



**ASAM REVIEW COURSE 2023**

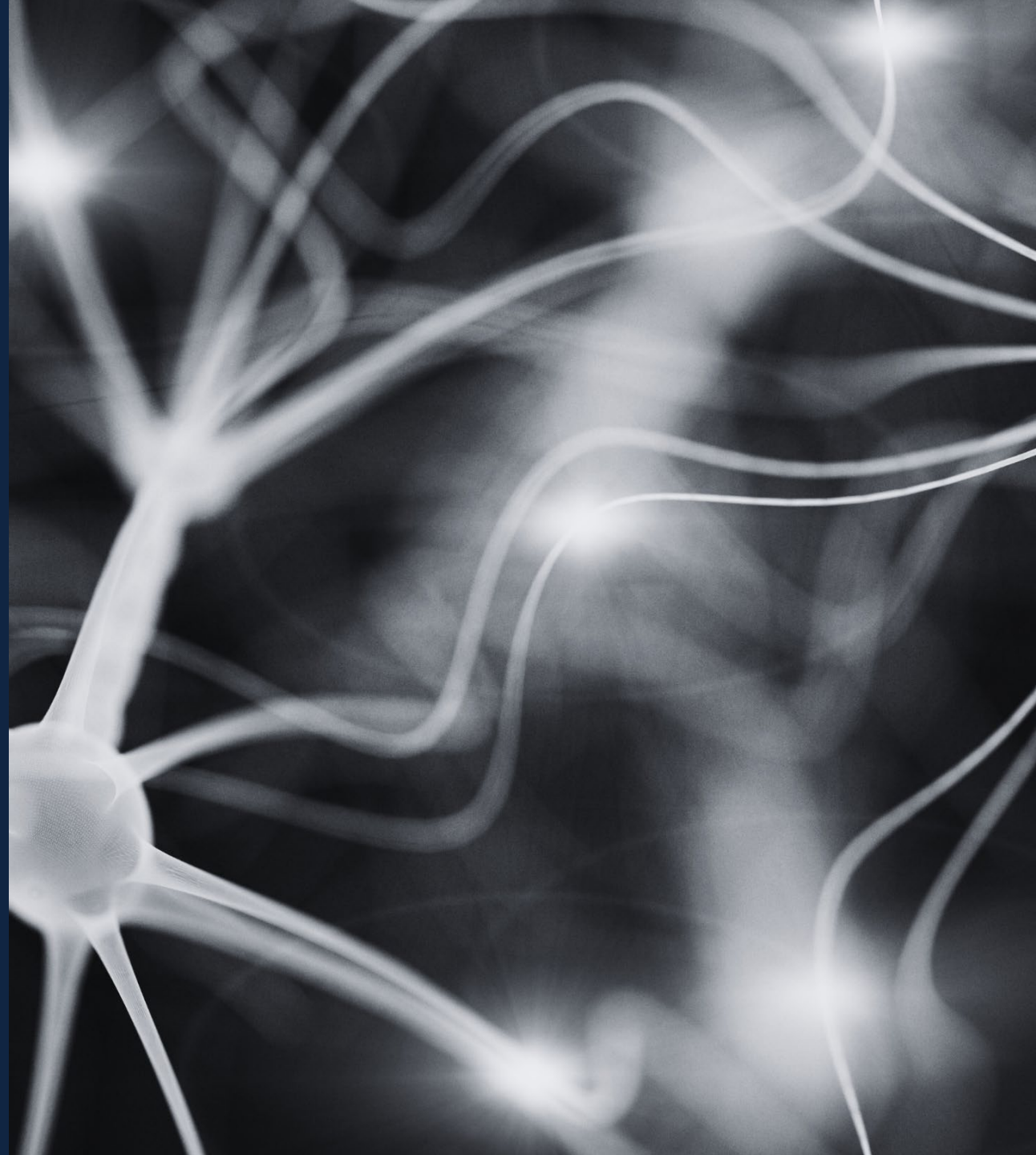
# **Neurobiology of Addiction: Key Concepts and Models**

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# Financial Disclosure

Petros Levounis, MD, MA

- No relevant disclosures

# LEARNING OBJECTIVE

**Identify** key neurotransmitters, brain pathways, and brain structures implicated in addiction and addiction treatment.

