

The Science of Opioid Use Disorder

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Disclosure statement

I have no relevant financial interests to disclose.

Learning Objectives

- After participating in this activity, practitioners should:
 1. Understand how the reward circuit functions in opioid use disorder, including major neurotransmitter systems and their associated structures.
 2. Be able to explain the difference between tolerance, withdrawal, dependence and addiction in terms patients and families will understand.
 3. Be able to apply evidence-based approaches in diagnosis, treatment and referral for opioid use disorder.

Outline

- Review of addiction
- Neuroanatomy of the reward circuit
- Two models of cognitive impairment
- Research on executive functioning in addiction
- Evidence-based treatment for OUD

A brief review of addiction

- Tolerance
- Withdrawal
- Dependence

- And a little something more

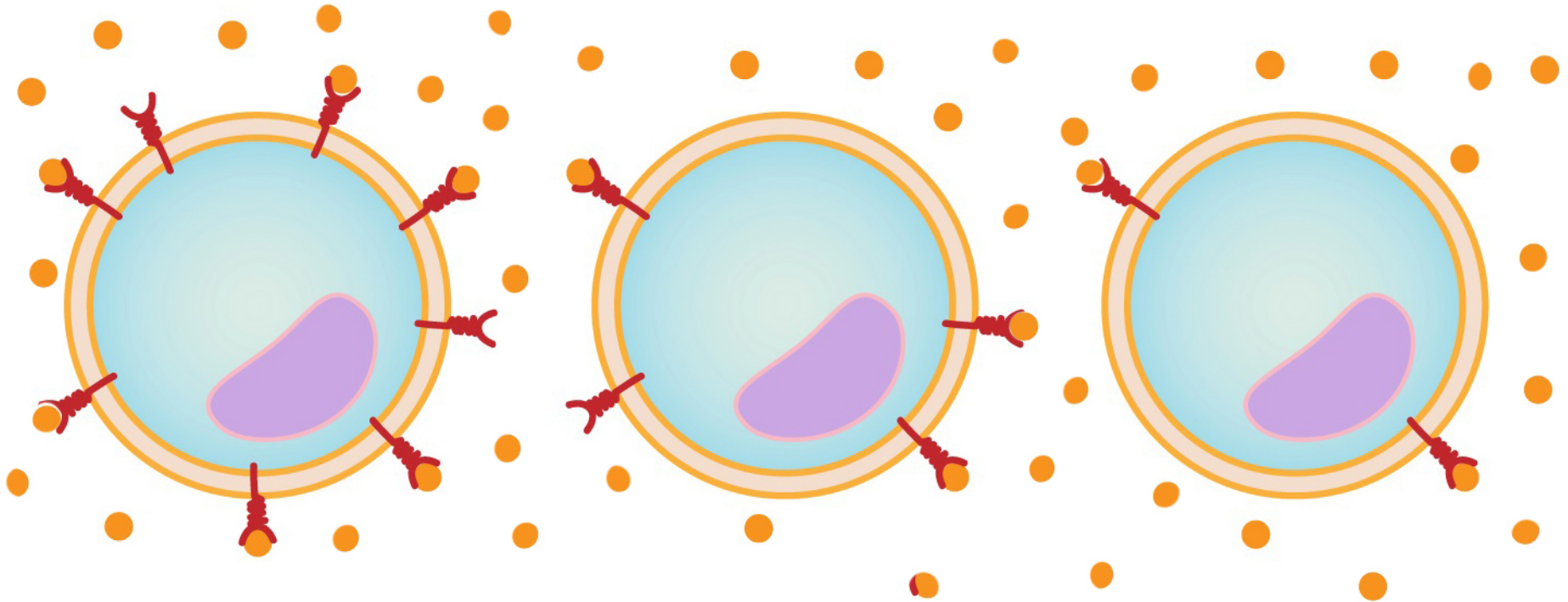
Tolerance

- Tolerance is the need to take more of a drug to get the same effect.

What Causes Tolerance?

- The brain makes adjustments so it functions normally when the drug is present, and abnormally when it's not.
- Think of tolerance like driving with the brakes on—you have to push harder on the gas to get up to highway speed.
- The harder you push on the gas, the harder you have to push on the brake to stay under the speed limit.

downregulation



time



Withdrawal

is what happens when the gas pedal is all the way to the floor – and you suddenly take your other foot off the brake.



Withdrawal

COWS

<u>Symptoms</u>	<u>Scores</u>	<u>Examples</u>
Resting pulse rate	0-4	0=80 or less; 1= 81-100; 2=101-120; 4=120 or greater
Sweating	0-4	0=none; 4=sweat streaming from face
Restlessness	0-5	0=sits still; 5=unable to sit still (even for a few seconds)
Pupil size	0-5	0=normal; 5=dilated (only iris rim visible)
Bone or joint aches	0-4	0=none; 4=severe discomfort
Runny nose or tearing	0-4	0=none; 4=constant
GI upset	0-5	0=none; 5=multiple episodes of vomiting or diarrhea
Tremor	0-4	0=none; 4=gross tremor

Dependence

Tolerance + Withdrawal

Dependence

Kosten TR. The neurobiology of opioid dependence: implications for treatment. Sci Pract Perspect. 2002 Jul;1(1):13-20

Is dependence the same as addiction?



Is dependence the same as addiction?

No.

Think clonidine: Nobody craves blood pressure medicine.

Think venlafaxine: Nobody builds a criminal lifestyle around antidepressants.

A little something more

Addiction: a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences.

