The Biology of Addiction

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Medical Model of Addiction

Pathophysiology of Addiction

- To identify changes that drugs of abuse produce in a vulnerable brain to cause addiction.

Individual Risk of Addiction

- To identify specific genes and non-genetic factors that determine an individual's risk for (or resistance to) addiction.
- About 50% of the risk for addiction is genetic, but this heritability is highly complex with many hundreds of genes involved, each contributing a minute fraction.
- The remaining 50% of risk is presumably mediated by a range of environmental factors (early life adversity, peer pressure, etc.).

Only through an improved understanding of the biology of addiction will it be possible to develop better treatments and eventually cures and preventive measures.

Definition of Drug Addiction

Drug addiction (officially called a "substance use disorder") is defined solely on the basis of behavioral abnormalities:

- **Loss of control over drug use.**
- **Compulsive drug seeking and drug taking despite horrendous adverse consequences.**
- **Increased risk for relapse despite years of abstinence.**

Other terms, such as "drug abuse" are less clearly defined and are usually used to describe patterns of drug use that are less severe than addiction.

Sobering fact: In 2019, we lack objective measures (brain scan, blood test, genetic test) that assist in making the diagnosis of addiction or tracking its treatment.

Scope of Drug Addiction

Enormous impact of drug addiction on humanity:

~25% of the U.S. population has a diagnosis of drug abuse or addiction.

~50% of U.S. high school graduates have tried an illegal drug; use of alcohol and tobacco is more common.

>$500 billion incurred annually in the U.S. by addiction:

- **Loss of life and productivity**
- **Medical consequences (e.g., AIDS, lung cancer, cirrhosis)**
- **Crime and law enforcement**

While we are currently in the midst of an opioid epidemic, we should avoid a "whack-a-mole" approach and focus on the entire addiction syndrome.

- **Avoid focus on a given drug popular at the moment, since waves of different drug use characterize drug addiction in the U.S. over the past century.**

Diverse Chemical Substances Cause Addiction

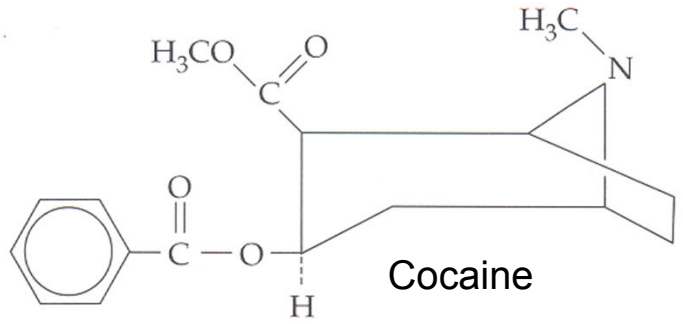
Only a very small fraction of a ~billion chemicals cause the specific syndrome of addiction:

- **Opiates or "opioids" (morphine, heroin, oxycontin, hydrocodone, etc.)**
- **Stimulants (cocaine, amphetamine, methamphetamine, methylphenidate)**
- **Tobacco products (nicotine)**
- **Alcohol (ethanol)**
- **Marijuana (cannabinoids)**
- **PCP (phencyclidine or angel dust; also ketamine)**
- **Sedative/hypnotics (barbiturates, benzodiazepines)**
- **MDMA (ecstasy)**

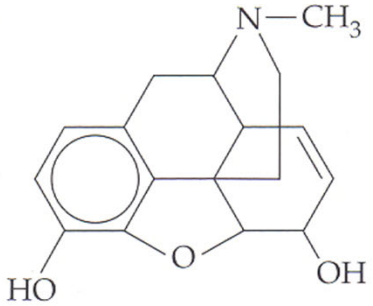
What is unique about these particular substances that imbue them with the ability to induce addiction?

Diverse Chemical Structures of Drugs of Abuse

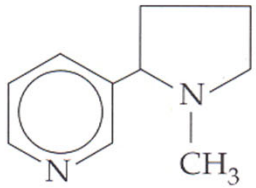
Drugs of abuse share nothing in common with respect to their chemical structures.



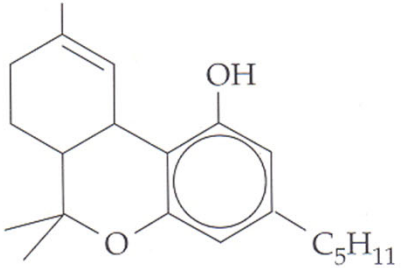
Cocaine



Morphine



Nicotine



Δ^9-tetrahydrocannabinol

CH_3-CH_2-OH

Ethanol

Animal Models of Drug Addiction

Drug self-administration

- Animals (mice, rats, monkeys) administer the same range of drugs that humans self-administer and a subset of animals show signs reminiscent of addiction (loss of control over drug intake, use of drug at the expense of food, sex, etc.).
- If left unchecked, a portion of animals overdose.

Relapse to drug self-administration

- Even after prolonged periods of withdrawal, animals relapse to drug self-administration.
- Relapse is triggered by the drug itself or by drug-associated cues or stress.