# Outline

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1

Neurotransmitters

2

The Fundamental  
Model

3

The New and  
Improved Model

4

Treatments

# Neurotransmitters

## Substance

Alcohol

Amphetamines & Cocaine

Benzodiazepines & GHB

Cannabis

Hallucinogens & MDMA

Nicotine

Opioids

Phencyclidine & Ketamine

## Endogenous Neurotransmitter

GABA / Glutamate\*

Dopamine

GABA

Anandamide

Serotonin

Acetylcholine

Endorphins

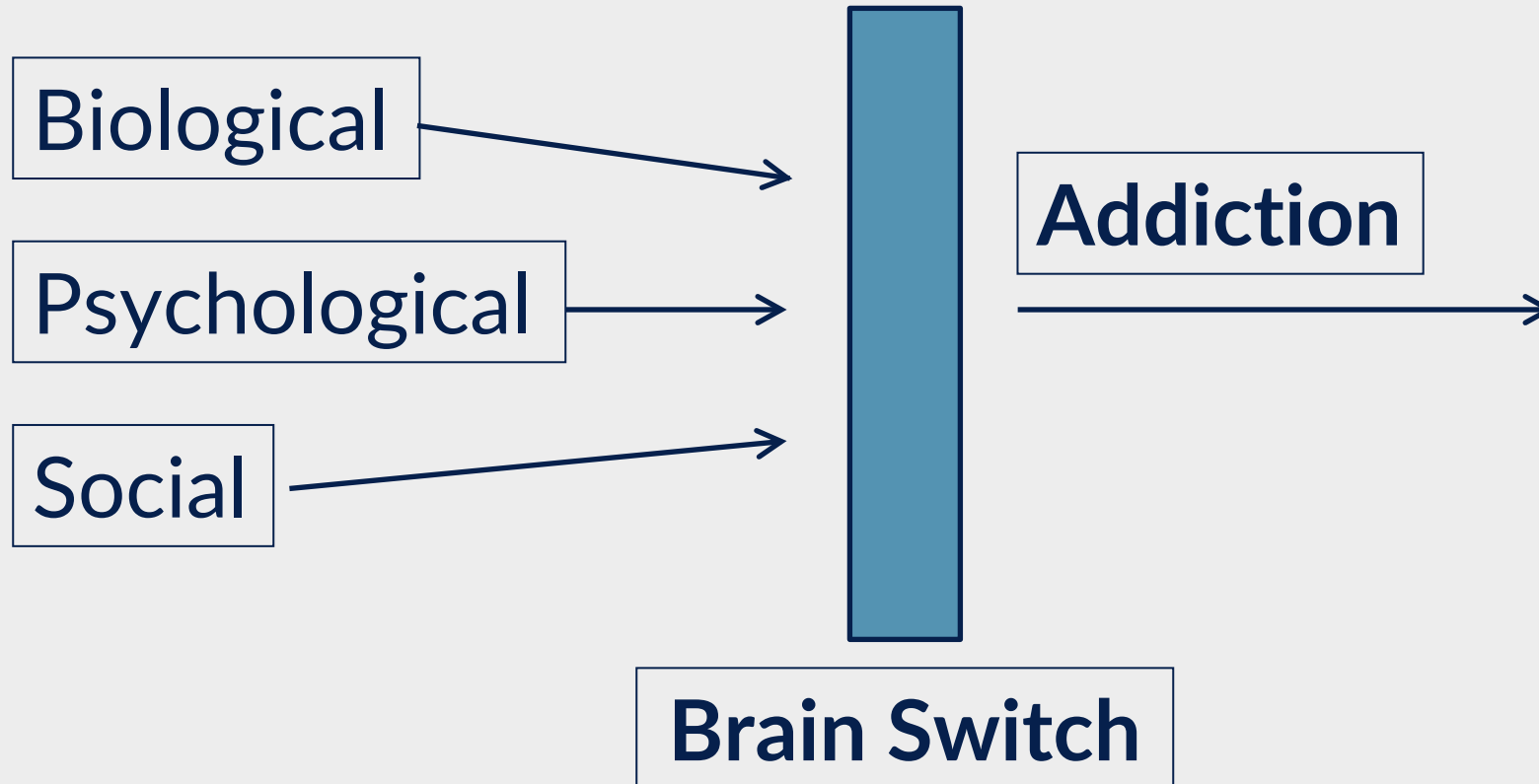
Glutamate\*

\*Drug acts as an antagonist at the NMDA subtype of the glutamate receptor.

# The Fundamental Model



# Addiction: A Biopsychosocial Illness





# The Root Cause of the Disaster

## ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

*To the Editor:* Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients<sup>1</sup> who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,<sup>2</sup> Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

JANE PORTER  
HERSHEL JICK, M.D.  
Boston Collaborative Drug  
Surveillance Program

