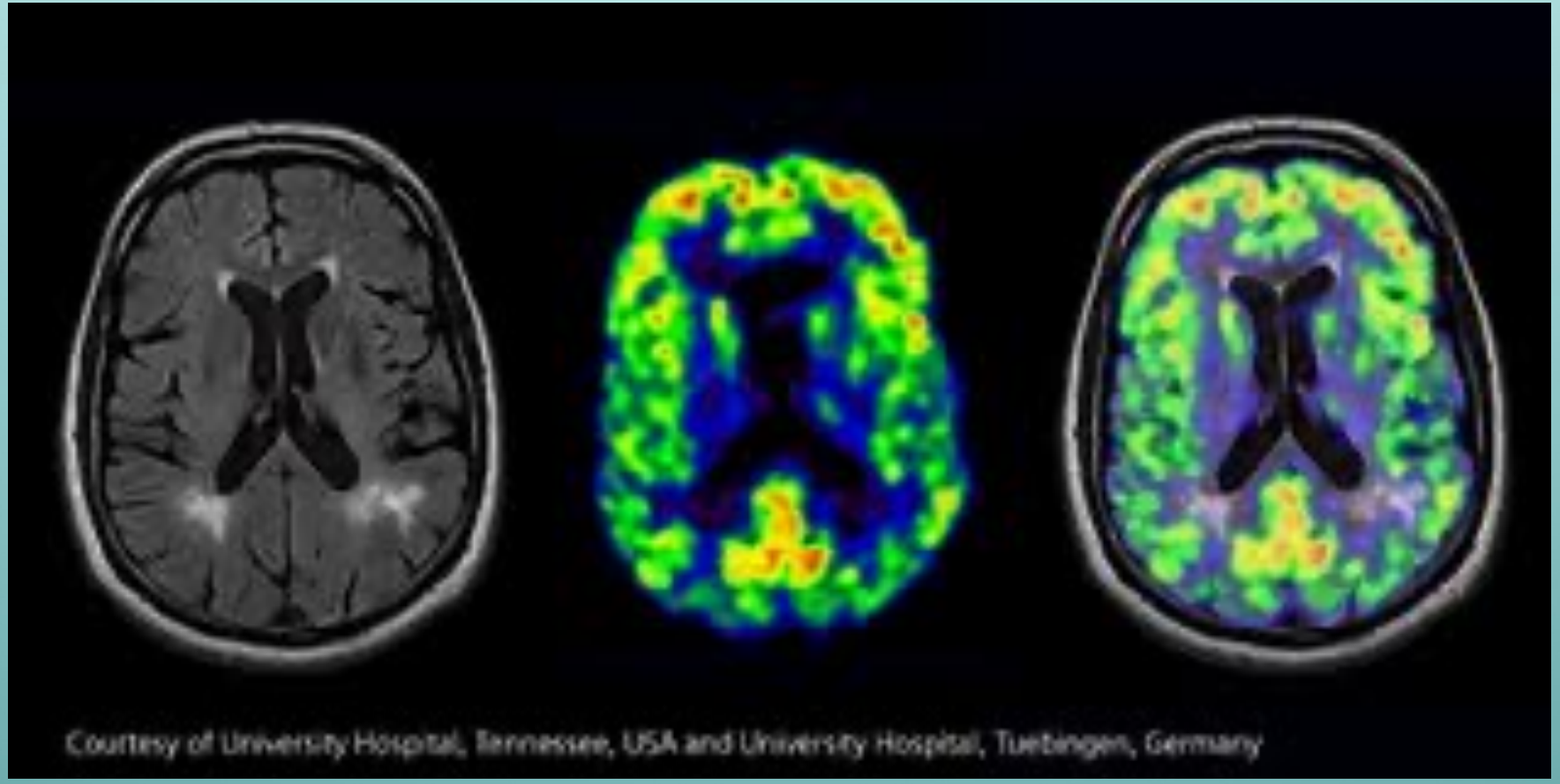
--less body sway

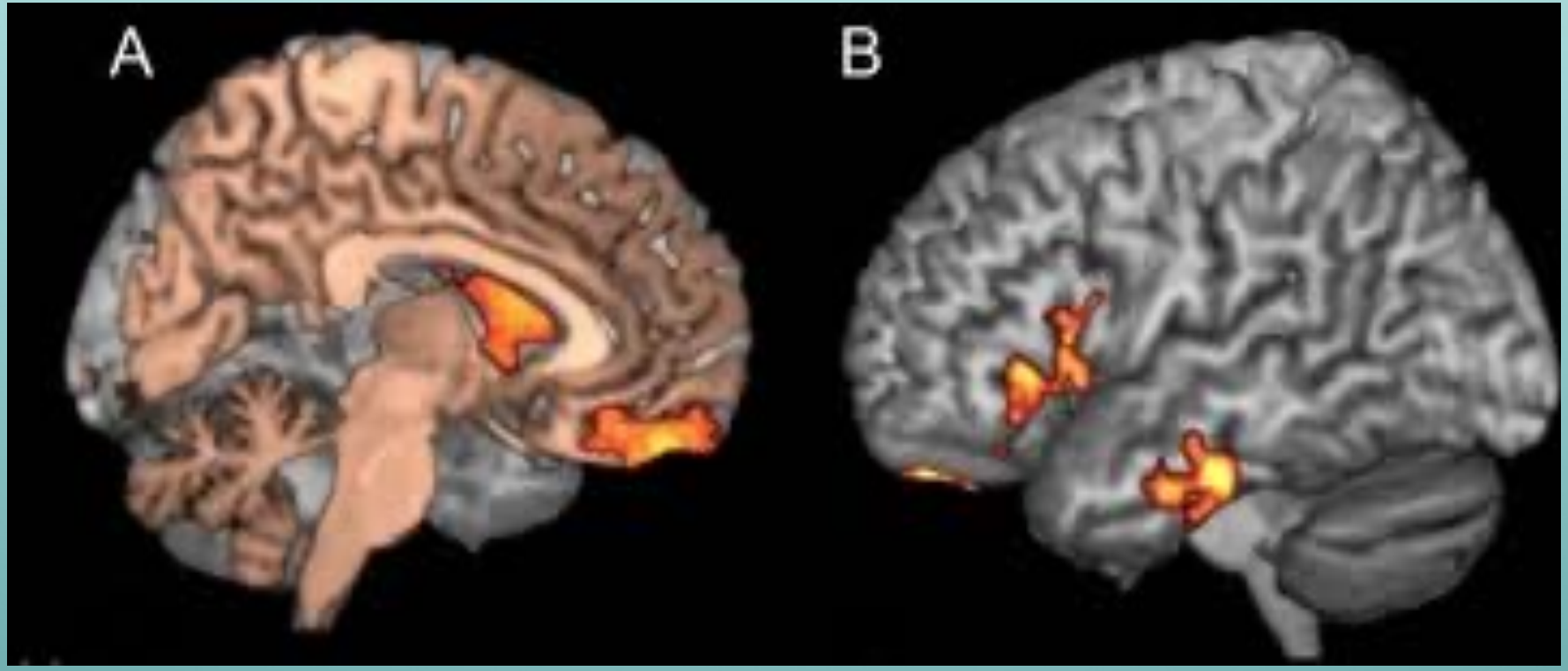
--less nausea

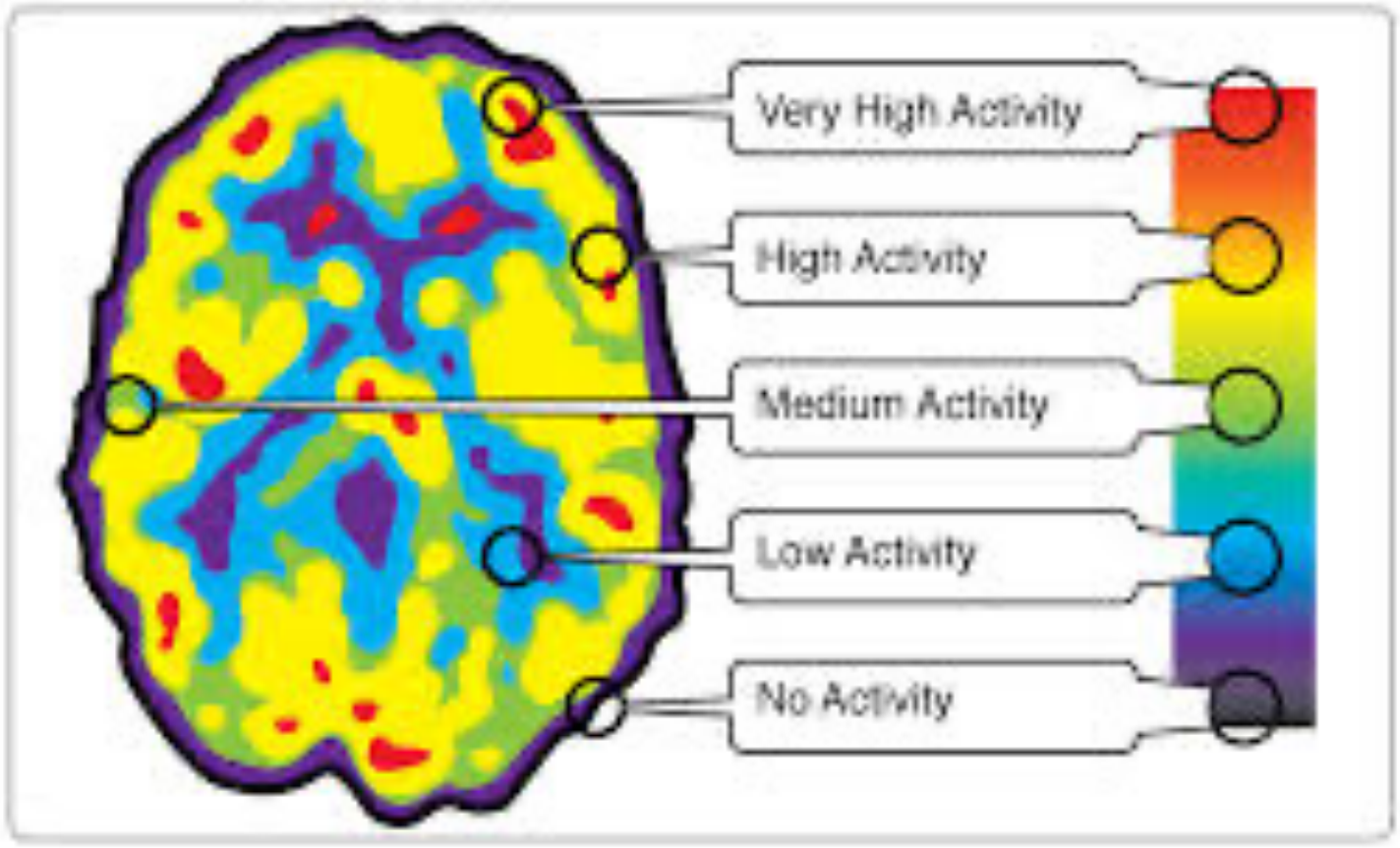
--less disorientation

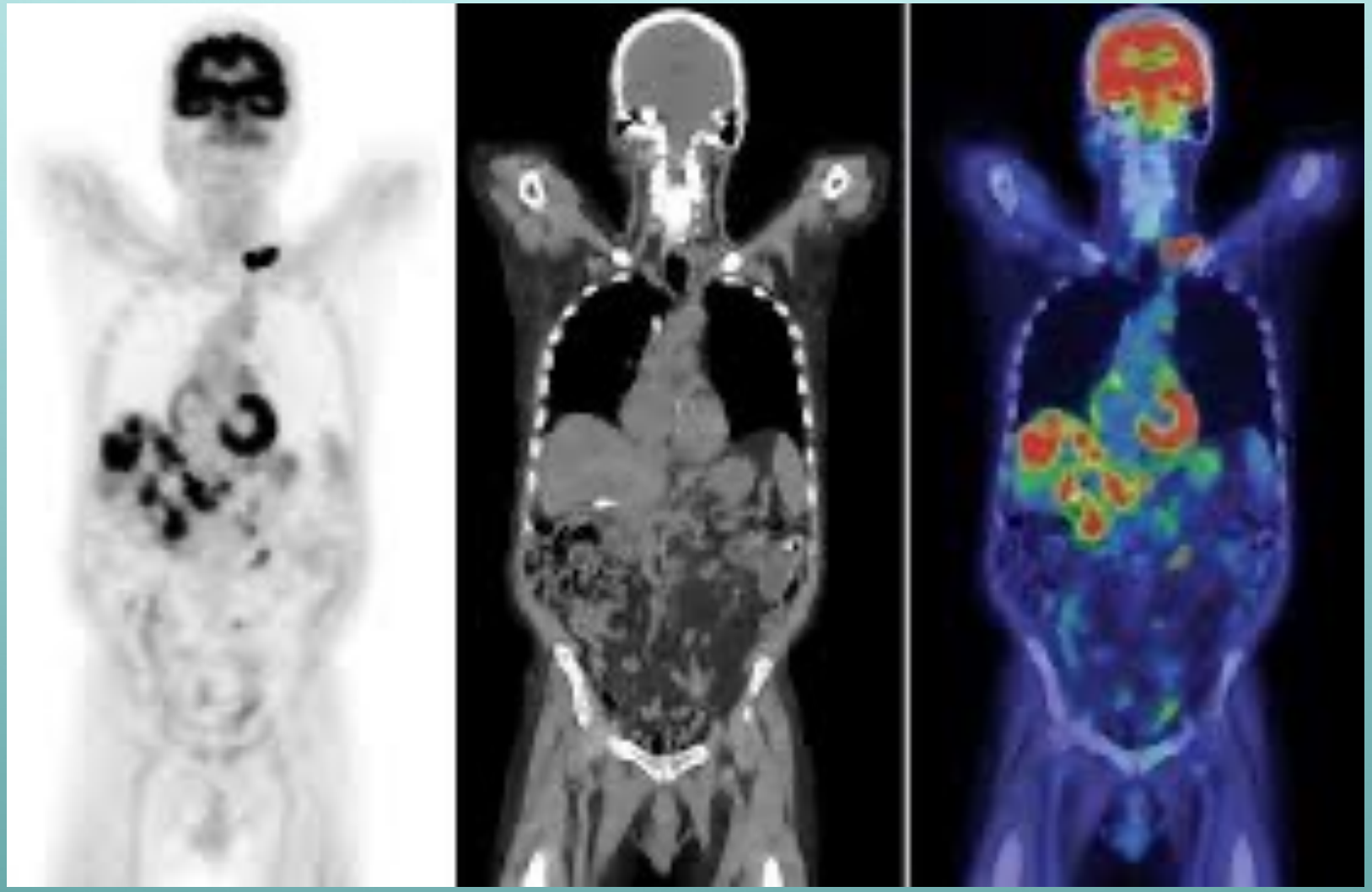
--better cognitive abilities and physical performance such as driving tests

--WEAKER WARNING SYSTEM


Courtesy of University Hospital, Tennessee, USA and University Hospital, Tuebingen, Germany