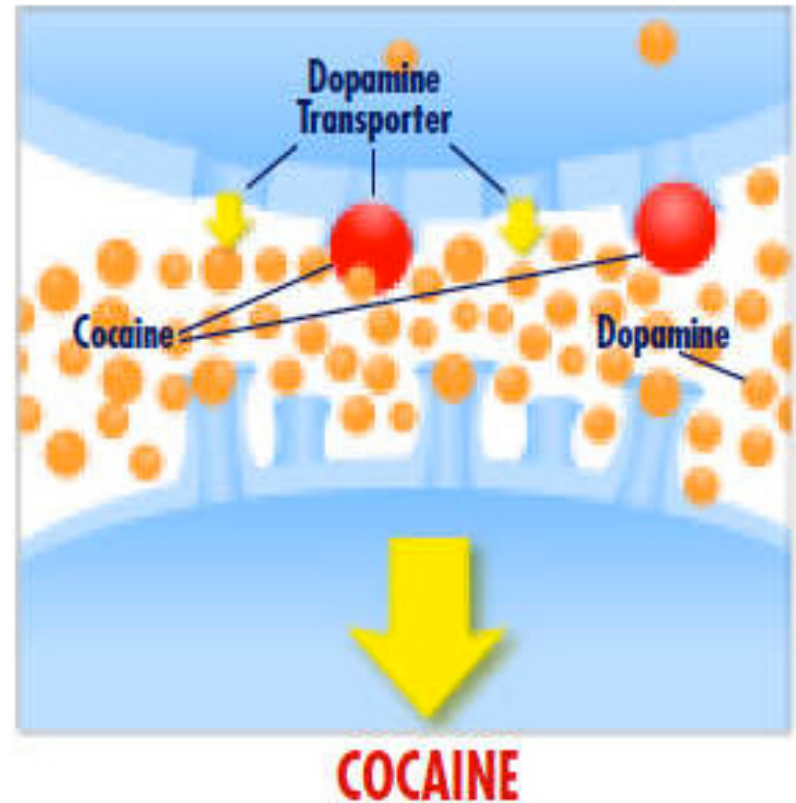
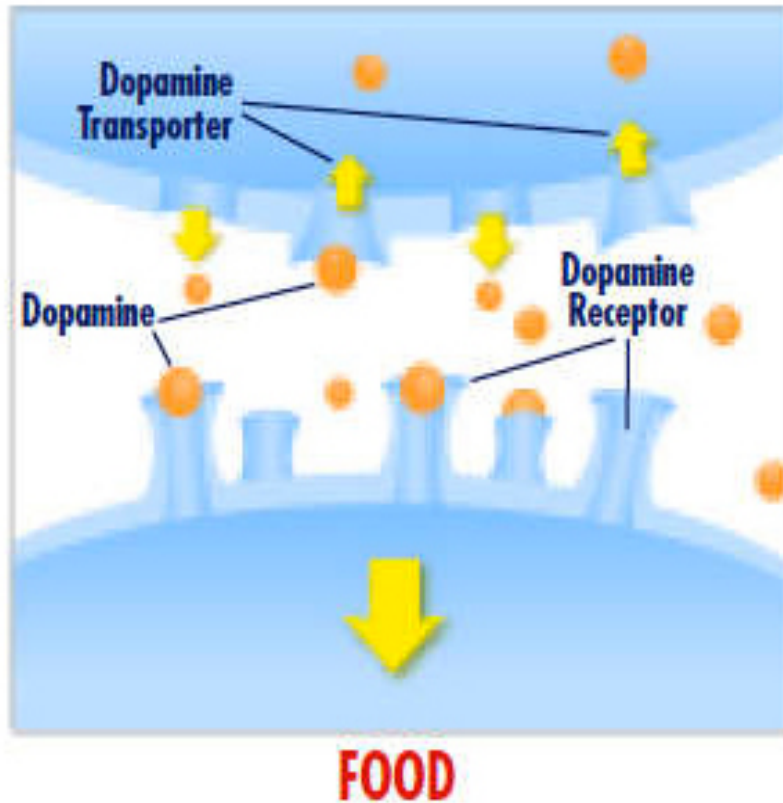
National Institute on Drug Abuse: www.drugabuse.gov

Models of addiction

- Moral—weak character
- Criminal—the war on drugs
- Recovery—a personal journey
- Social—psychology of addiction
- **Medical—addiction as disease**

Scientific basis increases moving down this list.

How does addiction get started?



Dopamine increases in response to natural rewards such as food. When drugs are taken, dopamine increases are exaggerated, and communication is altered.

<https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drugs-brain>

What sustains addiction?

- Conditioning based on memories of intense pleasure

Kosten TR. The neurobiology of opioid dependence: implications for treatment. Sci Pract Perspect. 2002 Jul;1(1):13-20



Think Pavlov, not schoolteachers.

What sustains addiction?

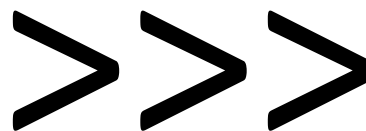
- *Salience* of drugs eclipses other stimuli, including natural consequences

Kosten TR. The neurobiology of opioid dependence: implications for treatment. Sci Pract Perspect. 2002 Jul;1(1):13-20

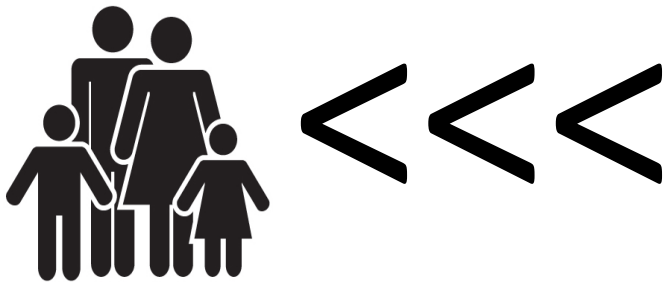


Photo copyright Suresh Eswaren. No changes made. <https://creativecommons.org/licenses/by-nc-nd/4.0/legalcode>