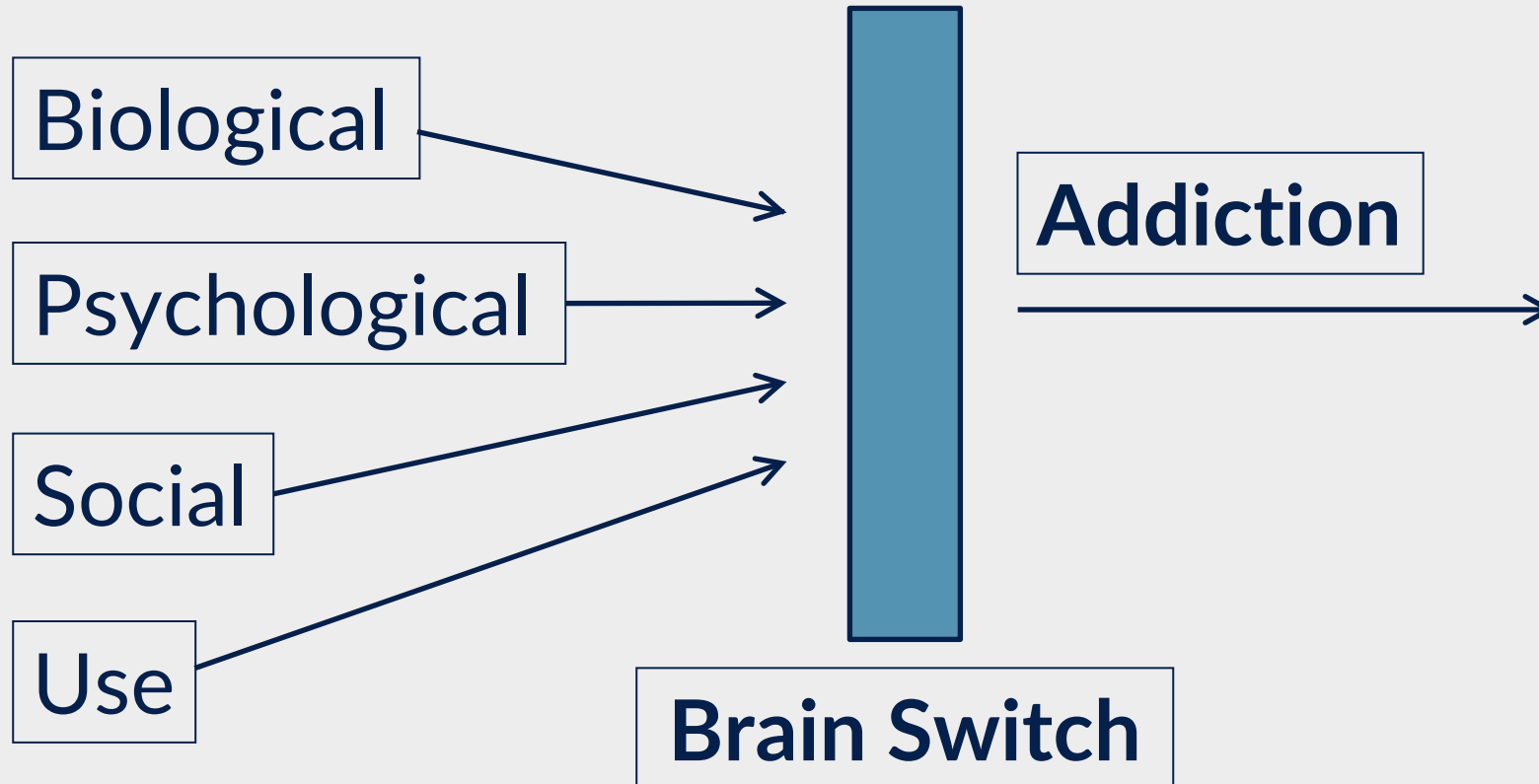
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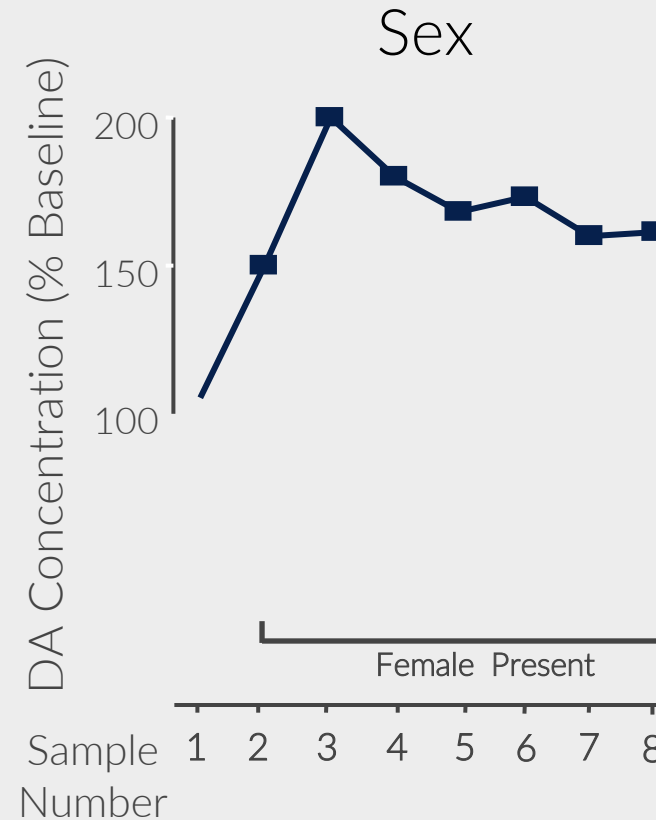
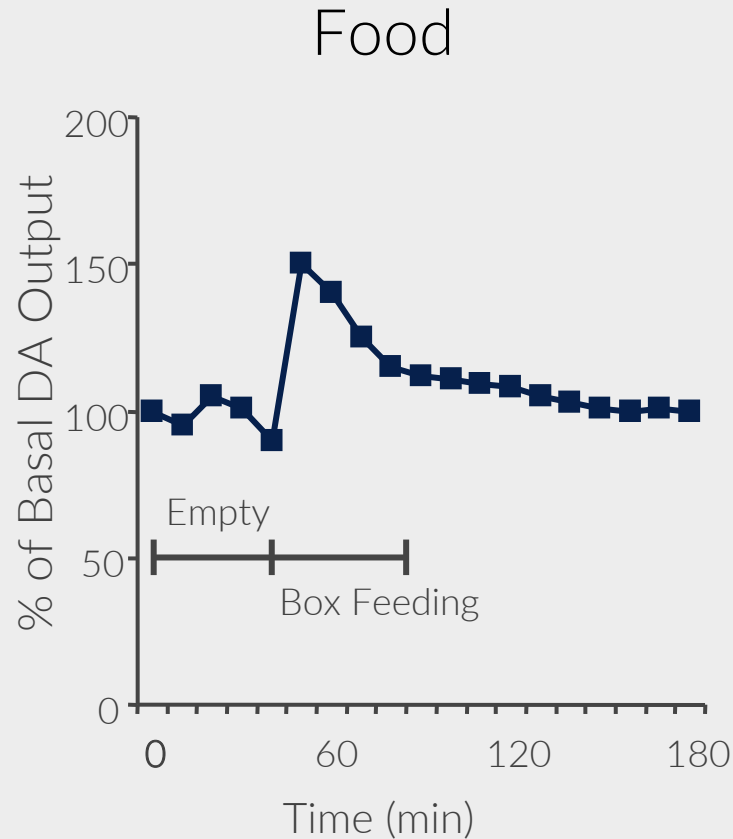
1. Jick H, Miettinen OS, Shapiro S, Lewis GP, Siskind Y, Slone D. Comprehensive drug surveillance. *JAMA*. 1970; 213:1455-60.
2. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. *J Clin Pharmacol*. 1978; 18:180-8.