A
B

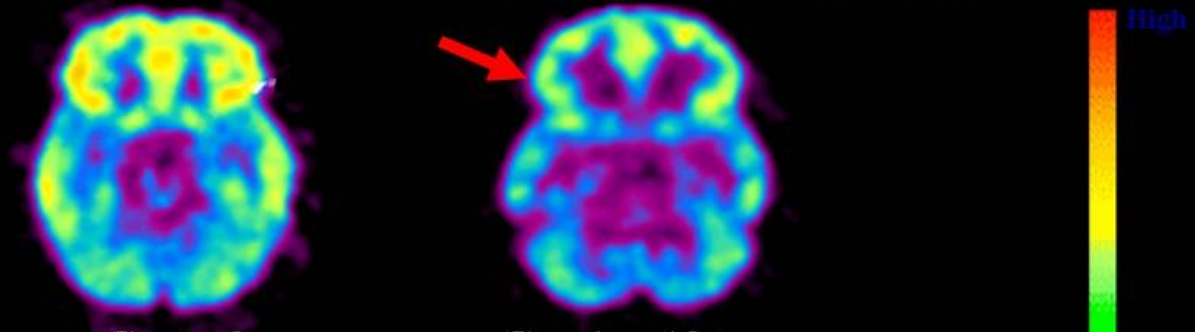

Very High Activity
High Activity
Medium Activity
Low Activity
No Activity




Normal
Cocaine
Obese

3. ADDICTION IS A DISEASE OF THE BRAIN
as other diseases it affects the tissue function

Decreased Brain Metabolism in *Drug Abuse Patient*

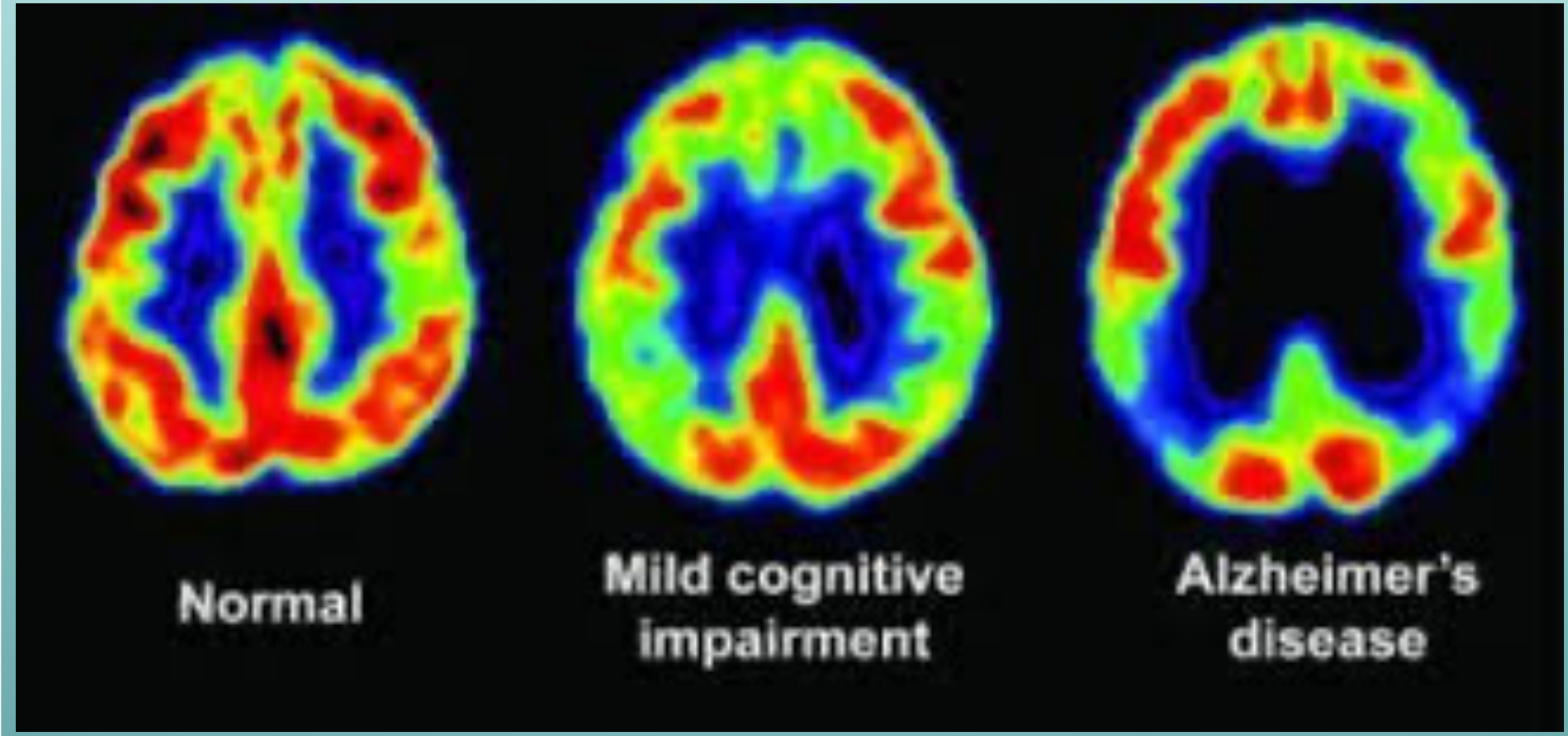


Control Cocaine Abuser

Decreased Heart Metabolism in *Heart Disease Patient*

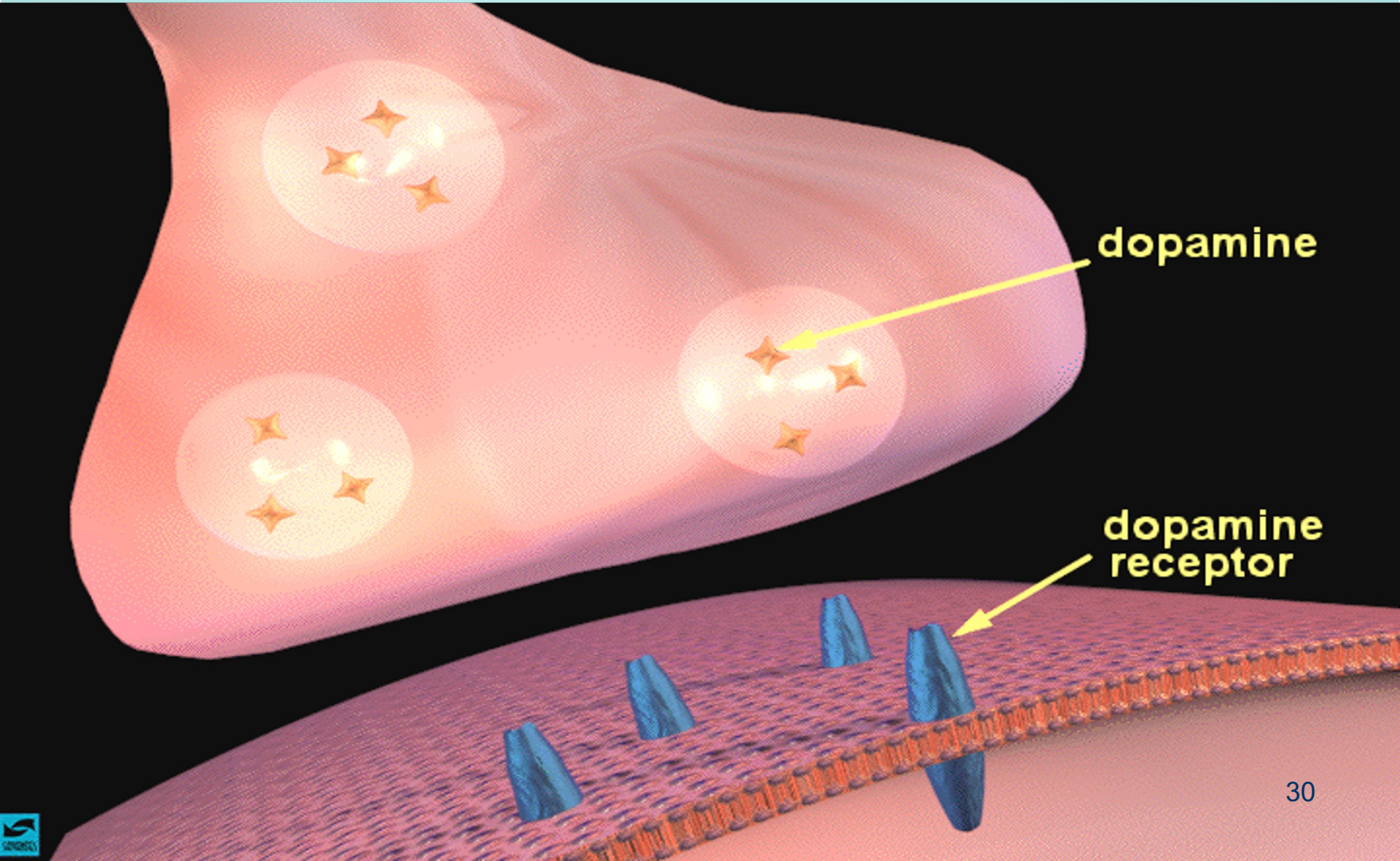