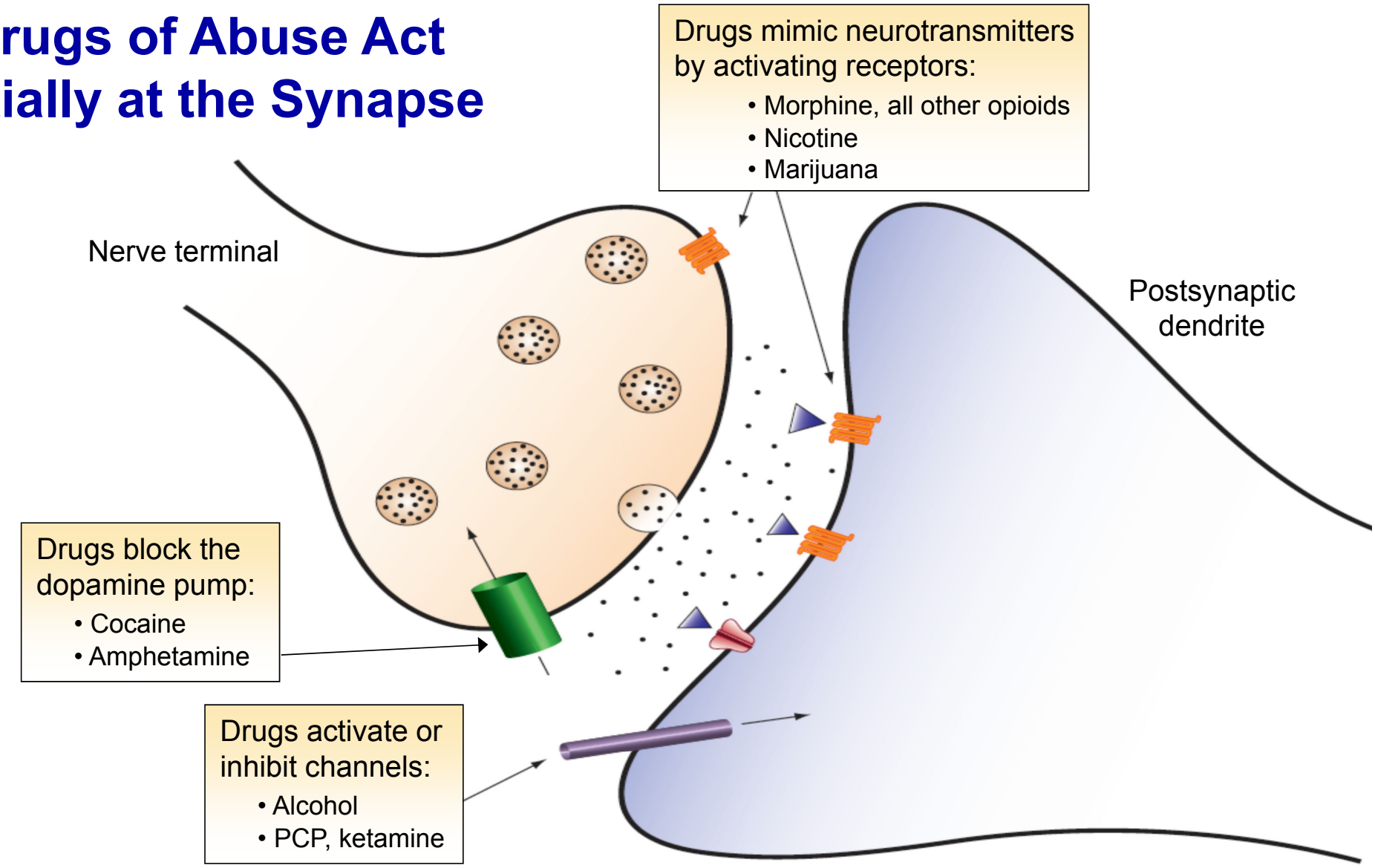
Conditioned place preference

- Animals learn to prefer a drug-paired environment.

Intra-cranial self-stimulation

- Drugs promote an animal's choice to electrically stimulate certain brain regions.