# Addiction: A Biopsychosocial Illness



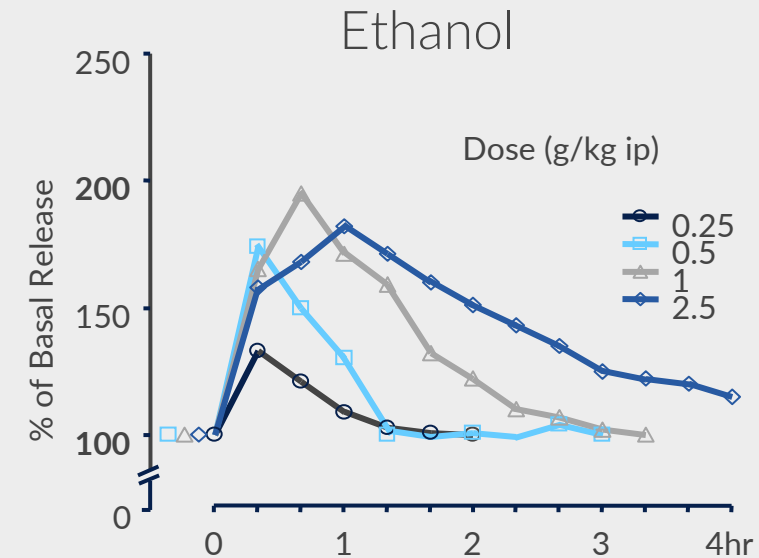
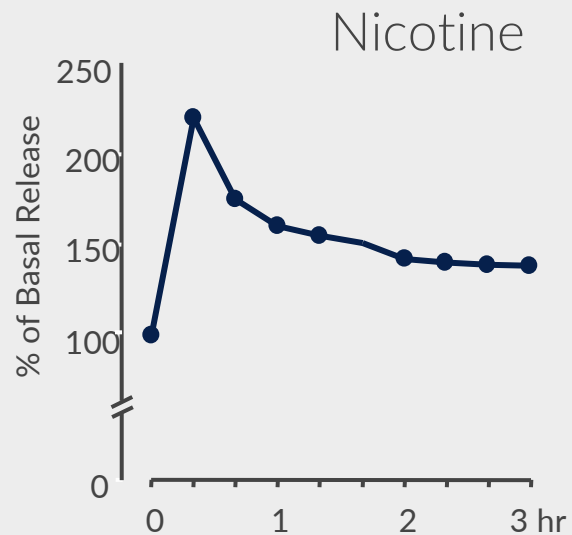
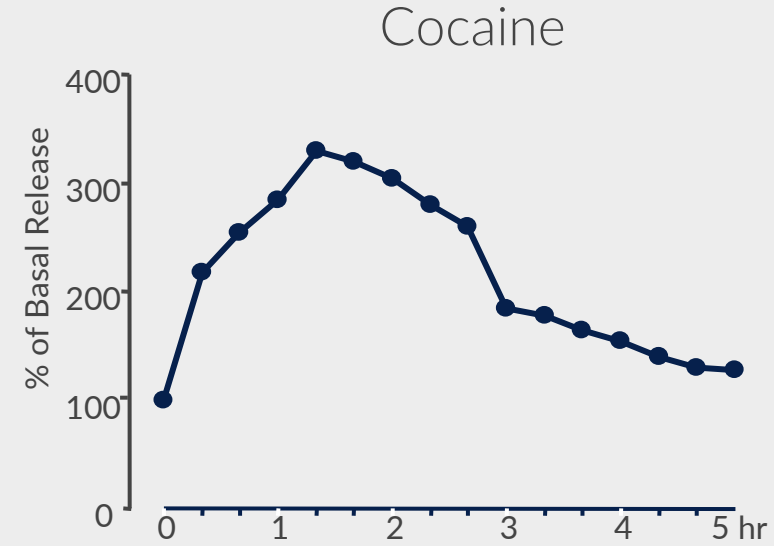
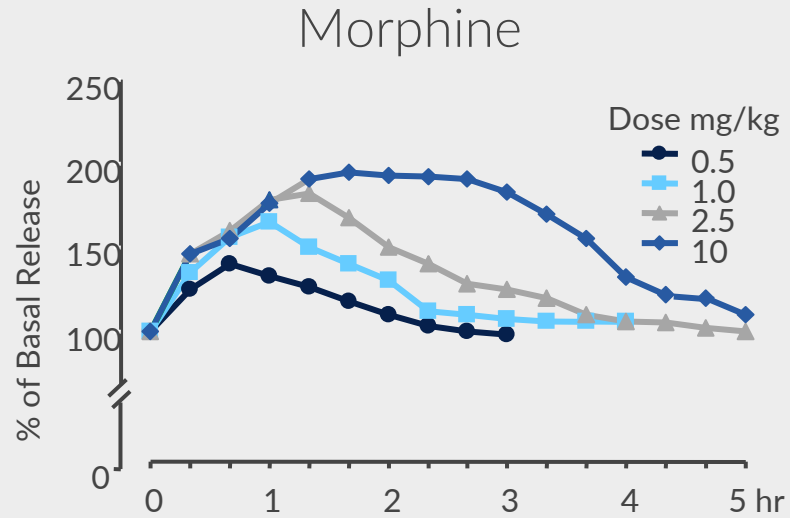
# Basal Ganglia (Nucleus Accumbens) and Binge/Intoxication



*Adapted from: Di Chiara et al, Neuroscience, 1999.*

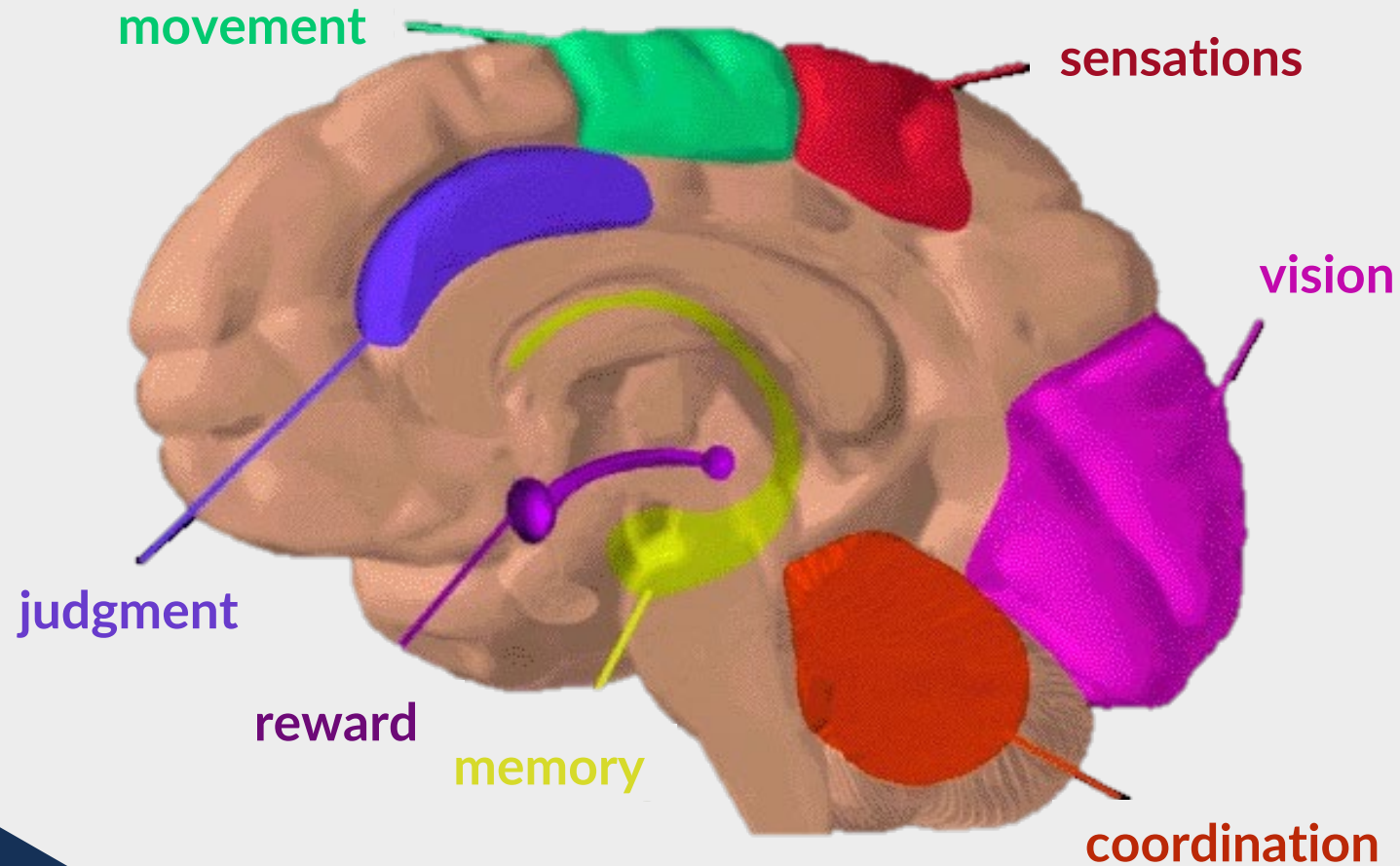
*Adapted from: Fiorino and Phillips, J Neuroscience, 1997.*