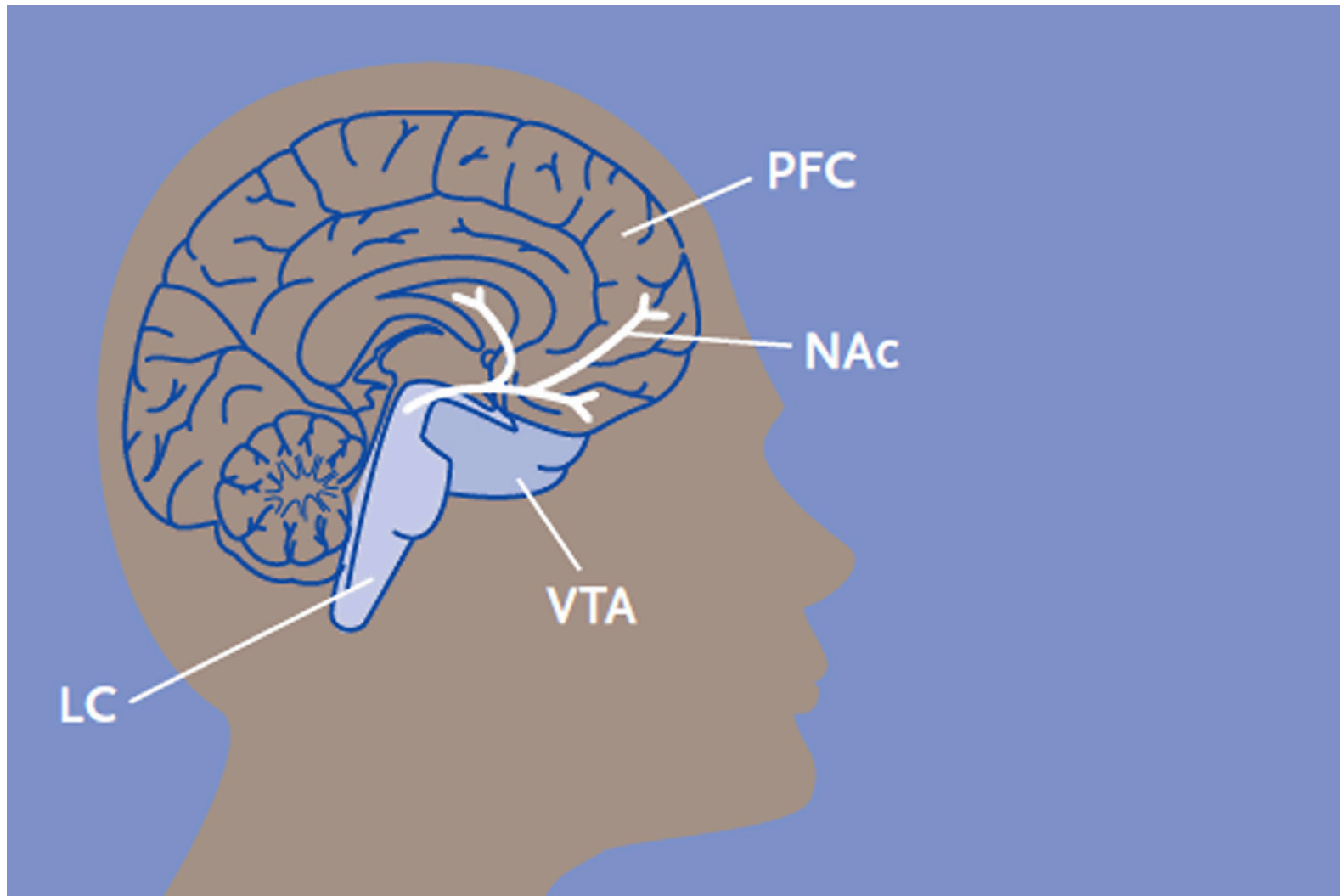
Salience in the healthy brain



Salience in the addicted brain



The reward circuit



Kosten TR. The neurobiology of opioid dependence: implications for treatment. Sci Pract Perspect. 2002 Jul;1(1):13-20

The reward circuit

- Prefrontal cortex: the seat of will
 - Glutamate: inhibition (though excitatory NT)
- Nucleus accumbens: the seat of pleasure
 - Dopamine: desire
 - Serotonin: satiety and inhibition

The reward circuit

- Ventral tegmental area: the seat of reward
 - Dopamine: pleasure
- Locus coeruleus: the seat of arousal
 - Norepinephrine: sympathetic response

Biomedical models of addiction

- **Changed set point**

Opioid use causes permanent structural and chemical changes that create a new biological and behavioral baseline for the addict.



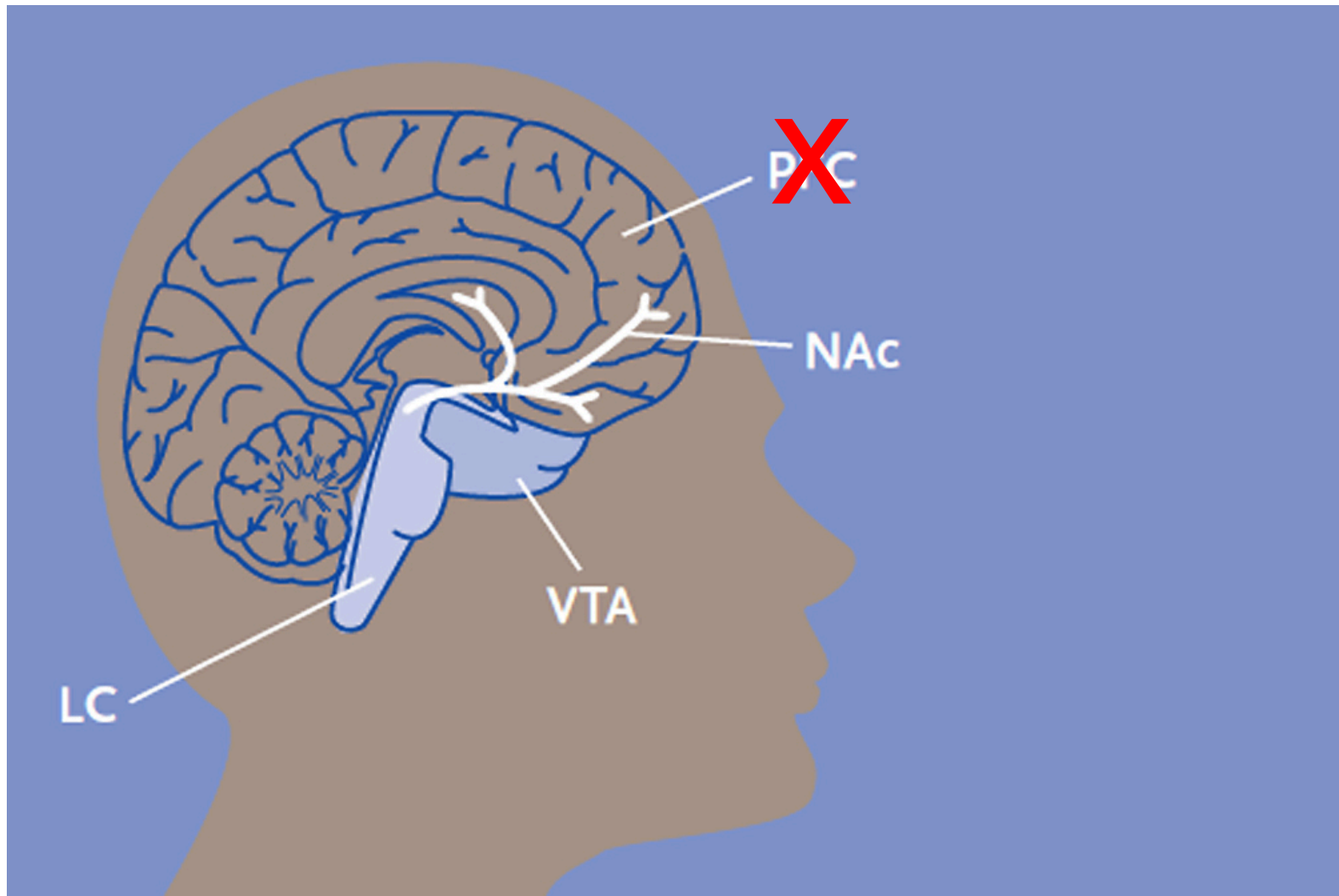
Biomedical models of addiction

- **Cognitive deficits**

Opioid use degrades prefrontal cortical inhibition of the drive to use, *undermining the addict's will* at a neurological level.