Healthy Heart Diseased Heart

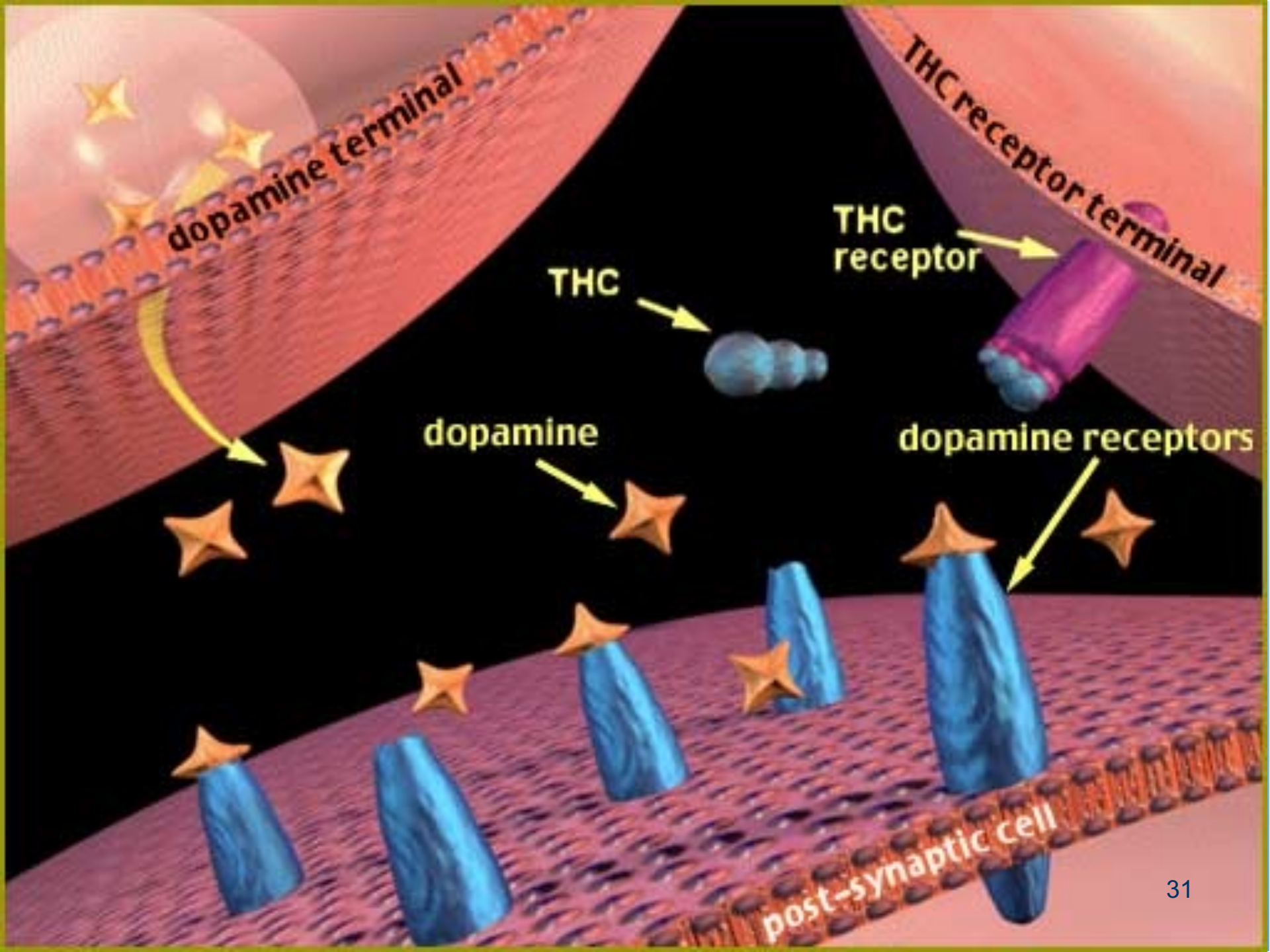
Sources: From the laboratories of Drs. N. Volkow and H. Schelbert


Normal
Mild cognitive impairment
Alzheimer's disease


Disruption in Brain Circuits
Involved in Reward and Punishment
High
Low
Control
Cocaine Abuser

How Neurons Work



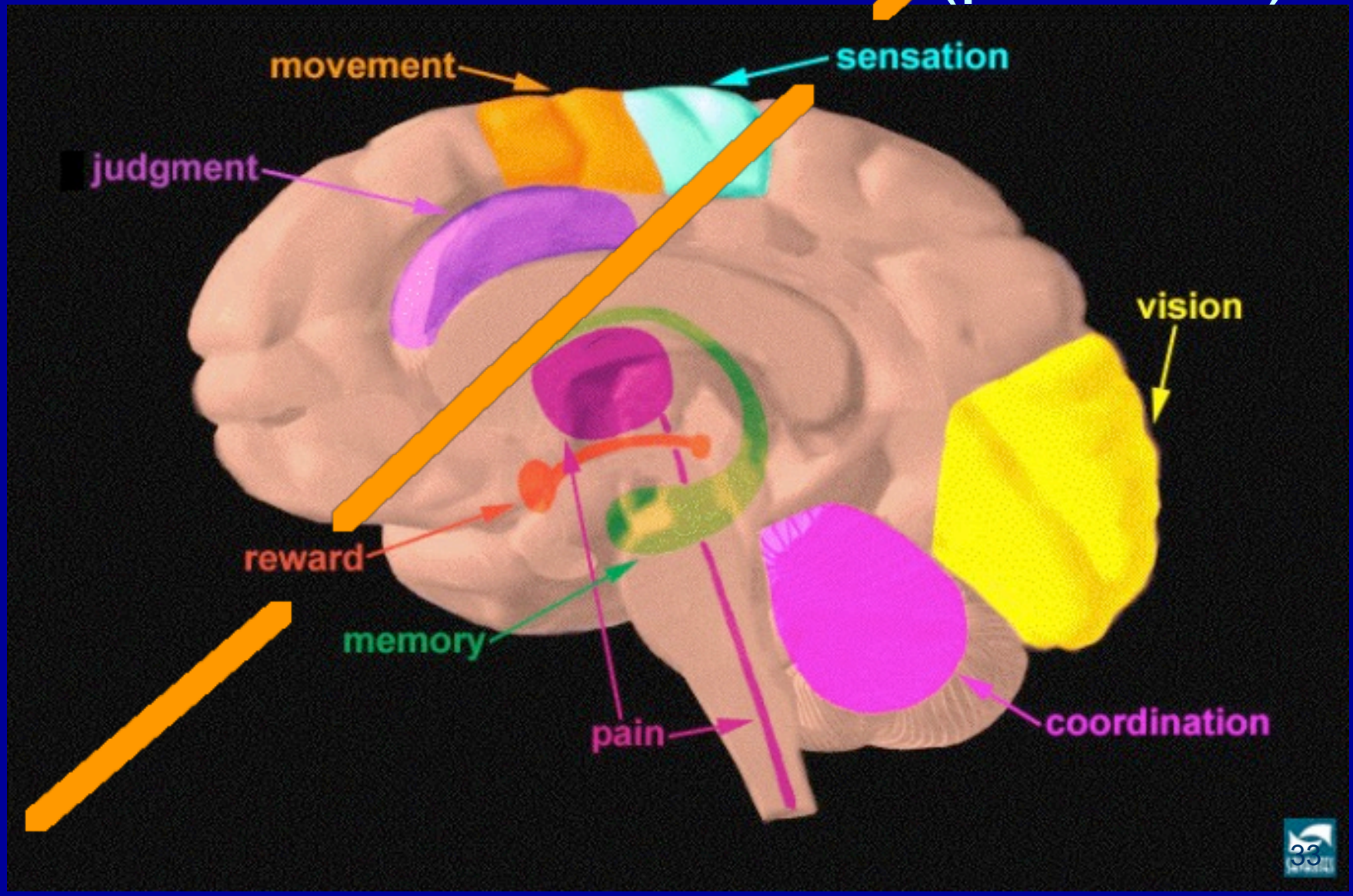

dopamine terminal
THC receptor terminal
THC
receptor
THC
dopamine
dopamine receptors
post-synaptic cell