# Effects of Drugs on Dopamine Levels



Adapted from: Di Chiara and Imperato, *Proceedings of the National Academy of Sciences USA*, 1988; courtesy of Nora D Volkow, MD.

# Prefrontal Cortex and Executive Function



# The New and Improved Model



# Three Novel Areas

Motivational Circuitry  
(Medial OFC)

Antireward Pathways  
(Extended Amygdala)

Interoception  
(Insula)

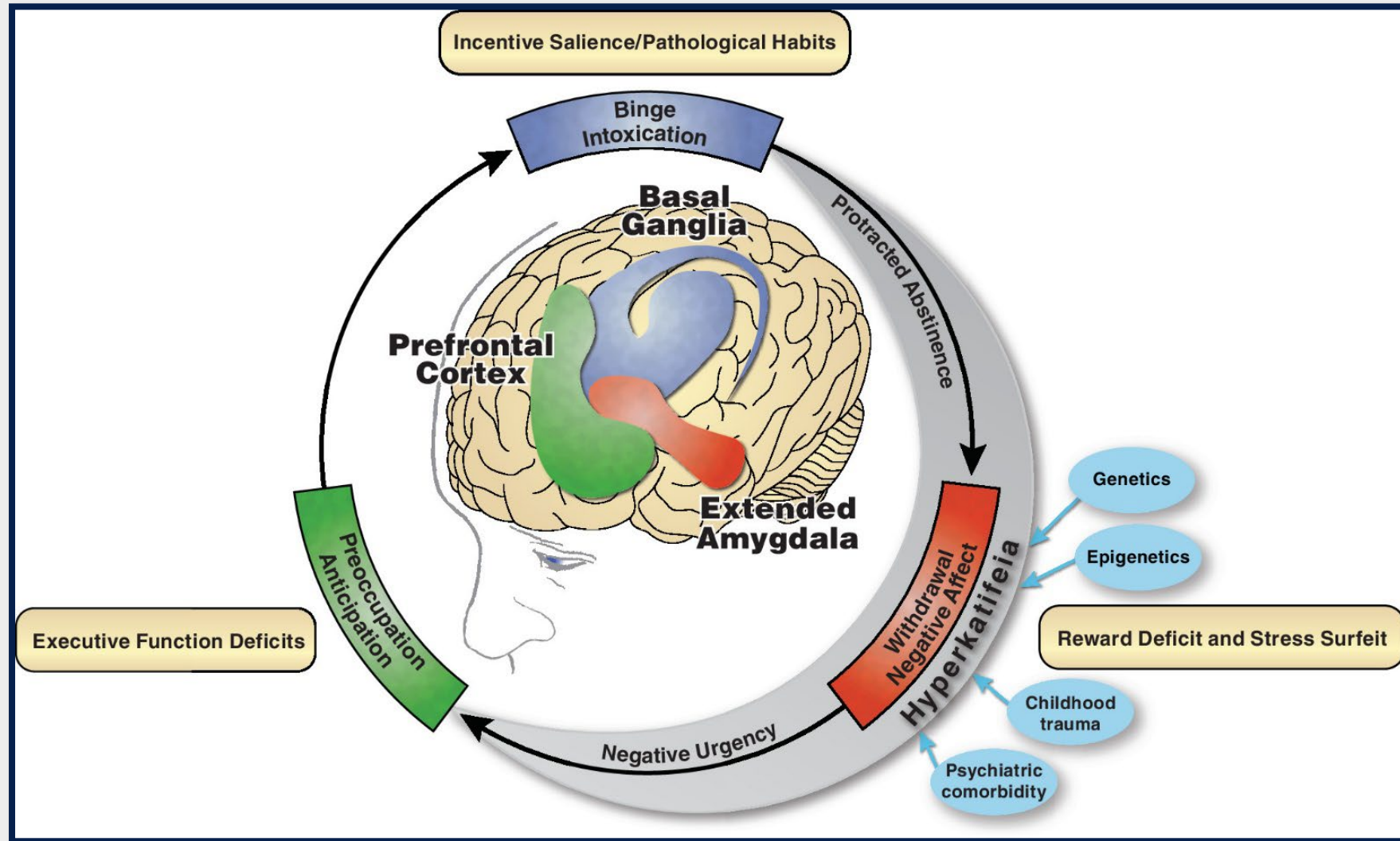
# Medial Orbitofrontal Cortex (OFC) and Preoccupation/Anticipation



*Levounis, Arnaout, and Marienfeld, Motivational Interviewing for Clinical Practice, 2017.*



# Extended Amygdala and Withdrawal/Negative Affect



# Reward Systems

## Game #1

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- A. A sure gain of \$250
- B. 25% chance to gain \$1,000,  
75% chance to gain nothing.



*Adapted from: Tversky and Kahneman, Science, 1981.*

# Reward Systems

## Game #1

---

- A. A sure gain of \$250 **84%**
- B. 25% chance to gain \$1,000,  
75% chance to gain nothing **16%**



*Adapted from: Tversky and Kahneman, Science, 1981.*

# Anti-Reward Systems

## Game #2

---

- A. A sure loss of \$750
- B. 25% chance to lose nothing,  
75% chance to lose \$1,000.