Kosten TR. The neurobiology of opioid dependence: implications for treatment. Sci Pract Perspect. 2002 Jul;1(1):13-20

Cognitive deficit model



Kosten TR. The neurobiology of opioid dependence: implications for treatment. Sci Pract Perspect. 2002 Jul;1(1):13-20

Domains of impairment

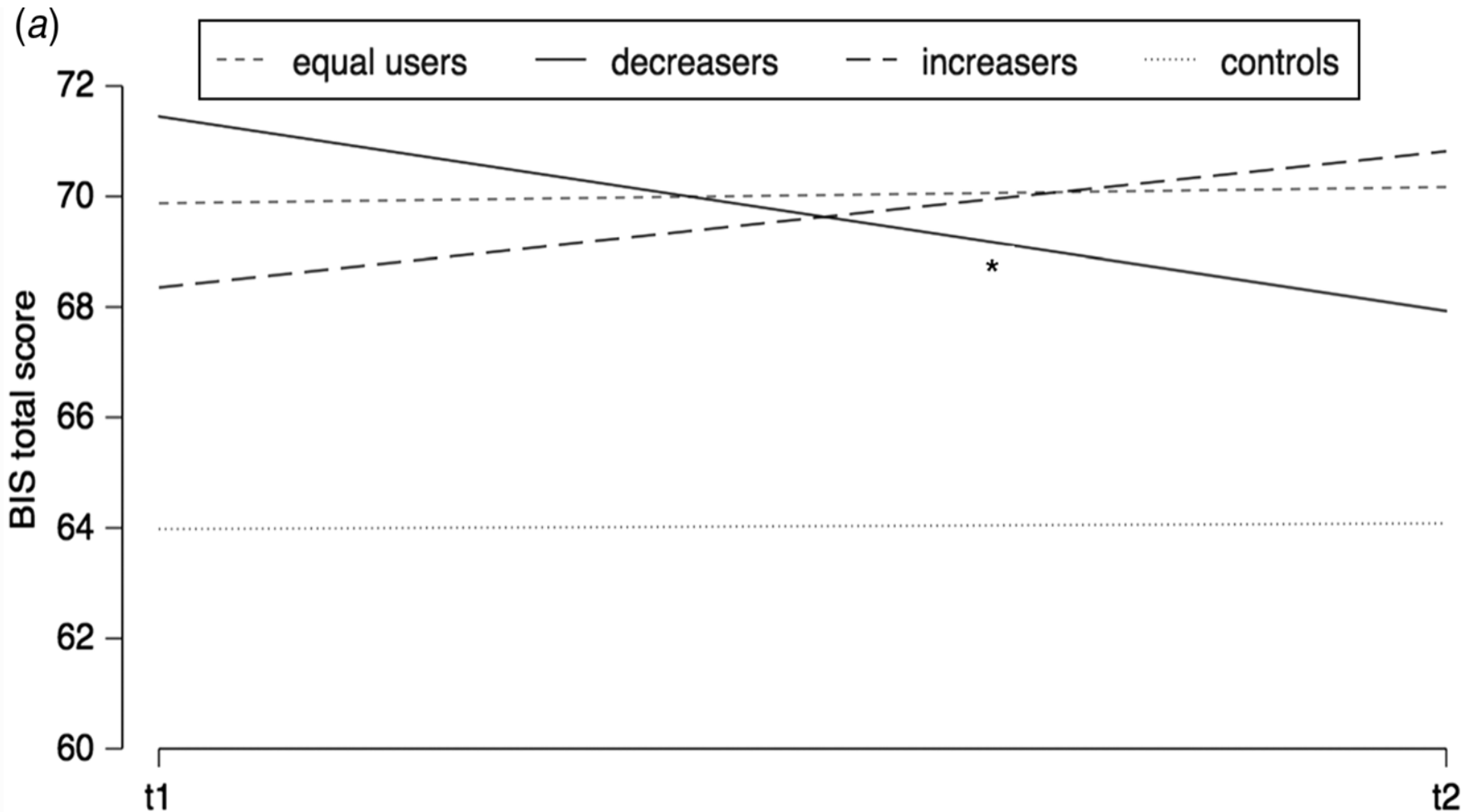
- Impulsivity
I'm not going to think too much before doing this.
- Reward hypersensitivity
I want to get high more than anything else.
- Harm hyposensitivity
I forgot how bad it felt the last time I went to jail.
- Increased risk-taking
My probation officer probably won't find out.
- Outcome myopia (e.g. temporal discounting)
I might go to jail again, but not right now.

Studies of decision-making

- Self-report
- Behavioral tasks
- Computational modeling
- Neuroimaging

Ekhtiari et al. Aberrant decision-making and drug addiction. Current opinion in behavioral sciences. 2017, 13:25-33

Self-reported impulsiveness in cocaine users



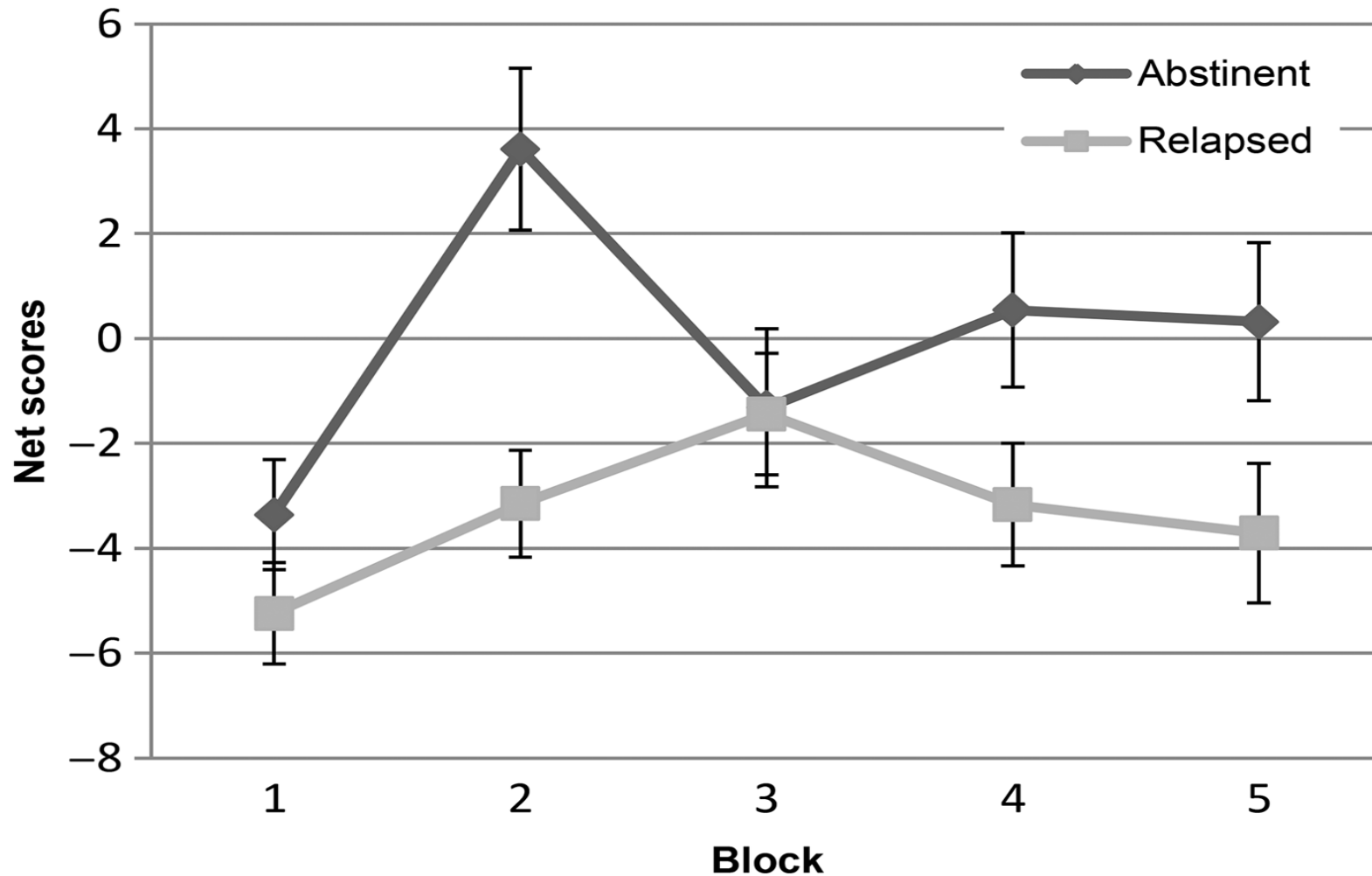
Hulka et al. Changes in cocaine consumption are associated with fluctuations in self-reported impulsivity and gambling decision-making. Psychol Med. 2015 Oct;45(14):3097-110.