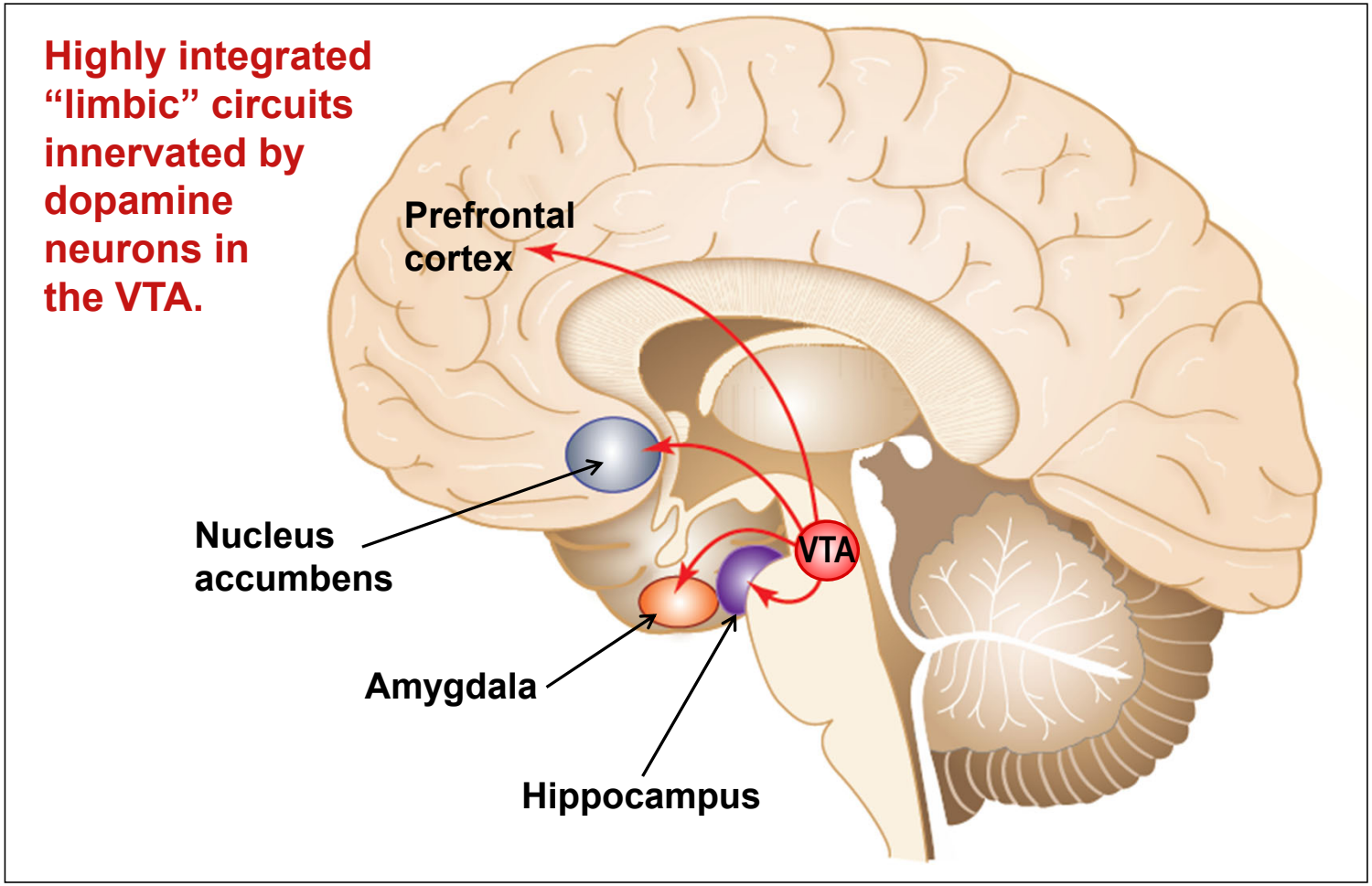
Drugs of Abuse Act Initially at the Synapse



Brain Reward Regions

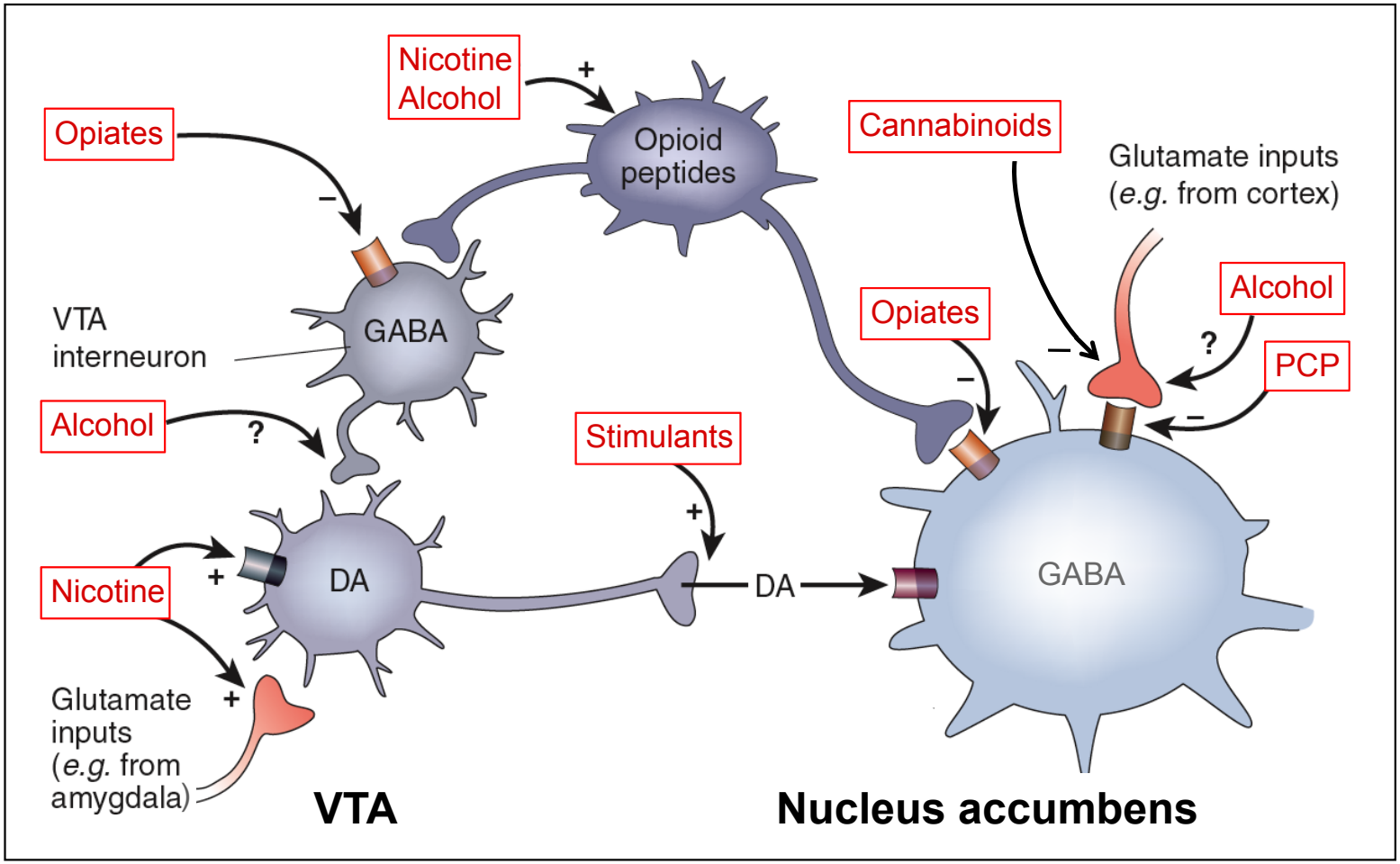
Drugs of abuse converge by acting on so-called "brain reward regions."