*Adapted from: Tversky and Kahneman, Science, 1981.*

# Anti-Reward Systems

## Game #2

---

- A. A sure loss of \$750 **13%**
- B. 25% chance to lose nothing,  
75% chance to lose \$1,000. **87%**



*Adapted from: Tversky and Kahneman, Science, 1981.*

# Human Nature

People avoid risks to ensure gains.

People take risks to avoid definite losses.

Psychology trumps probability.

# The Ultimate Gatekeeper: Insula

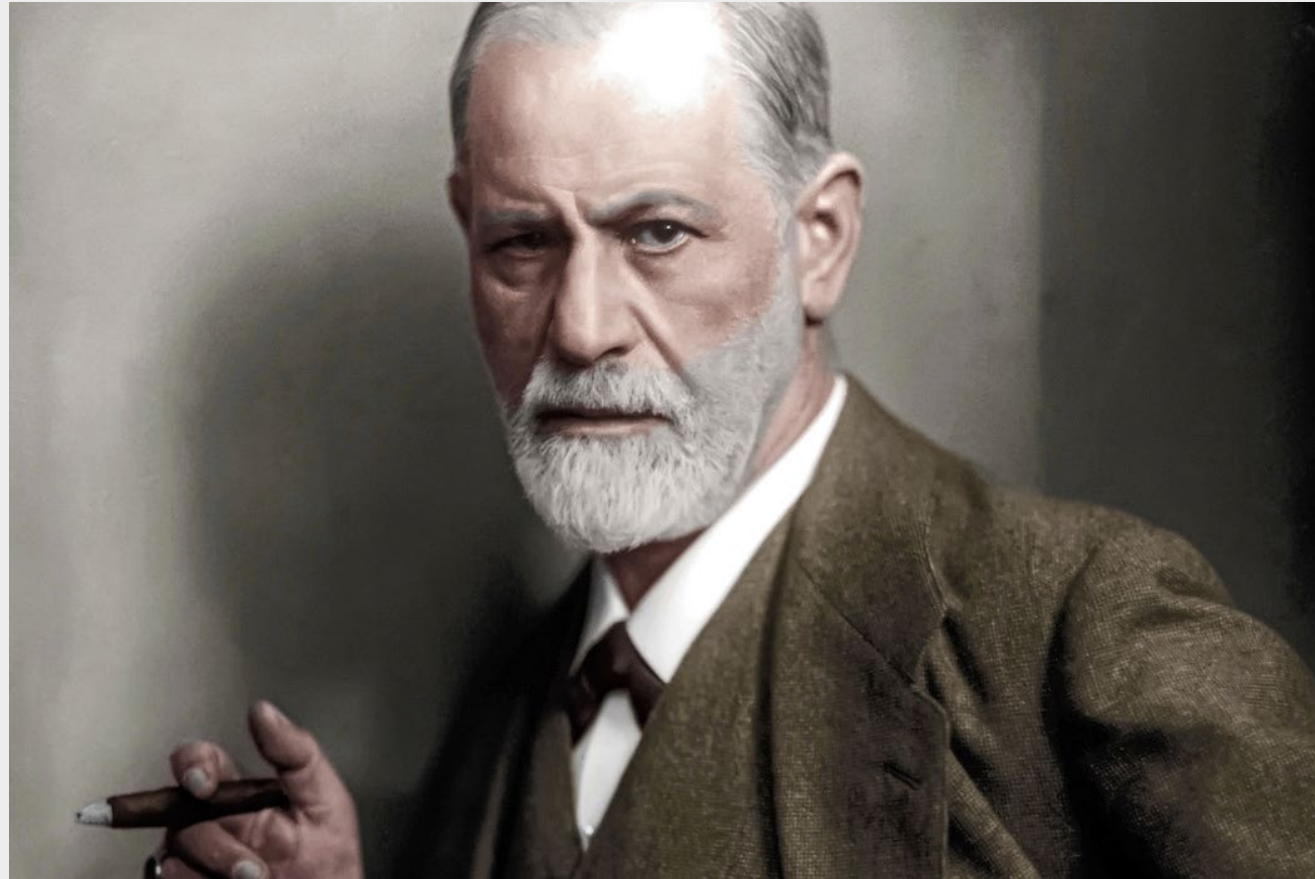


# Treatments





# 1<sup>st</sup> Wave: Psychoanalysis



# 2<sup>nd</sup> Wave: Boot Camps

The prototype, synanon, was founded in California in 1958 to address heroin addiction. The goal was to:

- break down defenses,
- bust through denial, and
- reshape the individual's personality.