Iowa Gambling Task



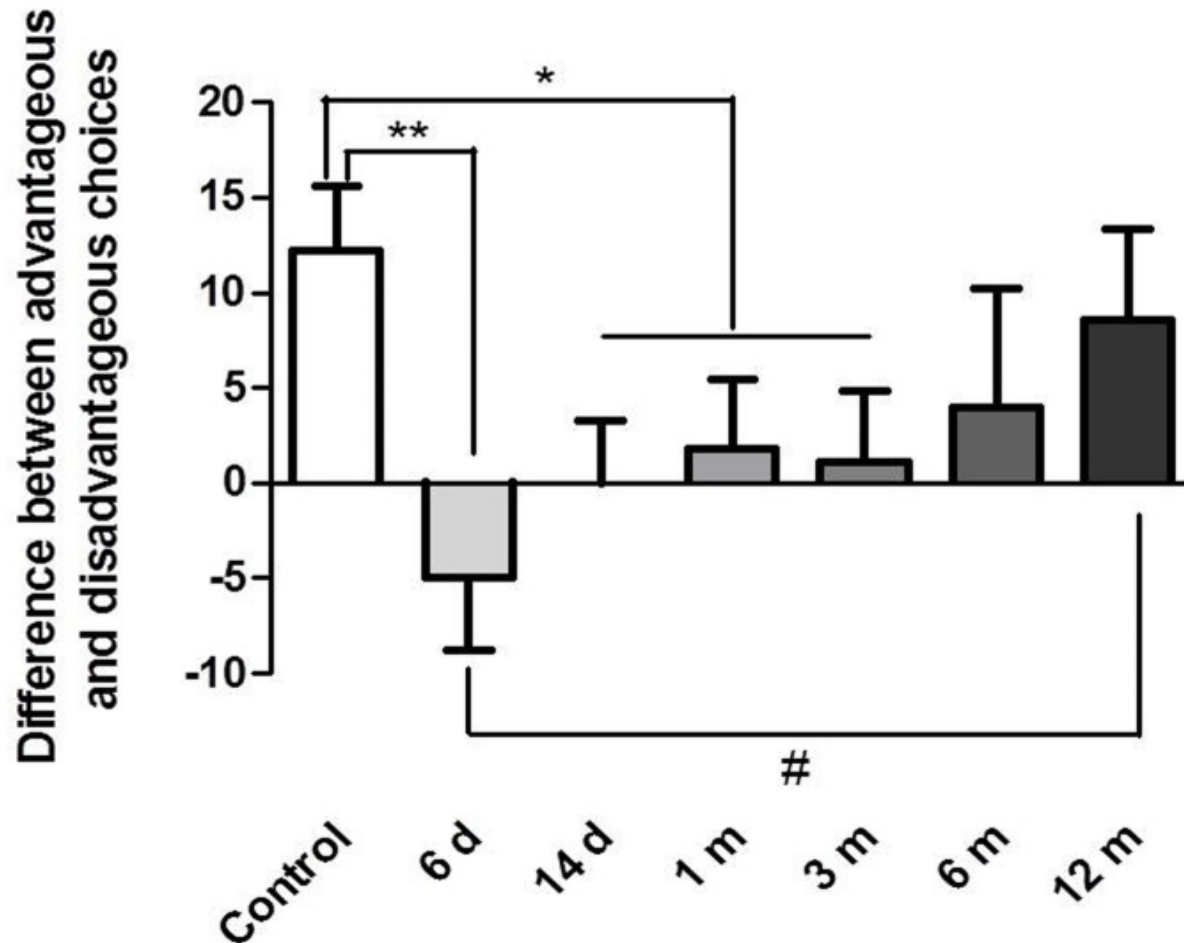
Bechara et al. Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 1994, 50:7-15.

IGT and relapse in substance-dependent individuals



Stevens et al. Impulsive choice predicts short-term relapse in substance-dependent individuals attending an in-patient detoxification programme. *Psychol Med.* 2015 Jul;45(10):2083-93.