Addiction = Reward Deficiency Syndrome

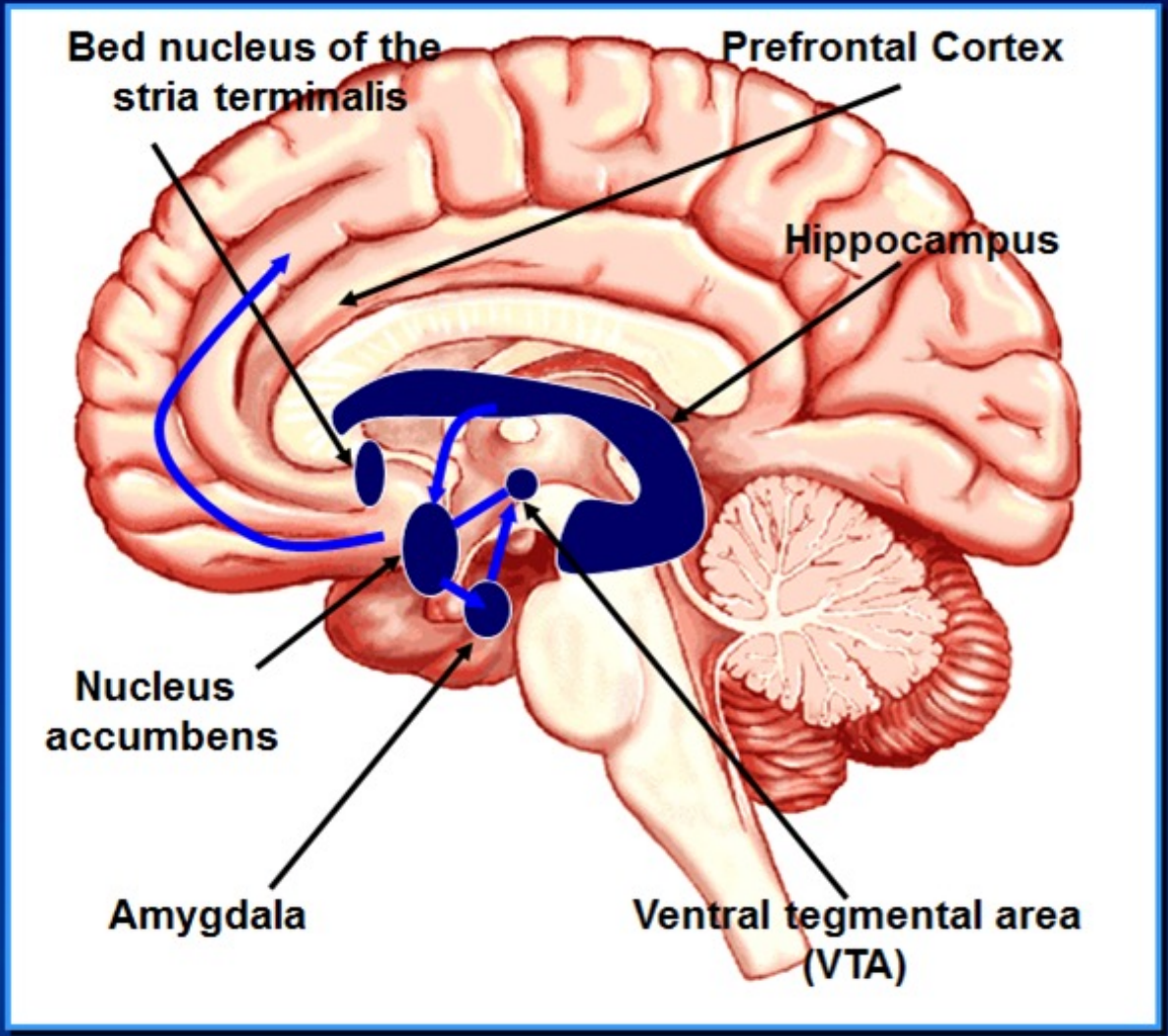
- A decrease in endogenous neurotransmitters leads to a sense of incompleteness, decreased pain tolerance, uneasiness, and anxiety.

- Since 85-90% of the US population is exposed to alcohol or drugs during their lifetime, the person genetically predisposed to addiction is very likely to find what replaces or “fixes” their ‘reward deficiency’.

New Brain Old Brain (primitive)



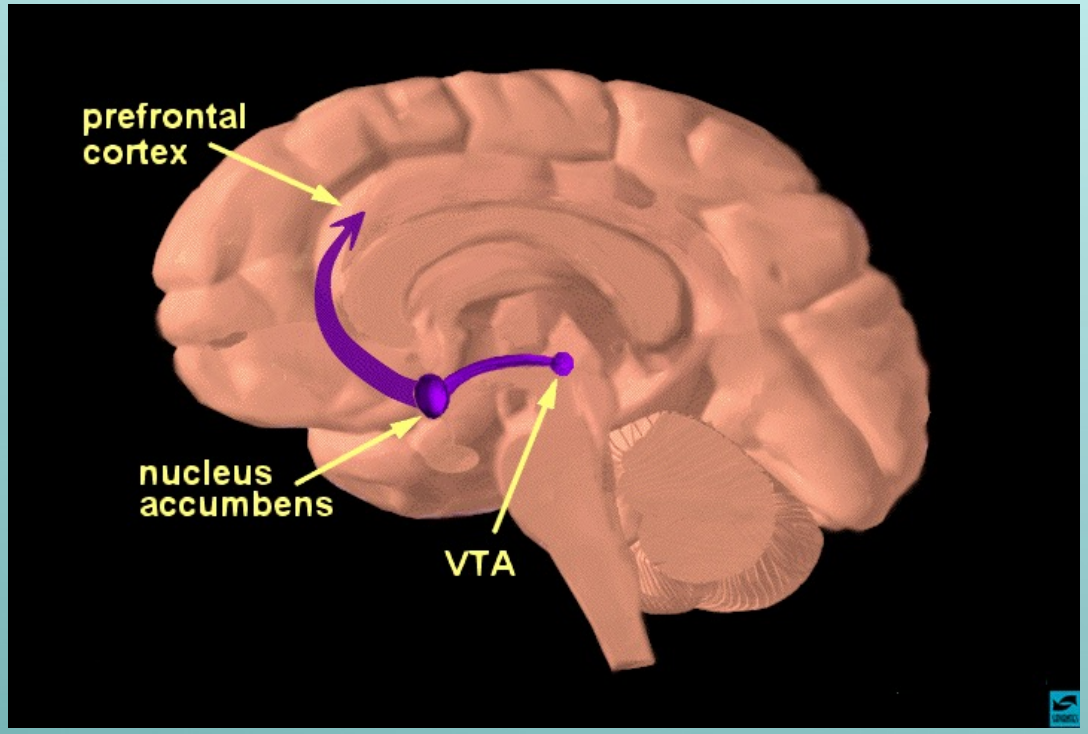
Relapse and Conditioning



- Repeated alcohol use has caused "conditioning" to occur in related circuits
- Now "cues" associated with alcohol use can activate the reward and withdrawal circuit
- This can evoke anticipation of alcohol or feelings similar to withdrawal that can precipitate relapse in an abstinent patient

Source: Messing RO. In: Harrison's Principles of Internal Medicine. 2001:2557-2561.

Why Do We Use Drugs?



BRAIN REWARD PATHWAY

- Food
- Water
- Sex
- Child Rearing
- PRIMARY DRUG

Neurochemistry of Addiction
Neuroadaptation

- 2 changes occur once a drug is abused and these are permanent ='neuroadaption'.

- 10 8
- 3 ?
- 13

Neuroadaptation Cascade

10 8

8

16

Neuroadaptation Cascade

10 8 6

8

16

Neuroadaptation Cascade

10 8 6

8 6

16

Neuroadaptation Cascade

10	8	6
	8	6
	---	---
	16	12

Neuroadaptation Cascade

10 8 6 4

8 6

---

16 12

Neuroadaptation Cascade

10 8 6 4

8 6 4

---

16 12

Neuroadaptation Cascade

10	8	6	4
	8	6	4
	16	12	8

Neuroadaptation Cascade

10 8 6 4 2 1 1

8 6 4 2 1 0

----

16 12 8 4 2 1

- Dopamine deprivation produces chronic unpleasant feelings, depression and a loss of motivation, which leads to the urge/need to take the drug to feel better.

Memory and Control Circuits

As the reward circuits become blunted the addict also loses ability to curb the need to seek and use drugs

Memory of the drug becomes more powerful than the drug itself

Frontal brain regions required to exert inhibitory control over desires and emotions are affected

Conditioned Learning

- Pavlov's Dog
- Experiences a learned or conditioned response to the substance and starts to anchor the drug use with the associated activity/environment
- These triggers or cues increase DA and glutamate and increase cravings and withdrawal symptoms
- These memories and responses become hardwired or implanted into the brain
  - Long Term potentiation, Emotional Memory Formation, Synaptic Plasticity

Prefrontal Cortex (PFC)

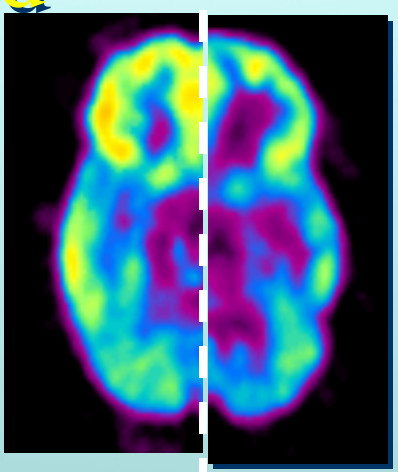
- Hypofrontality
- Top down failure
- Unhealthy PFC unable to choose less dominant but healthier behaviors
- Emotional memory of drug use over powers the rational memory regarding consequences
- Weakened braking system

Orbitofrontal Cortex

- Addiction also involves disruption of circuits involving compulsive behavior and drive
- Intermittent dopamine release results in OFC dysfunction via the striato-thalamo-orbitofrontal circuit
- Hyperactivity in the OFC associated with craving
- Pathology in the OFC has been observed in patients with OCD, Tourette's Syndrome, impulsivity – Glutamate also involved in these disorders

Non-Addicted Brain

Addicted Brain

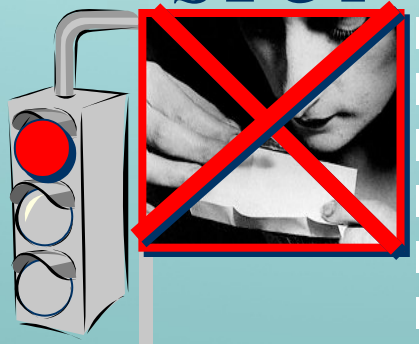


Control
CG

Saliency
NAc

Drive
OFC

Memory
Amygdala

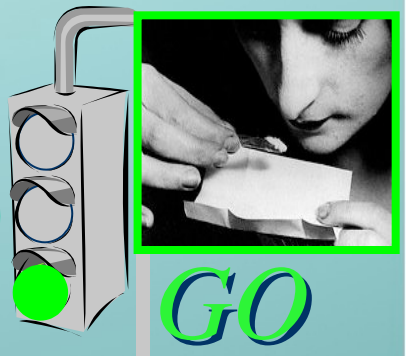


Control

Saliency

Drive

Memory



Adapted from: Volkow et al., J Clin Invest 111(10):1444-1451, 2003.