This reward circuitry is very old from an evolutionary perspective and mediates responses to natural rewards (food, sex, social interactions, etc.).

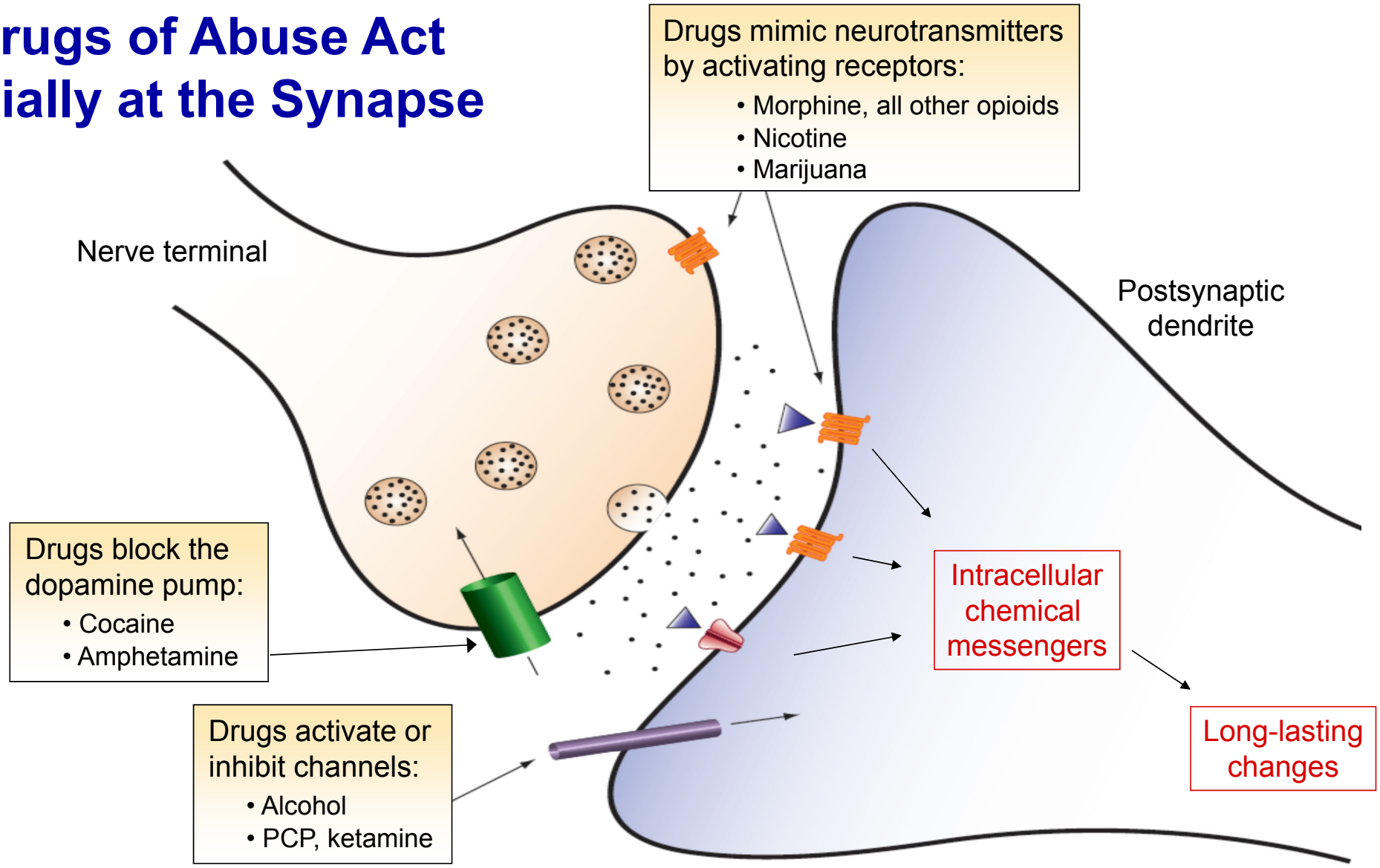


Convergence of Drugs of Abuse on the VTA-Nucleus Accumbens Reward Circuit