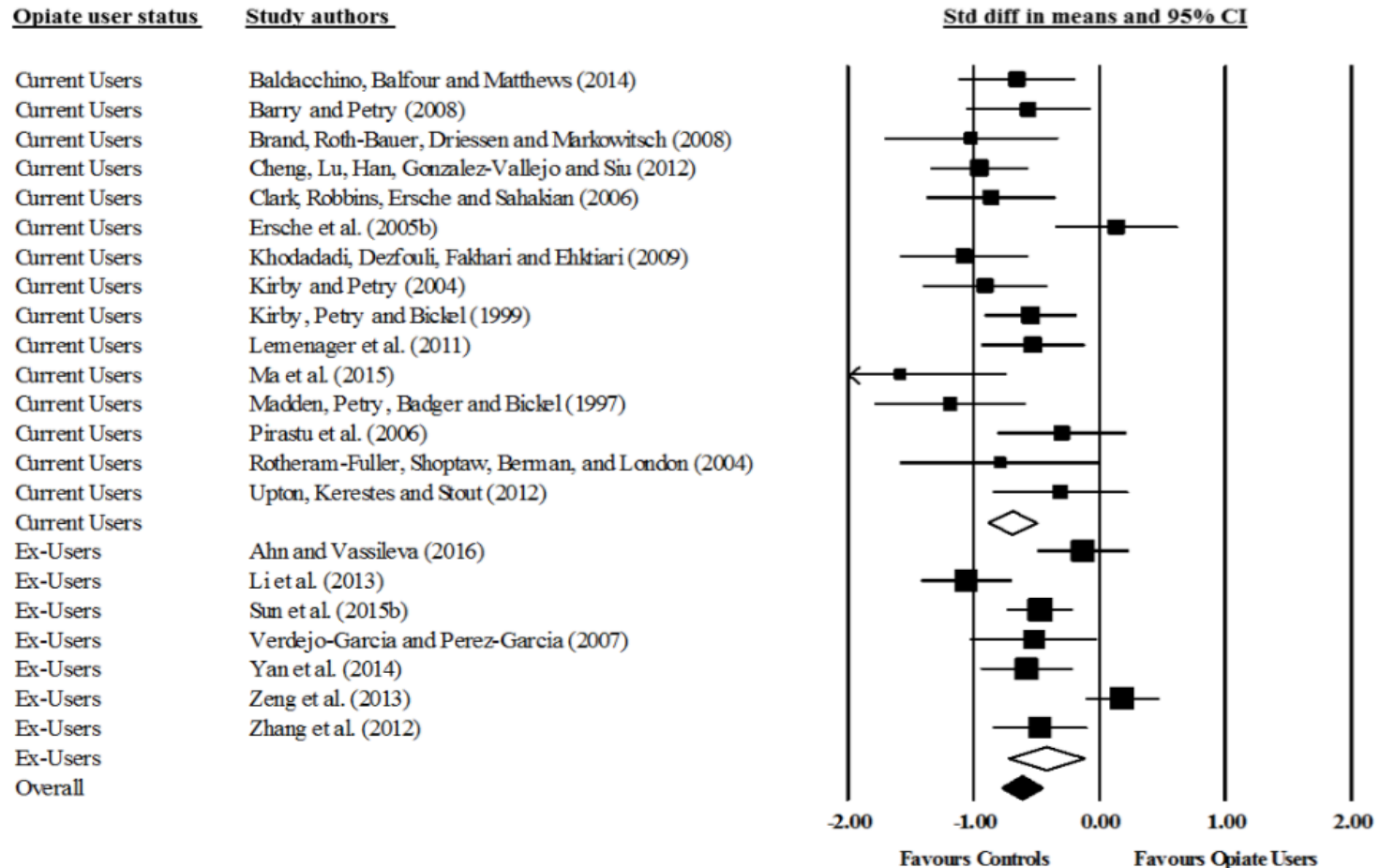
IGT and abstinence in methamphetamine users



Decision-making ability on the Iowa Gambling Task (IGT) in METH abusers at different abstinence times and healthy controls over 100 card choices.

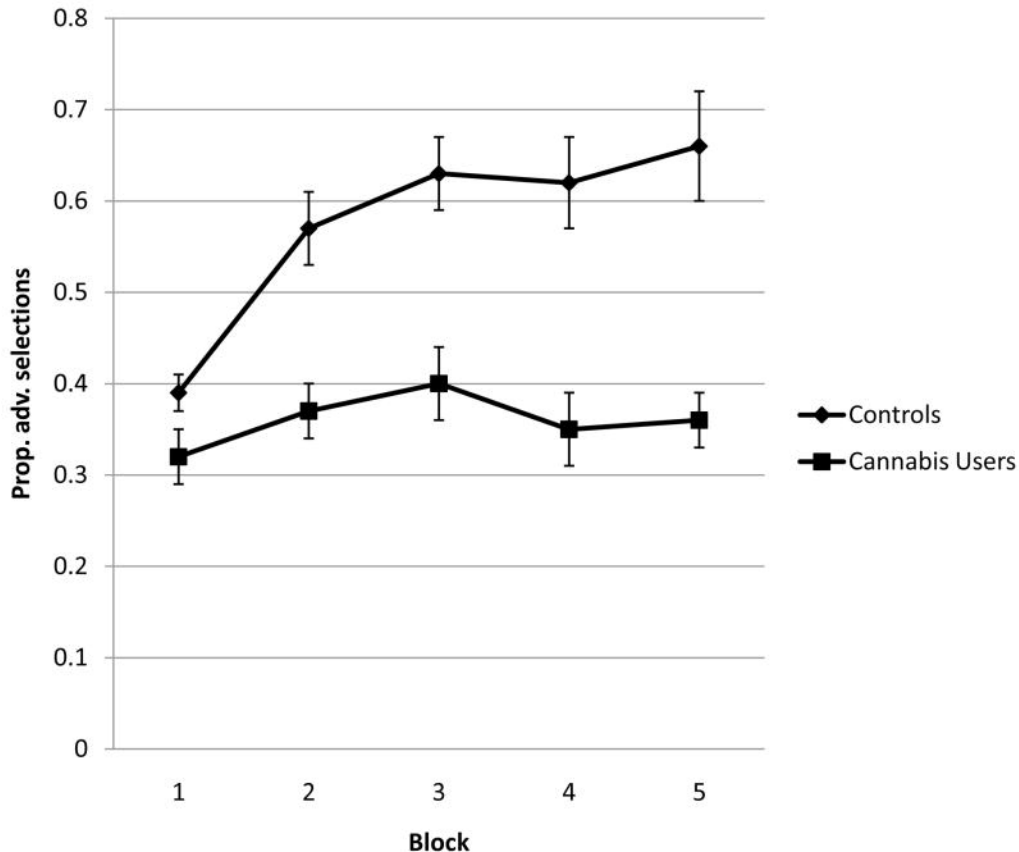
Wang et al. Effects of length of abstinence on decision-making and craving in methamphetamine abusers. PLoS One. 2013 Jul 24;8(7):e68791.

Decision-making in opioid users



Biernacki et al. Decision-making ability in current and past users of opiates: A meta-analysis. *Neurosci Biobehav Rev.* 2016 Sep 17;71:342-351.