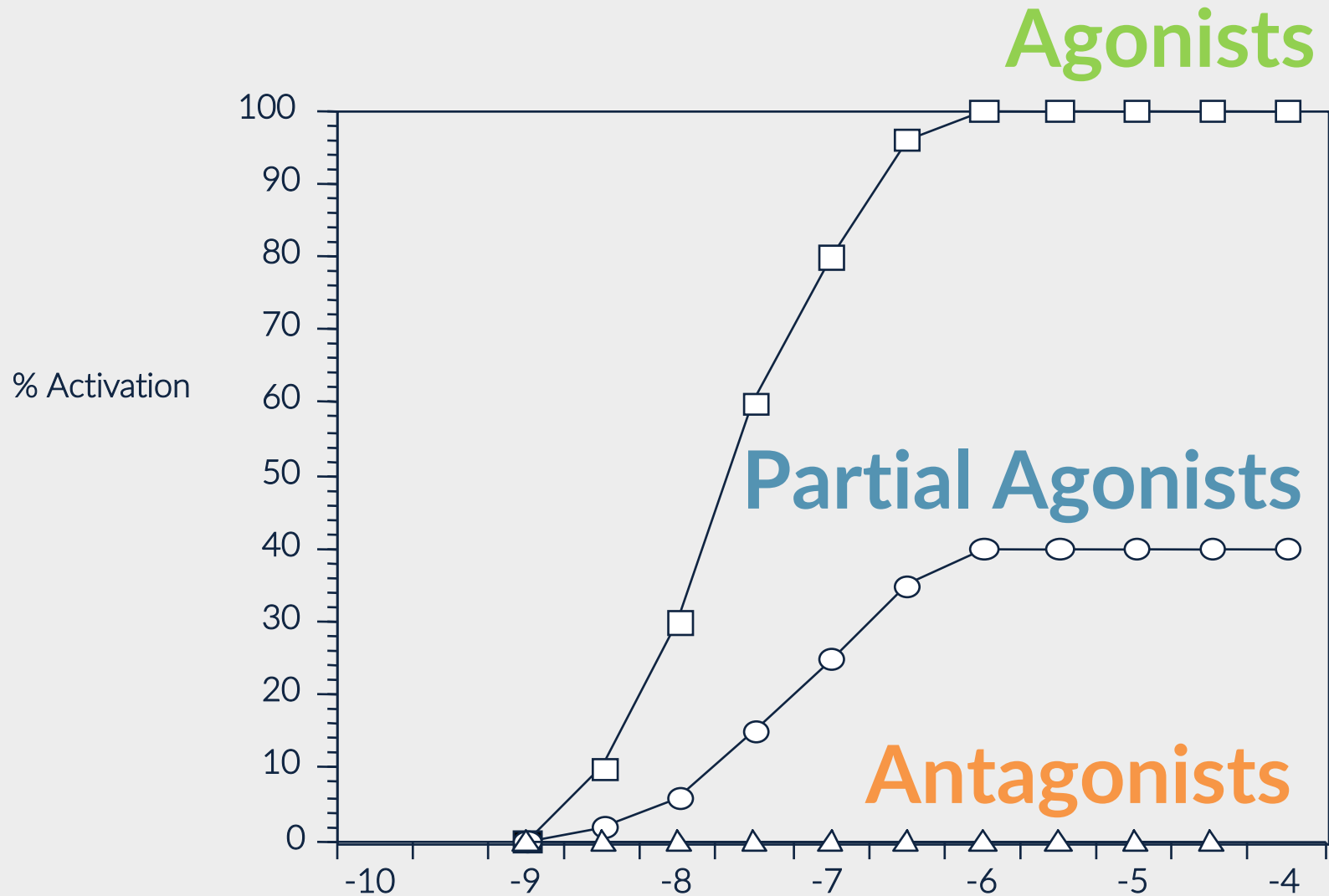
# 3<sup>rd</sup> Wave: Current Treatments

Medications

Mutual Help

Psychotherapy and  
Counseling

# Medications

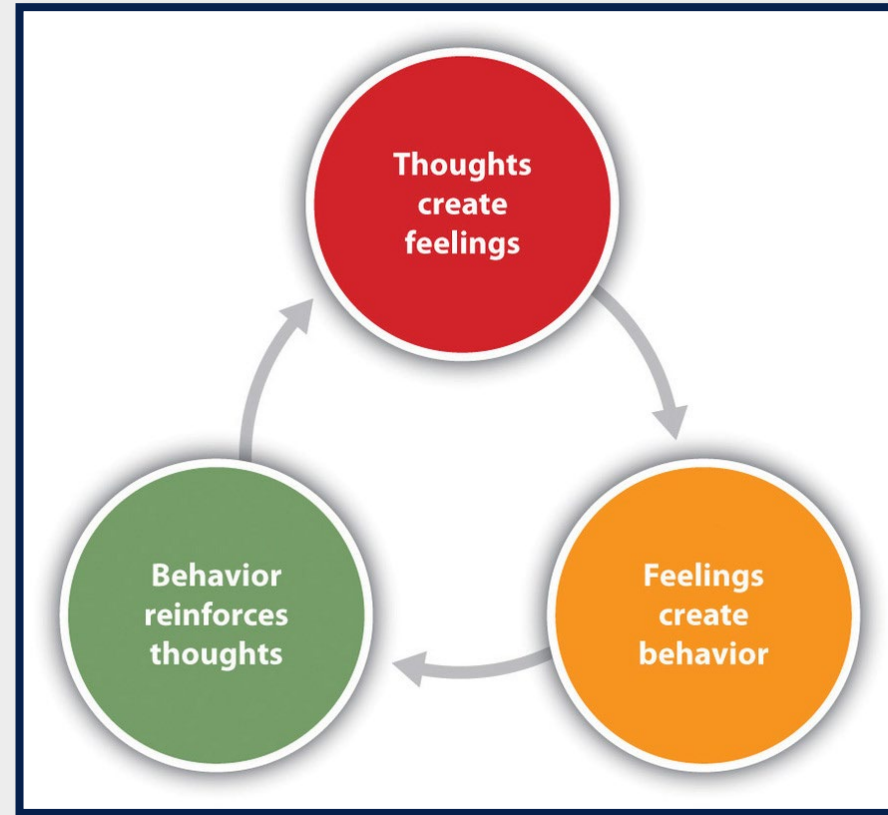


Renner, Levounis, LaRose, Office-Based Buprenorphine Treatment of Opioid Use Disorder, American Psychiatric Association Publishing, 2018.

# Mutual Help

MEDICAL STAFF	PATIENTS	WHAT MEDICAL STAFF THINK PATIENTS THINK
1. Housing	1. Inner Peace	1. Housing
2. Government	2. God	2. Outpatient Treatment
3. Medical Services	3. Medical Services	3. Medical Services
4. Outpatient Treatment	4. AA	4. Job
5. Job	5. Housing	5. Trusting People
6. Community	6. Spirituality	6. AA
7. Trusting People	7. Outpatient Treatment	7. Inner Peace
8. Inner Peace	8. Community	8. Community
9. God	9. Government	9. Government
10. Spirituality	10. Trusting People	10. Spirituality
11. AA	11. Job	11. God

# Cognitive Behavioral Therapy & Motivational Interviewing



# 4<sup>th</sup> Wave: Mindfulness

“Between stimulus and response there is a space. In that space is our power to choose our response. In our response lie our growth and our freedom.”

Victor E. Frankl



Frankl, *Man's Search for Meaning*, 1959.  
Zerbo, Schlechter, Desai, and Levounis, *Becoming Mindful*, 2017.

## Report Your Status

Have you used today?  Yes  No

How strong is your craving right now?

6

What triggers are affecting this craving?