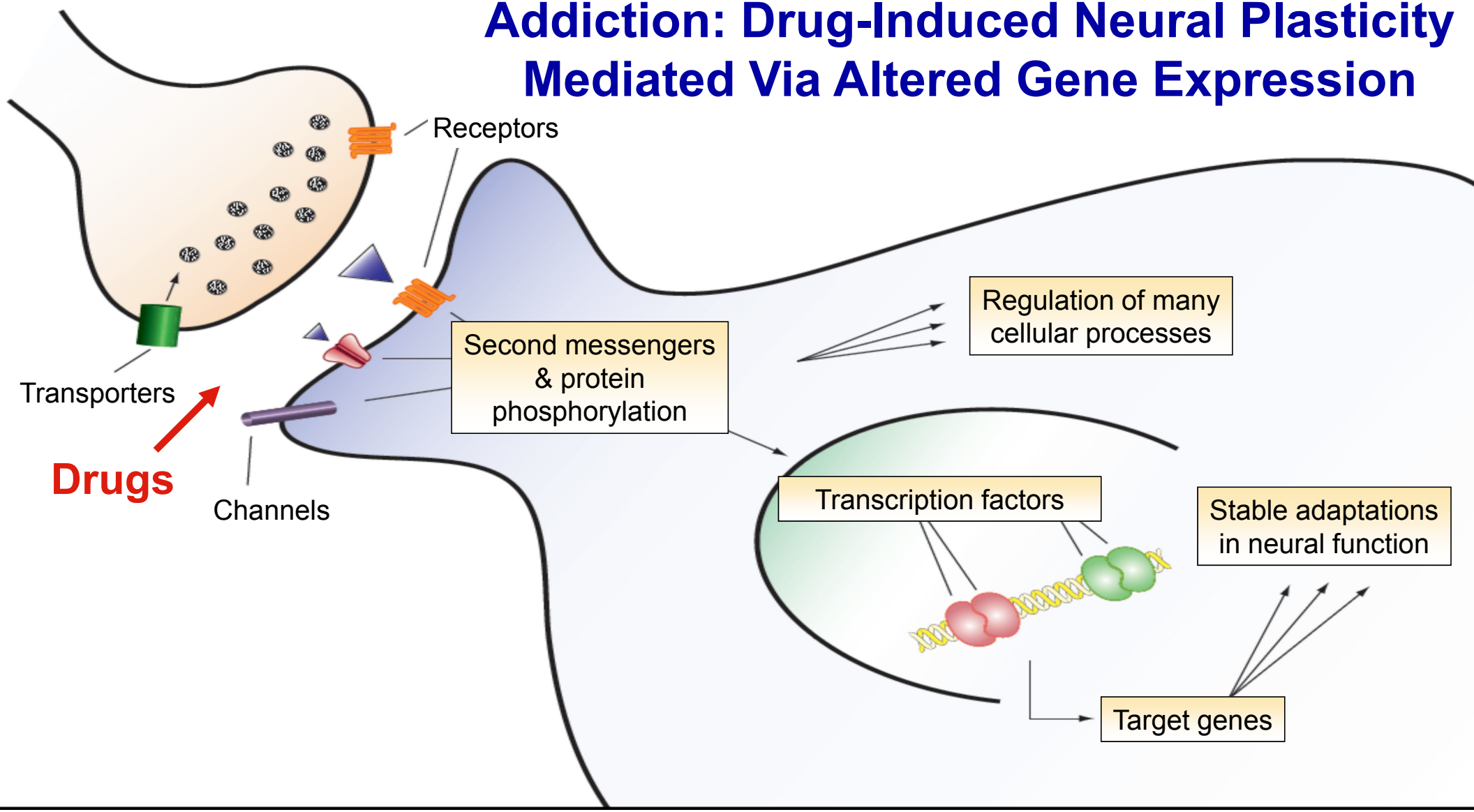
All drugs of abuse, despite their very different chemical structures and very different initial protein targets, converge by producing shared functional effects on the brain's reward circuitry.