- **Type I alcoholic**
  - 75%, older onset, +guilt, fear, no fighting
- **Type II alcoholic**
  - 25%, young, fearless, fights, thrill seeking
- “ 100 Points to reach addiction..”

Stress: The Anti-reward System

- Stress increases Corticotrophin Releasing Factor (CRF)
- CRF causes increase in DA and glutamate in the addict's limbic region
- Elevated CRF increases craving and relapse
- CRF interaction with DA resets hedonic set point
- CRF is activated for several months after withdrawal (PAWS)
- Early Childhood Trauma changes brain's response to stress and increases vulnerability for addiction later in life

Addiction: Effects on Learning

- The brain circuits involved in declarative memory ("knowing what") are distinct from those involved in non-declarative or procedural ("knowing how") memory.
- Procedural learning is rigid, life-long and partially unconscious.
- Addiction stereotypes important procurement skills through Procedural Learning.

Denial

- DENIAL -reengineers the conscious interpretation of reality to ensure addiction runs in stealth mode.
- Insight deficient
- VTA & Nac, Prefrontal Cortex, Hippocampus
- Brain is hardwired for denial – Addiction hijacks denial system
- Interferes with seeking treatment and leads to relapse

Treatment

- DENIAL
  - patient and family members
- MET, MI,
- Al-Anon
- Allow patient to experience consequences

Avoid Spikes in DA

- Avoid situations that cause spikes in DA
- Relapse Prevention Therapy – avoid triggers and cues – people, places and things
- External Cues: cash, Friday night, using buddy
- Internal Cues: loneliness, celebration, anger
- Smoking Cessation-
  - Success Doubles!

Stress

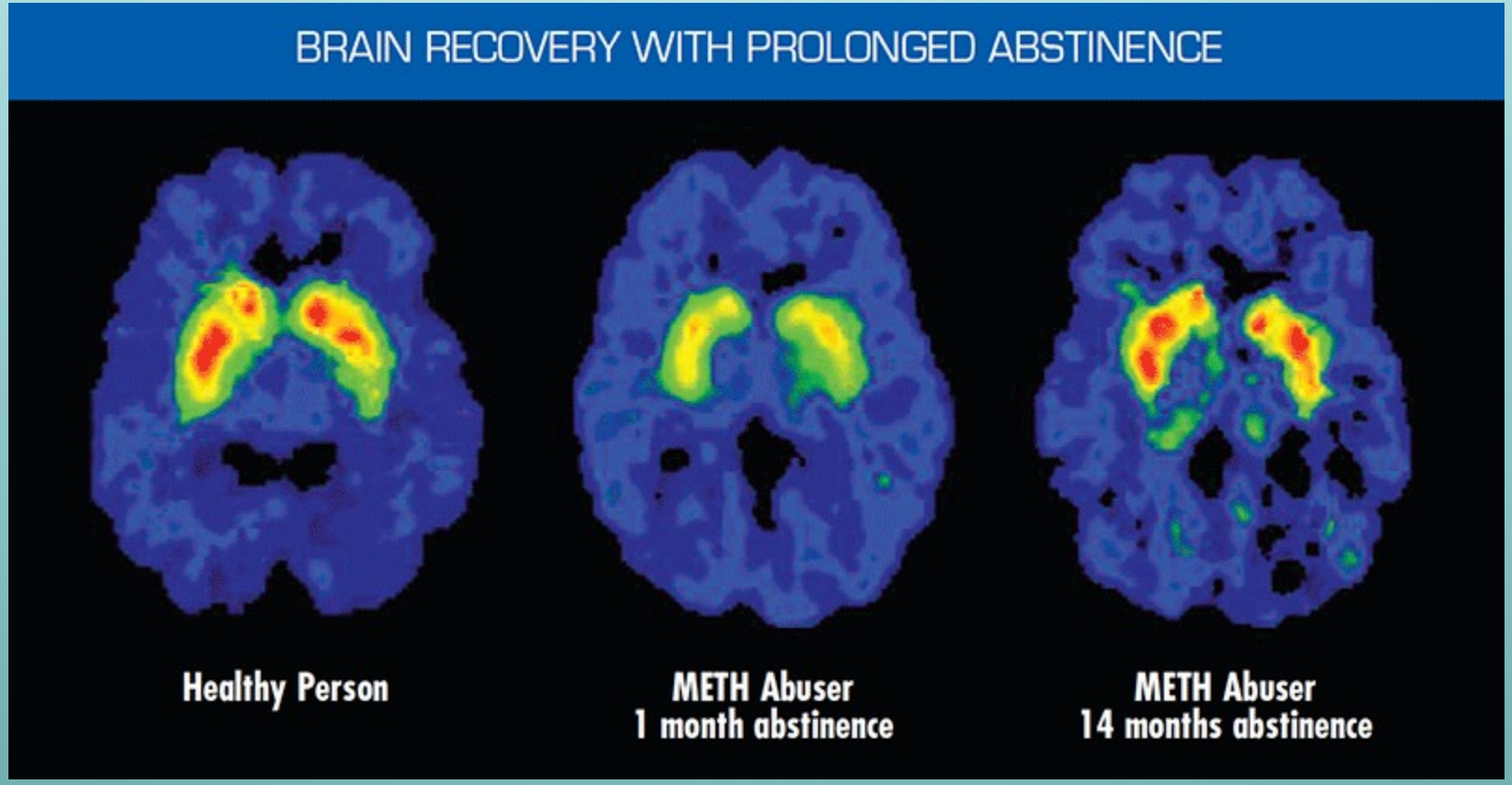
- Learn new ways to handle and manage stress
- CBT
- Relaxation Therapy
- Yoga
- Meditation
- Prayer
- Coping Strategies
- Exercise
- Medications

Pharmacological Treatments

- Naltrexone (Vivitrol shot)
- Campral (acamprosate)
- Baclofen
- Topamax (topiramate)
- Neurontin
- Depakote
- NAC (N-Acetyl Cysteine)
- Suboxone/methadone – harm reduction/ pain
- Antabuse (disulfiram)
- Chantix/ Wellbutrin/ Nicotine

Allow Brain to Heal

- Time without DA spikes allows brain to heal
- Hypofrontality resolves – regains control over behavior and choice
- Hedonic set point returns to baseline – normal pleasures become pleasurable again
- Mood, energy and sleep improve


BRAIN RECOVERY WITH PROLONGED ABSTINENCE
Healthy Person
METH Abuser
1 month abstinence
METH Abuser
14 months abstinence

12 Step Programs

- Denial- powerlessness, surrender
- Avoidance of DA Spikes- environment, character defects, making amends, daily inventory, daily mediation /prayer
- Spiritual Awakening – life of serenity and peace: much happier than before onset of addiction
- Service

Summary

- Addiction is a primary chronic brain disorder
- Addiction affects the brain's reward circuitry (RDS)
- Addiction affects brain circuits involving memory, impulse control, and judgment resulting in nonsensical pursuit of "rewards"
- Addiction is NOT a choice
- Addiction must be treated as a chronic disease similar to HTN, diabetes, asthma, CAD, OCD

Questions?