Computer modeling of decision-making in cannabis users

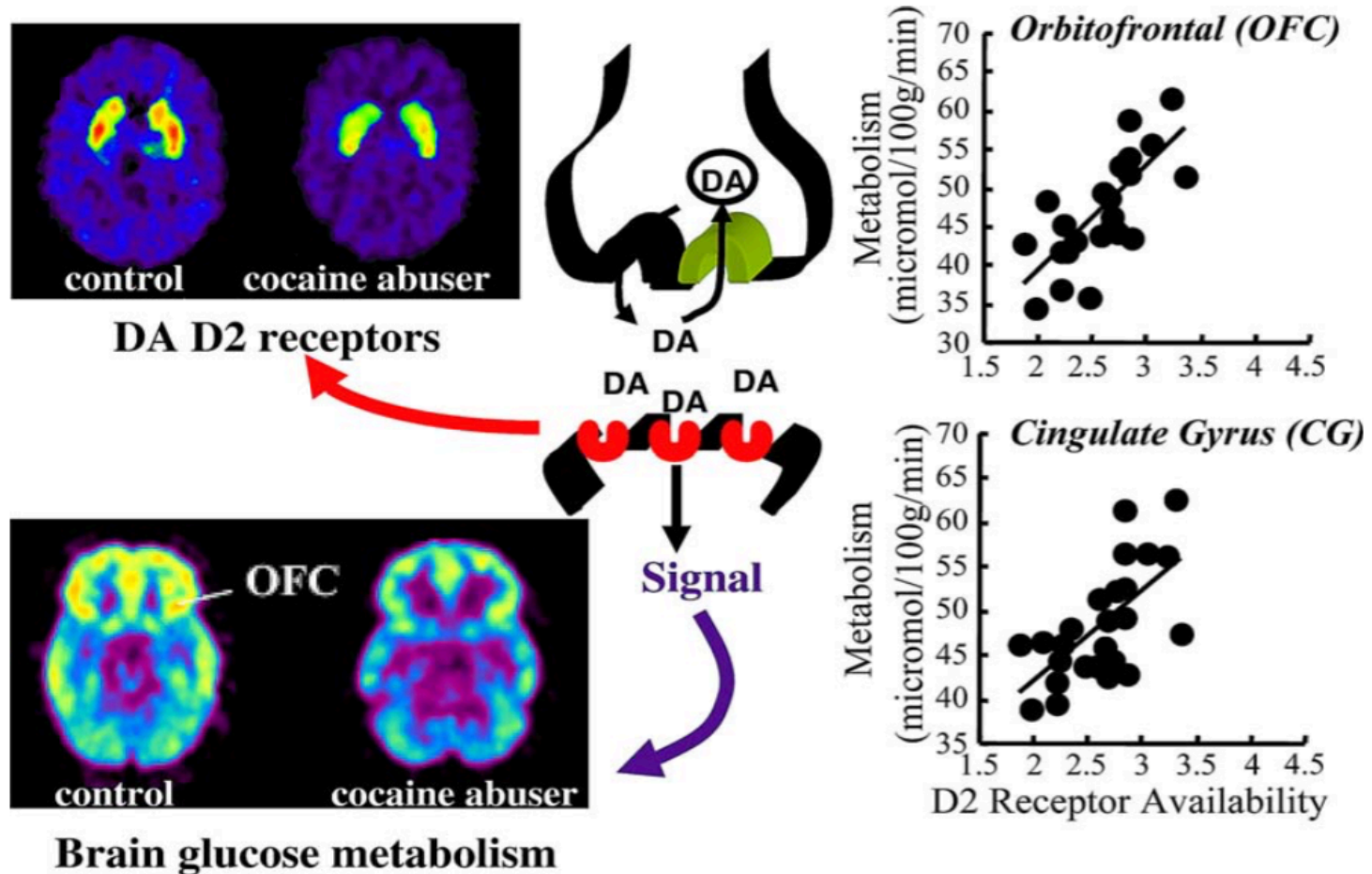


Compared to non-using controls, cannabis users:

- Ignored loss magnitude.
- Were more influenced by recent gains.
- Made decisions that were less consistent with their expectancies.

Fridberg et al. Cognitive Mechanisms Underlying Risky Decision-Making in Chronic Cannabis Users. J Math Psychol. 2010 Feb 1; 54(1): 28–38.

Imaging studies

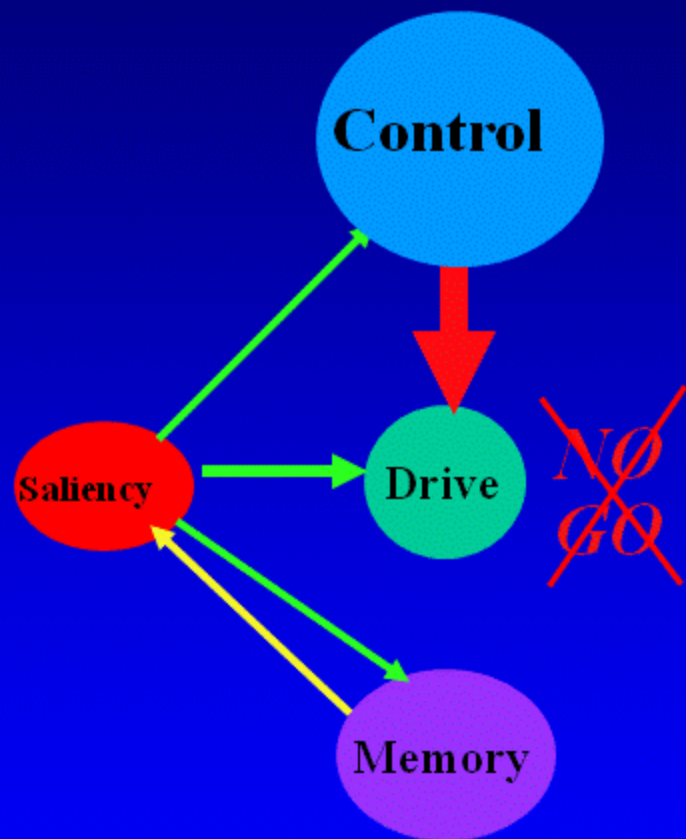


Changes in dopamine receptor density in ventral striatum and OFC metabolism cocaine addicts versus health controls.

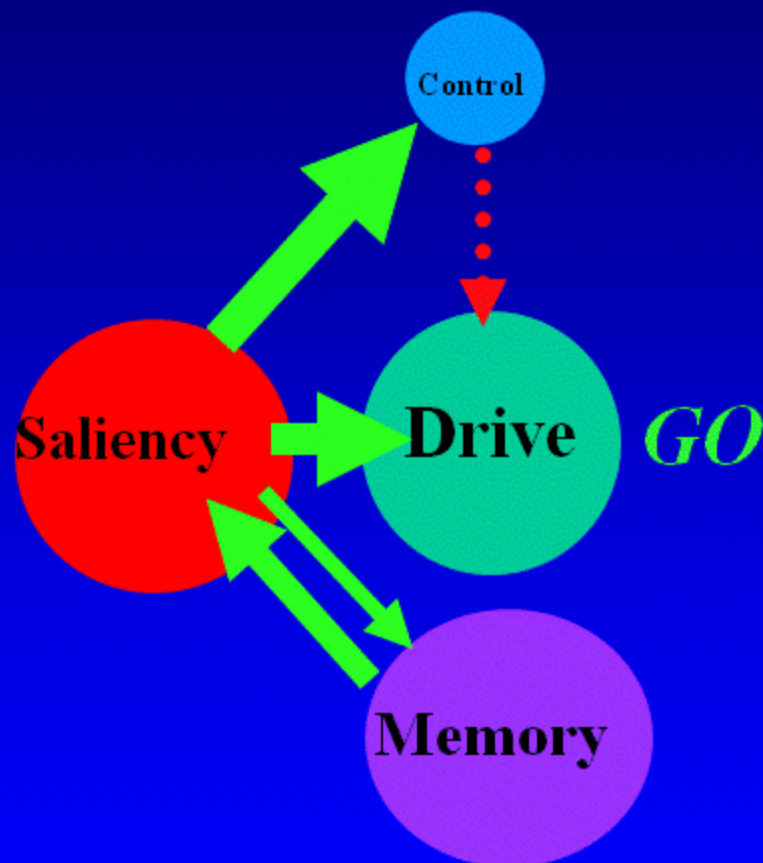
Volkow et al. The addicted human brain viewed in the light of imaging studies: brain circuits and treatment strategies. *Neuropharmacology*. 2004;47 Suppl 1:3-13.