Drugs of Abuse Act Initially at the Synapse



Addiction: Drug-Induced Neural Plasticity Mediated Via Altered Gene Expression



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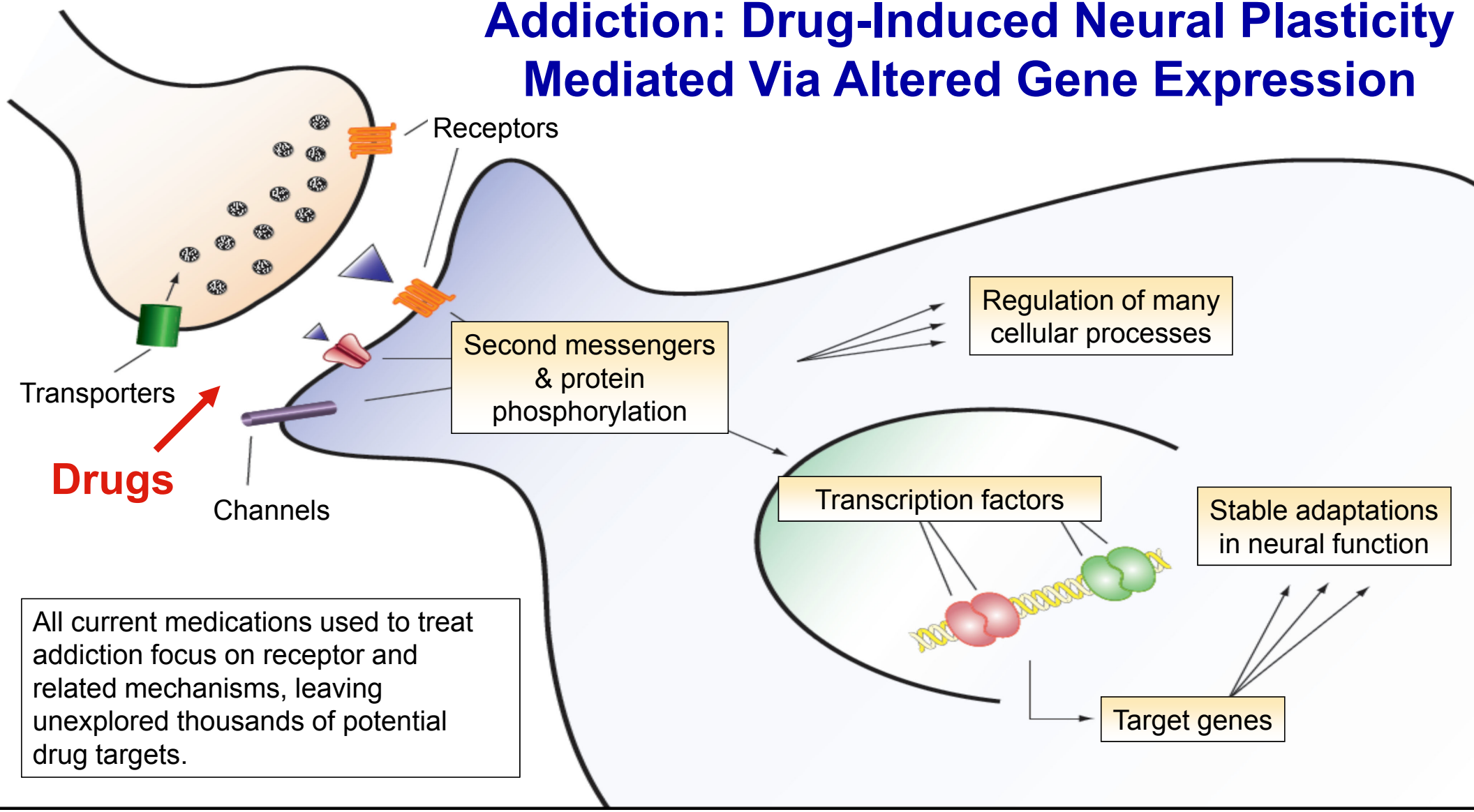
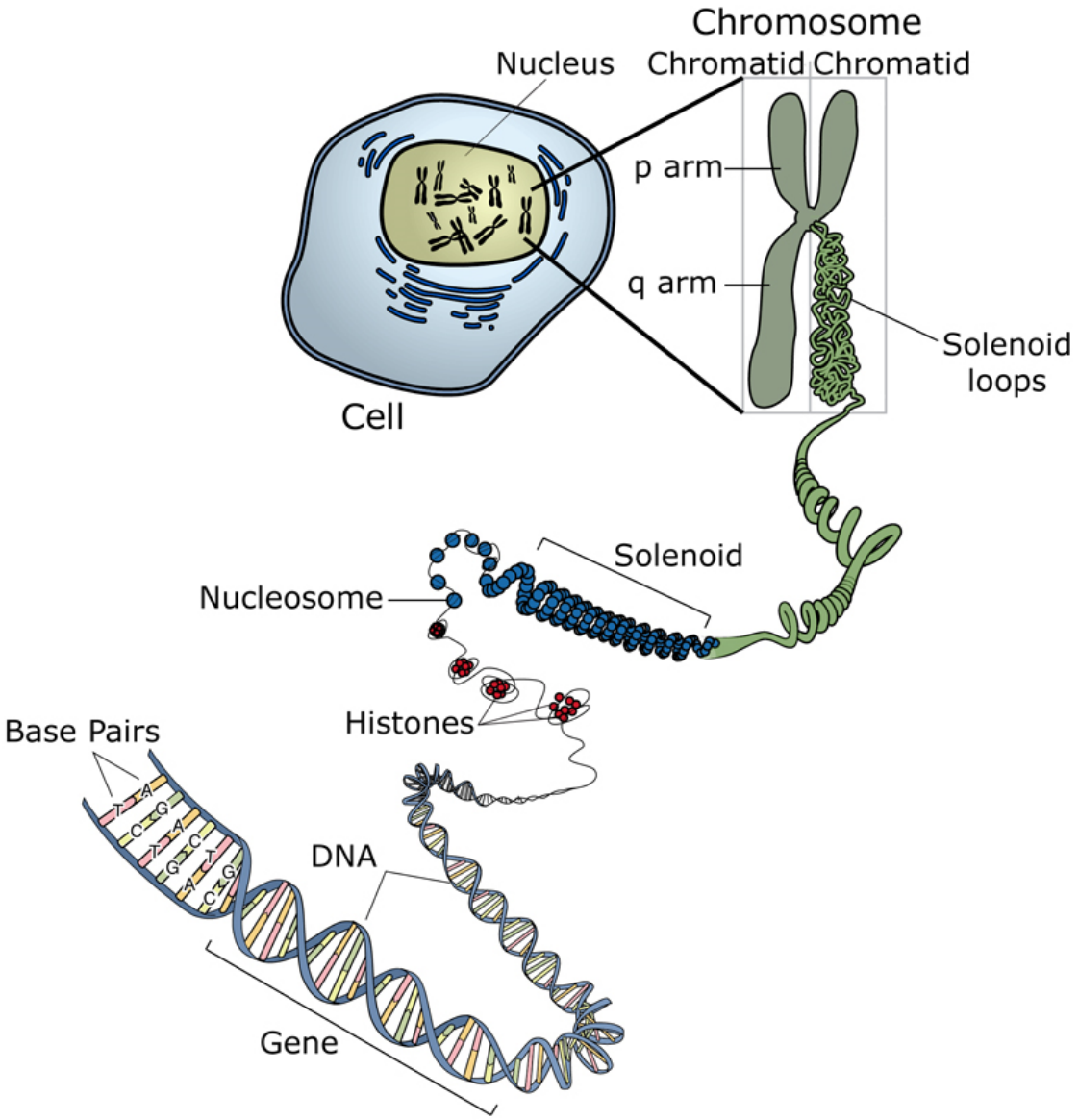


All current medications used to treat addiction focus on receptor and related mechanisms, leaving unexplored thousands of potential drug targets.