Medical / PAWS

- Next is overview of general classes of medications
- Relapse prevention
- Recovery Enhancement
- Craving Reduction

Medications

- Relapse Prevention
- Recovery Enhancement
- Recovery Management
- Anti-Craving

Alcohol

- Antabuse
  - Makes you sick
  - Take for “ occasions” or daily
- Naltrexone- Opiate Blocker
  - Block Euphoria
  - Craving Reduction
- Campral - Glutamate / GABA
  - Very low Side Effects

Alcohol- FDA approved

disulfiram (Antabuse) for the motivated patient who wants sobriety; makes you sick if drink

naltrexone (Pill or **Vivitrol** shot)- (probably) works better for some depending on genetic metabolism. Less euphoria and decreased cravings; Opiate blocker, GREAT if Alcohol AND opiate relapse a concern

acamprosate (Campral) may be considered for the patient with some established sobriety, may help with post-withdrawal sleep problems as well, maybe better for Fam Hx negative and women

Alcohol

- Anti-epileptic Medications (antiSeizure)
- Topamax
- Gabapentin (Neurontin)

R/B

Alcohol - Newer

topiramate (Topamax) is top choice given evidence for efficacy: side effects " Dop-amax", tingling, funny taste, wt loss side effects; taper up slowly to 200-300mg

gabapentin (Neurontin) is emerging as a potential good option either alone or as an adjunct to naltrexone and may help with sleep/anxiety/withdrawal/ chronic pain. (300 TID vs 600 TID)

baclofen GABA-B muscle relaxer, mixed evidence, known effective and safer in patients with cirrhosis and may benefit anxiety/withdrawal, dose may need to be titrated up to 100**-** 150 mg/d, cautiously and can't stop abruptly

varenicline (Chantix) Reduced craving and less heavy drinking days. **Consider if Alcohol and Smoker** wanting to quit. *Don't use Chantix with nicotine replacement patch, gum, etc.*

ondansetron (Zofran) has some positive evidence but may be limited to specific genetic pattern and not straightforward to formulate.

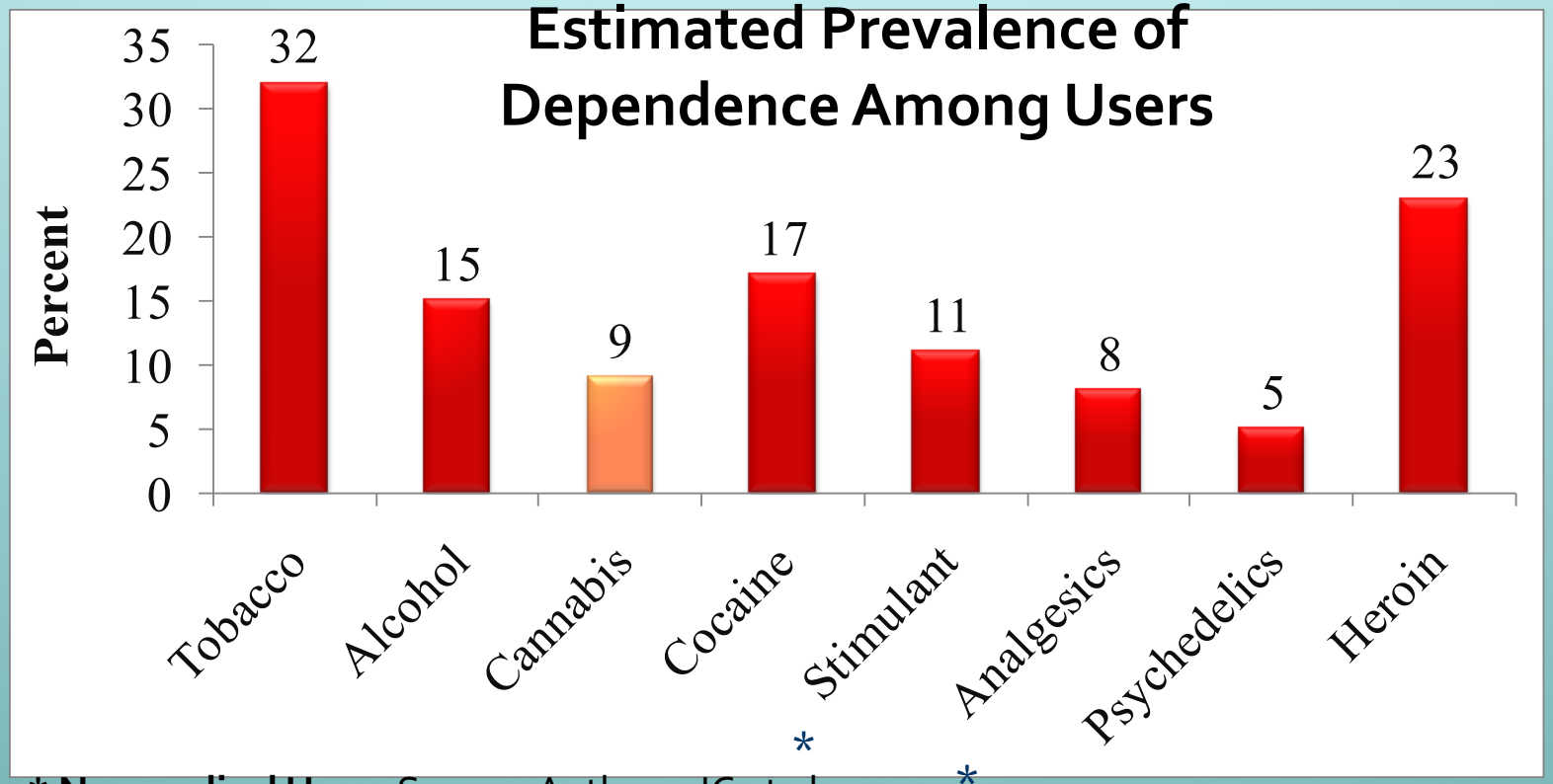
- **PTSD and Alcohol:** Naltrexone and Antabuse, may help both, and cravings; Topamax

Tobacco

- NRT (nicotine replacement)
  - Patch
  - lozenge
- Wellbutrin
- Chantix

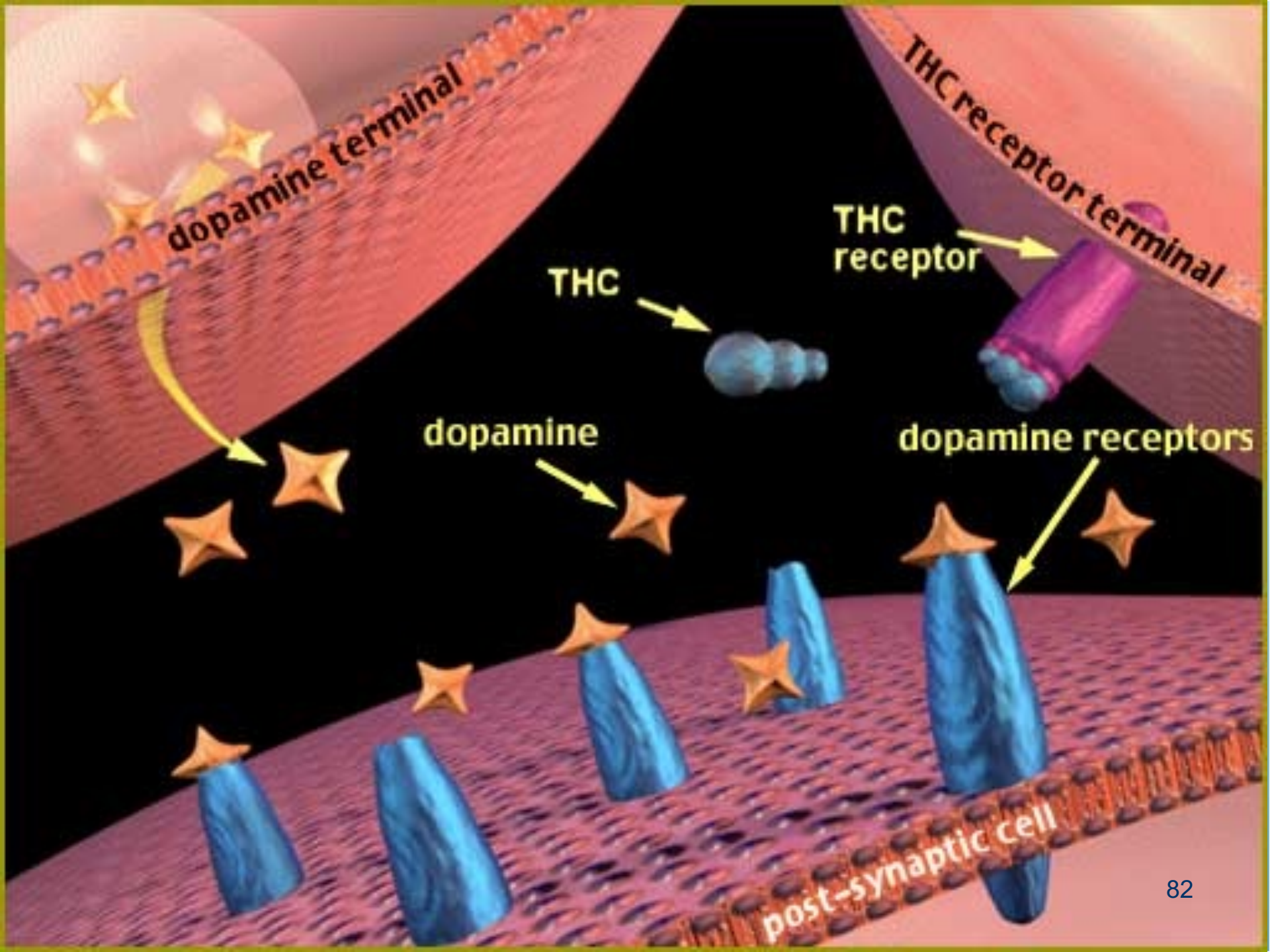
- Stray Cat theory

" Users" who develop " Addiction"