HUNGRY  n/a

ANGRY  n/a

LONELY  n/a

TIRED  n/a

SOCIAL PRESSURE  n/a

PAIN  n/a

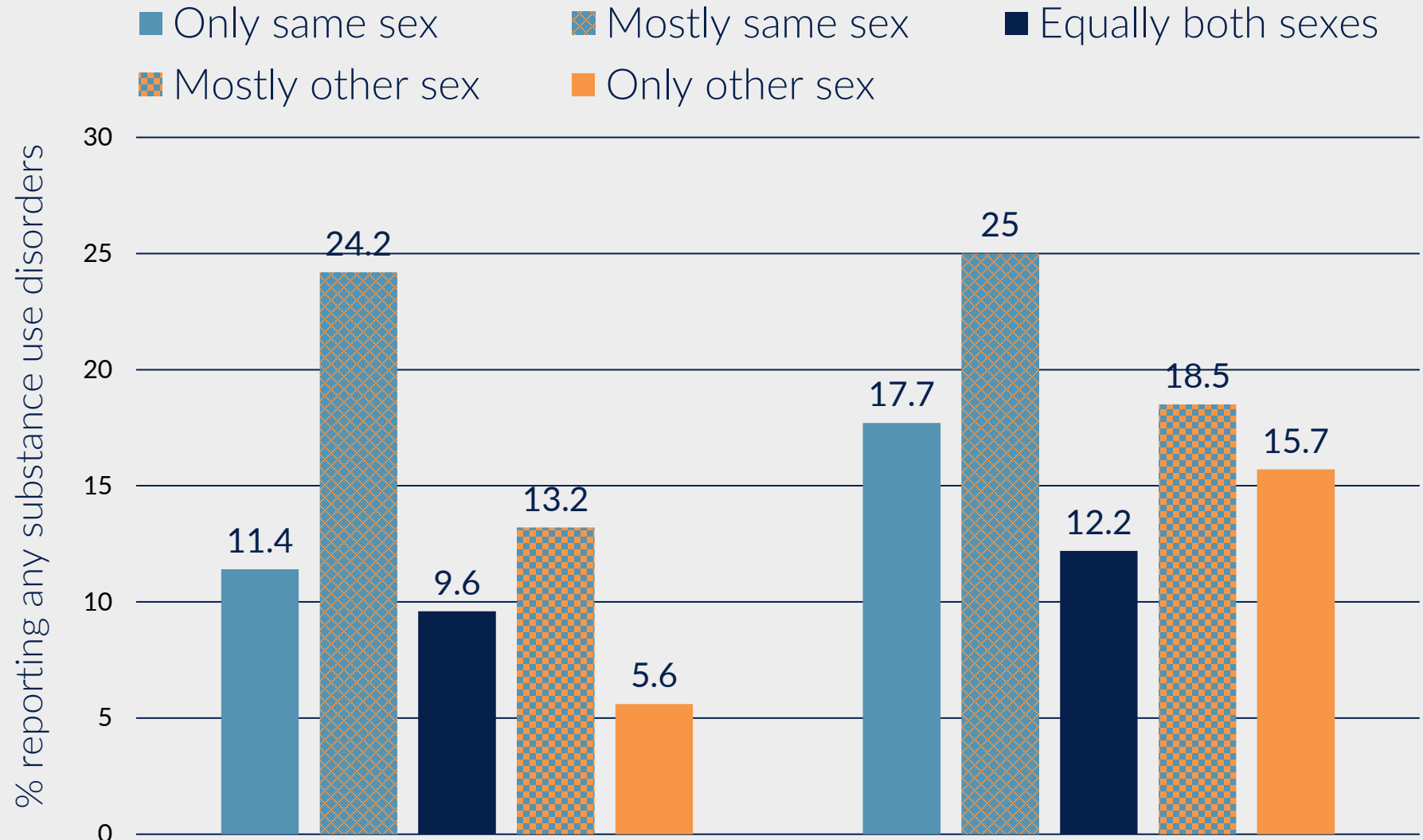
OTHER  n/a

SUBMIT

# Digital Therapeutics (CBT Apps)



# And Back to Psychodynamics . . .



McCabe, *Addiction*, 2009, Courtesy of Sean E. McCabe, PhD.

Levounis and Yarbrough, *LGBTQ Mental Health*, 2020.

# Neurotransmitters



## Substance

Alcohol

Amphetamines & Cocaine

Benzodiazepines & GHB

Cannabis

Hallucinogens & MDMA

Nicotine

Opioids

Phencyclidine & Ketamine

## Endogenous Neurotransmitter

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Acetylcholine

Endorphins

Glutamate\*

\*Drug acts as an antagonist at the NMDA subtype of the glutamate receptor.

# In Summary

Addiction is the war between the hijacked pleasure and reward pathways of the basal ganglia and the executive function of the prefrontal cortex.

Motivational circuitry, the anti-reward pathways, and interoception complete the 2023 model of addiction.

Pharmacological Treatments:  
agonists, antagonists,  
and partial agonists.

Psychosocial Treatments:  
mutual help, CBT,  
motivational interviewing,  
and mindfulness.

Know your  
neurotransmitters!

# Knowledge Check



At her 10th college reunion, Anna bumps into Marie, her old roommate from their junior year abroad. “Anna!” Marie exclaims. “Do you remember sipping wine and snacking on brie and crackers at the café by the Seine? And that waiter? Jacques... Mon Dieu.” Anna has been sober for several years but suddenly feels an intense craving for alcohol. What part of Anna’s brain, most likely, got activated by Jacques, the hot waiter, just now?

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- A. Medial Orbito-Frontal Cortex (OFC)
- B. Lateral Orbito-Frontal Cortex (OFC)
- C. Hippocampus and Extended Amygdala
- D. Insula

Robert has been addicted to Candy Crush Saga since high school. He must also study for the ABPM boards on Friday. It's now 10 pm on Thursday evening, and he hasn't started looking at the lectures. "Hmmm..." he thinks to himself. "If I get some Swedish fish to grab some candies, I can reach Lollipop Meadow by midnight, which will give me such a sense of accomplishment that I will have a clear head tomorrow to tackle any question. Perfect plan, to Lollipop Meadow it is!" What part of Robert's brain was activated by Lollipop Meadow?

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- A. Medial Orbito-Frontal Cortex (OFC)
- B. Lateral Orbito-Frontal Cortex (OFC)
- C. Hippocampus and Extended Amygdala
- D. Insula

Which part of the brain is responsible for integrating, giving meaning, and helping people understand sensations such as hot, cold, hungry, full, and thirsty—along with cravings for a drug such as tobacco?

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- A. Medial Orbito-Frontal Cortex (OFC)
- B. Lateral Orbito-Frontal Cortex (OFC)
- C. Hippocampus and Extended Amygdala
- D. Insula




# Thank You





# Get in Touch

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