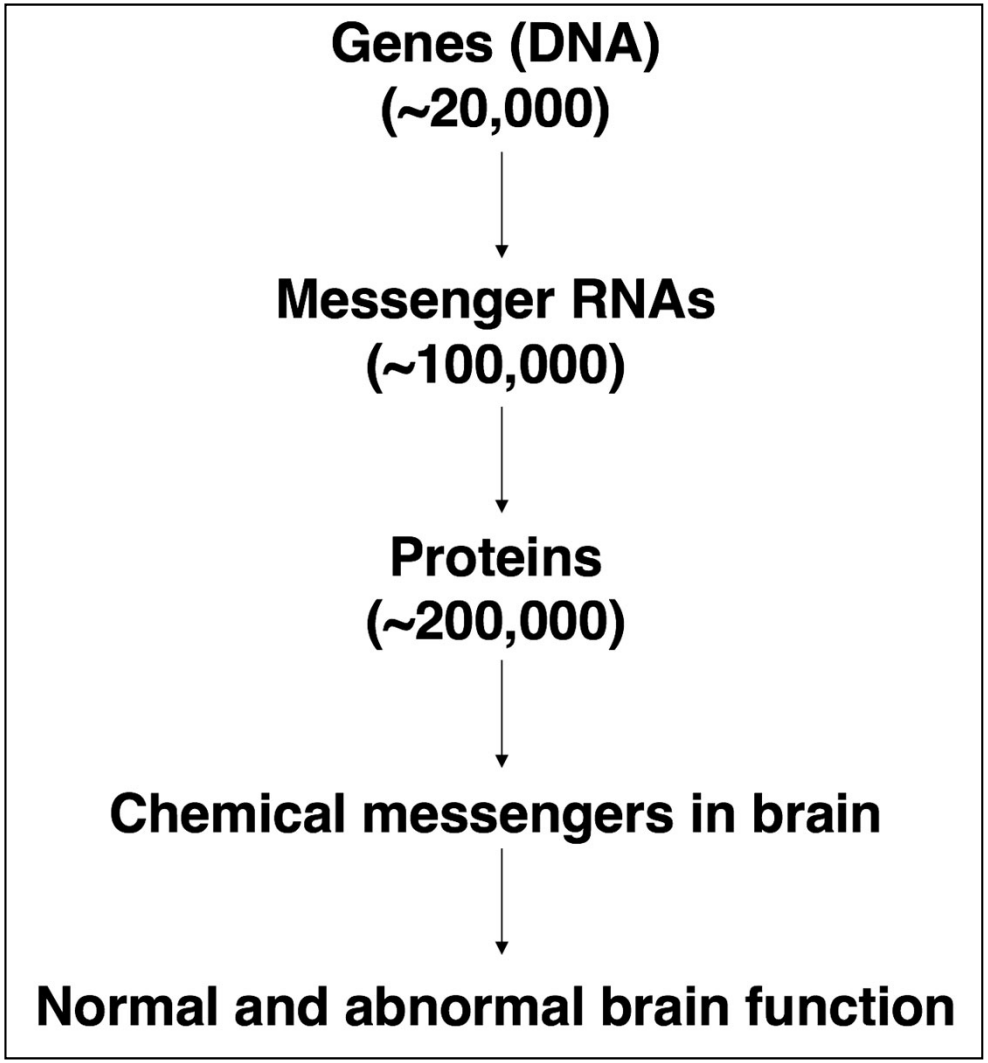
Chromatin Studies Offer Major Advances

- **Help identify drug-regulated genes.**
- **First ever look at transcriptional mechanisms *in vivo*.**
- **Unique mechanisms of long-lasting adaptations.**

The knowledge that addiction is roughly 50% genetic and 50% non-genetic (presumably environmental) suggests the importance of so-called epigenetic mechanisms.