*** Nonmedical Use** Source: Anthony JC et al., 1994

American Psychiatric Association's Diagnostic Manual (DSM) has included marijuana use disorders since 1980.
DSM-5 added Marijuana Withdrawal as a diagnosis.
2014 Mass. General Hospital study confirms withdrawal syndrome.


dopamine terminal
THC receptor terminal
THC
THC receptor
dopamine
dopamine receptors
post-synaptic cell

Opiates

- Agonist (at the cell receptor)
  - Methadone +++
  - Buprenorphine + -
    - Suboxone = Bup + Nar
    - Subutex = Bup only
    - Sublocade Shot (30 day) Bup only
- Antagonist (at the cell receptor)
  - Naltrexone pill and shot (Vivitrol) - - -
  - Narcan shot or nasal spray - - -

Opiates

Naltrexone (Vivitrol) **Complete** opiate blocker, monthly shot. RISK is not the medicine, but if use enough to overcome the block, may overdose, and tolerance is re-set to zero.

Suboxone/ Methadone- Usually not chosen after completing treatment at Pavillon- is an option- ask questions!

Suboxone/ Methadone

Vivitrol


Vivitrol
Vivitrol


Vivitrol
for Opiate
Addiction
Treatment


Full Nasal Kit -
Store in one place

Evzio (autoinjector)

New Rx- Nov. 2015 $ 37.50

Raise of Hands

- 1. Should always use
- 2. In General, usually good plan
- 3. In General, usually hurts more than helps
- 4. Should never use

How to get through surgery…

- **Make** a plan…
- **Share** the plan…
- **Follow** the plan…
- No **secrets**….

Other cool stuff…

- **Tobacco**
  Chantix- nicotine blocker, helps alcohol cravings too. **Wellbutrin**, Nicotine Replacement: patchs, gum, lozenges. *We usually Don't use Chantix with nicotine replacement patch, gum, etc.*
- **Cocaine :** Possibly Helpful: Topamax, NAC, Antabuse, Nuvigil, TCAs, Wellbutrin, Baclofen, Suboxone if opiates Likely NOT helpful: SSRIs, antipsychotics, and many others ; Vaccine under trial.
- **Marijuana**- NAC (n-acetyl cysteine) 1200mg bid , Neurontin
- **Benzodiazepines- Sedatives:** These are powerful GABA receptor agonists; Neurontin, Baclofen and maybe Topamax may help the withdrawal, which can be rather prolonged sometimes.

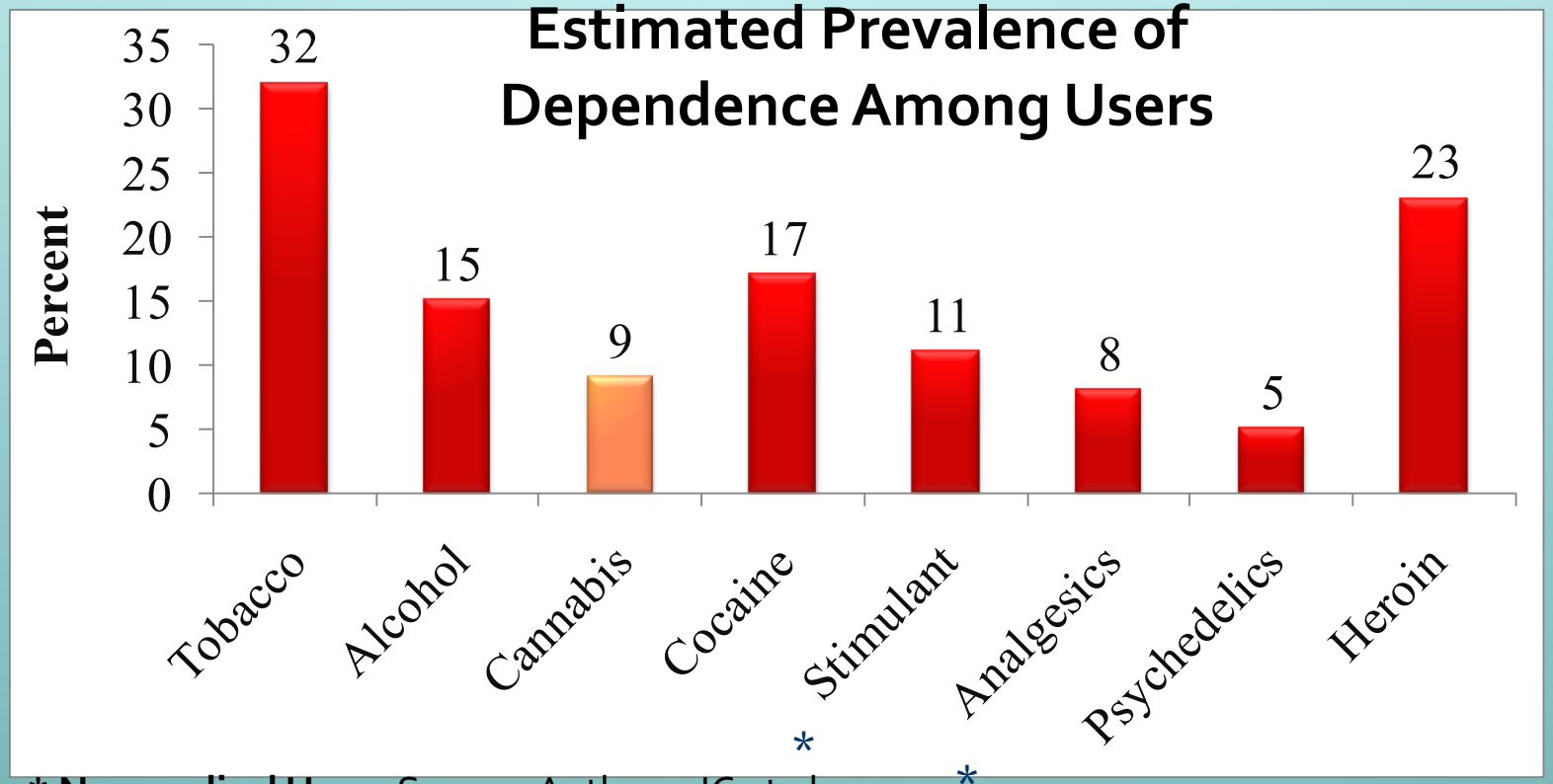
Specific Medications

- **Topamax**- Helpful for many issues, including abstinence with alcohol, cocaine, also great choice to consider for OCD, Tics, Gambling Disorder, Anxiety, Wt loss- Antagonizes Glutamate; GABA a agonist at non-benzo sites on GABA receptors; maybe even reduced smoking as well as alcohol in one study.
- **Neurontin**: GABA and NMDA systems- well known safety, excreted mainly by kidneys ; Quite good for withdrawal; also good for sleep, anxiety, chronic pain, headache prevention; neuralgias or neuropathy; *does even better when combined with Naltrexone for Alcohol.*
- **Baclofen**- Long term known safe, especially with liver problems, helps cravings and less anxiety; is muscle relaxer, so good with chronic pain or sleep problems too.

Specific Medications

- **Chantix**- provides low-level Dopamine activation and blocks nicotine; in smokers and drinkers, reduces both heavy drinking and cigs/ day
- **Odansetron** (Zofran) – the genetic panel for this one is not quite ready for prime-time.
- **Campral**- predictors of better response- Anxiety, physical dependence, Negative Family History, female, older onset alcoholism
- **Oxytocin**- one to watch. Seems to stop withdrawal as well as ativan in one study

" Users" who develop " Addiction"



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