Why Can't Addicts Just Quit?

Non-Addicted Brain



Addicted Brain



Because Addiction Changes Brain Circuits

Treatment

- 12-step groups—NA, AA, etc.
- Detoxification—many varieties exist
- Psychosocial treatment—substance abuse counseling, intensive outpatient treatment, residential “rehab”
- Medication-assisted treatment—antagonists or opioid replacement therapy (ORT)

Detoxification

- Not a treatment—more like debridement
- Usually medically supervised
- Useful as a bridge to psychosocial or methadone/buprenorphine maintenance treatment
- Very high relapse rates when used alone
- Elevated risk of overdose death within one month of any detox protocol

Nosyk B et al. A call for evidence-based medical treatment of opioid dependence. Health Aff (Millwood). 2013 Aug;32(8):1462-9.

Think of detox as preparation for treatment, not a treatment in itself.

Nosyk B et al. A call for evidence-based medical treatment of opioid dependence. Health Aff (Millwood). 2013 Aug;32(8):1462-9.

Naloxone rescue is not treatment.

It just stops an overdose victim
from dying at that moment.

Nosyk B et al. A call for evidence-based medical treatment of opioid dependence. Health Aff (Millwood). 2013 Aug;32(8):1462-9.

Psychosocial Treatment

- Very effective for many types of addiction
- An essential component of any opioid addiction treatment program
- **Not effective as a stand-alone treatment for opioid use disorders**

Nosyk B et al. A call for evidence-based medical treatment of opioid dependence. Health Aff (Millwood). 2013 Aug;32(8):1462-9.

Medication Assisted Treatment

Methadone



*Full agonist:
generates effect*

ORT

Buprenorphine



*Partial agonist:
generates limited effect*

ORT

Naltrexone



*Antagonist:
blocks effect*

Not ORT

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Full Agonist Treatment (ORT)

- Methadone
- Full agonist but long half-life
- Administered only in specially licensed methadone clinics when used for addiction treatment
- Can be used for pain treatment

Partial Agonist Treatment (ORT)

- Buprenorphine
- Partial agonist—harder to overdose
- Prescribers need special training and DEA certificate, but in theory can be administered in any prescriber's office.
- Can be used for pain treatment, no special training required

Advantages of ORT

- Consistent evidence to support efficacy
- Better treatment retention
- Fewer overdose deaths
- Less hospitalization
- Cost effectiveness

Dugosh K. A Systematic Review on the Use of Psychosocial Interventions in Conjunction With Medications for the Treatment of Opioid Addiction. J Addict Med. 2016 Mar-Apr;10(2):91-101.

Mattick R. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2008 Apr 16;(2).

Nosyk B et al. A call for evidence-based medical treatment of opioid dependence. Health Aff (Millwood). 2013 Aug;32(8):1462-9.

Disadvantages of ORT

- Potential for abuse and diversion of medication
- Lifelong treatment for many—up to 95 percent relapse when taper attempted
- Some people see ORT as “substituting one addiction for another.”
- ASAM criteria

Nosyk B et al. A call for evidence-based medical treatment of opioid dependence. Health Aff (Millwood). 2013 Aug;32(8):1462-9.

Antagonist Treatment (not ORT)

- Oral or long-acting injectable naltrexone (Vivitrol)
- Advantages:
 - Blocks high from opioids
 - Avoids stigma of ORT (doesn't "replace one addiction with another")
 - Appeals to people who favor abstinence
 - Can't be abused or diverted

Antagonist Treatment (not ORT)

- Disadvantages:

- Oral naltrexone no better than placebo

Minozzi S et al, Cochrane Database Syst Rev 2011

- Long-acting injectable naltrexone (Vivitrol) promising, but limited evidence

Lee J et al. Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. N Engl J Med. 2016 Mar 31;374(13):1232-42

Krupitsky E et al. Injectable extended-release naltrexone (XR-NTX) for opioid dependence: long-term safety and effectiveness. Addiction. 2013 Sep;108(9):1628-37

- High treatment dropout rates
 - May interfere with pain treatment

Economic Studies

Multiple studies support cost-effectiveness of ORT.

Barnett P et al. The cost-effectiveness of buprenorphine maintenance therapy for opiate addiction in the United States. *Addiction*. 2001 Sep;96(9):1267-78.

Barnett P et al. Comparison of costs and utilization among buprenorphine and methadone patients. *Addiction*. 2009 Jun;104(6):982-92.

Nosyk B et al. Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment. *CMAJ*. 2012 Apr 3;184(6).

Zarkin G et al. Benefits and costs of methadone treatment: results from a lifetime simulation model. *Health Econ*. 2005 Nov;14(11):1133-50.

Economic Studies

MAT* reduced hospital admissions and emergency department visits for Medicaid beneficiaries with opioid addiction compared with psychosocial treatment, abstinence, or detoxification.

Mohlman M et al. Impact of Medication-Assisted Treatment for Opioid Addiction on Medicaid Expenditures and Health Services Utilization Rates in Vermont. J Subst Abuse Treat. 2016 Aug;67:9-14. doi: 10.1016/j.jsat.2016.05.002. Epub May 2016.

*MAT = ORT in this study.

Take-Home Messages

- Addiction is a learning disorder with biological, psychological and social components.
- Historically, biology has taken a back seat in public policies for managing OUD.
- The science of OUD points to biology as a key component in managing the opioid epidemic.
- Most people with OUD can't just quit.
- Manage OUD accordingly.

Further reading

- Kosten TR. *The neurobiology of opioid dependence: implications for treatment*. Sci Pract Perspect. 2002 Jul;1(1):13-20
- Ekhtiari et al. *Aberrant decision-making and drug addiction*. Current opinion in behavioral sciences. 2017, 13:25-33
- Nosyk et al. *A call for evidence-based medical treatment of opioid dependence in the United States and Canada*. Health Aff (Millwood). 2013 Aug;32(8):1462-9.

Questions?