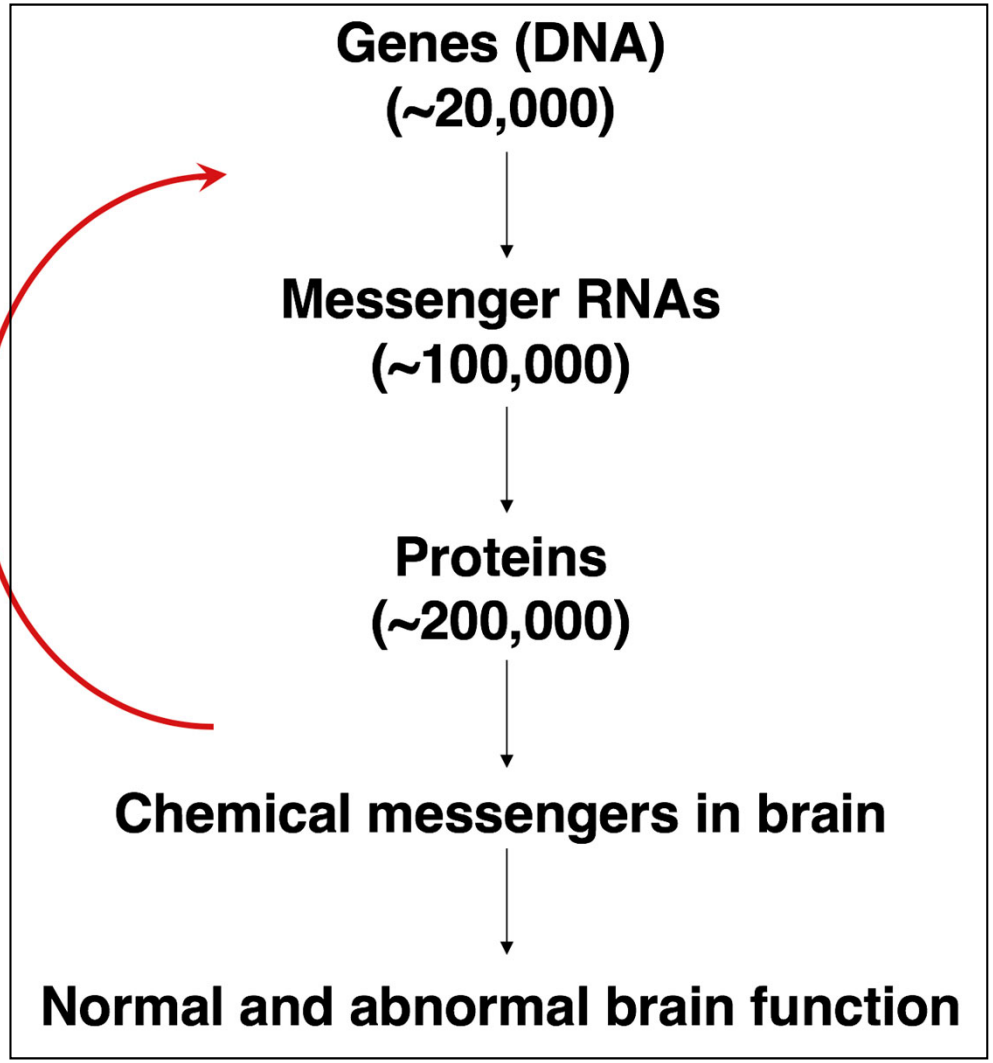


Genes Control Brain Function by Determining the Types and Amounts of Chemical Messengers in the Brain



Drugs of Abuse Regulate "Master Control Proteins" Called Transcription Factors

Master control proteins, or ***transcription factors***, control the expression of other genes

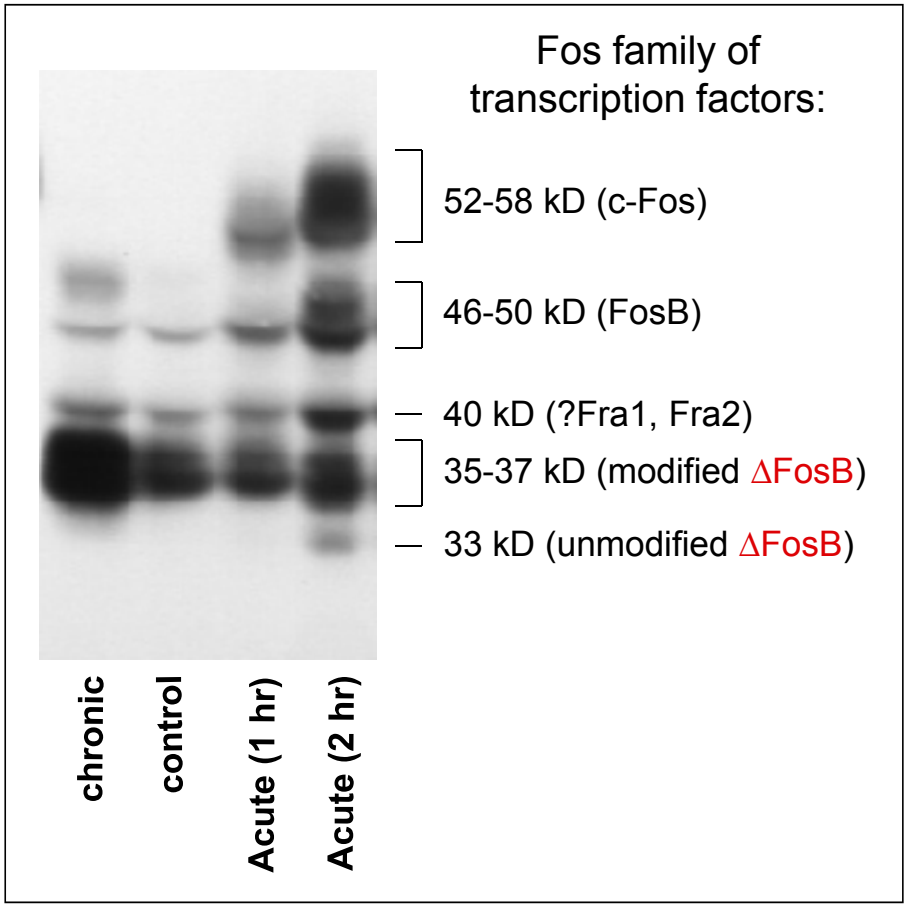


ΔFosB: A Molecular Switch for Addiction

High levels of ΔFosB, a type of transcription factor, are induced in NAc uniquely by chronic drug exposure, creating a "molecular switch."

ΔFosB induction then mediates sensitized drug responses.

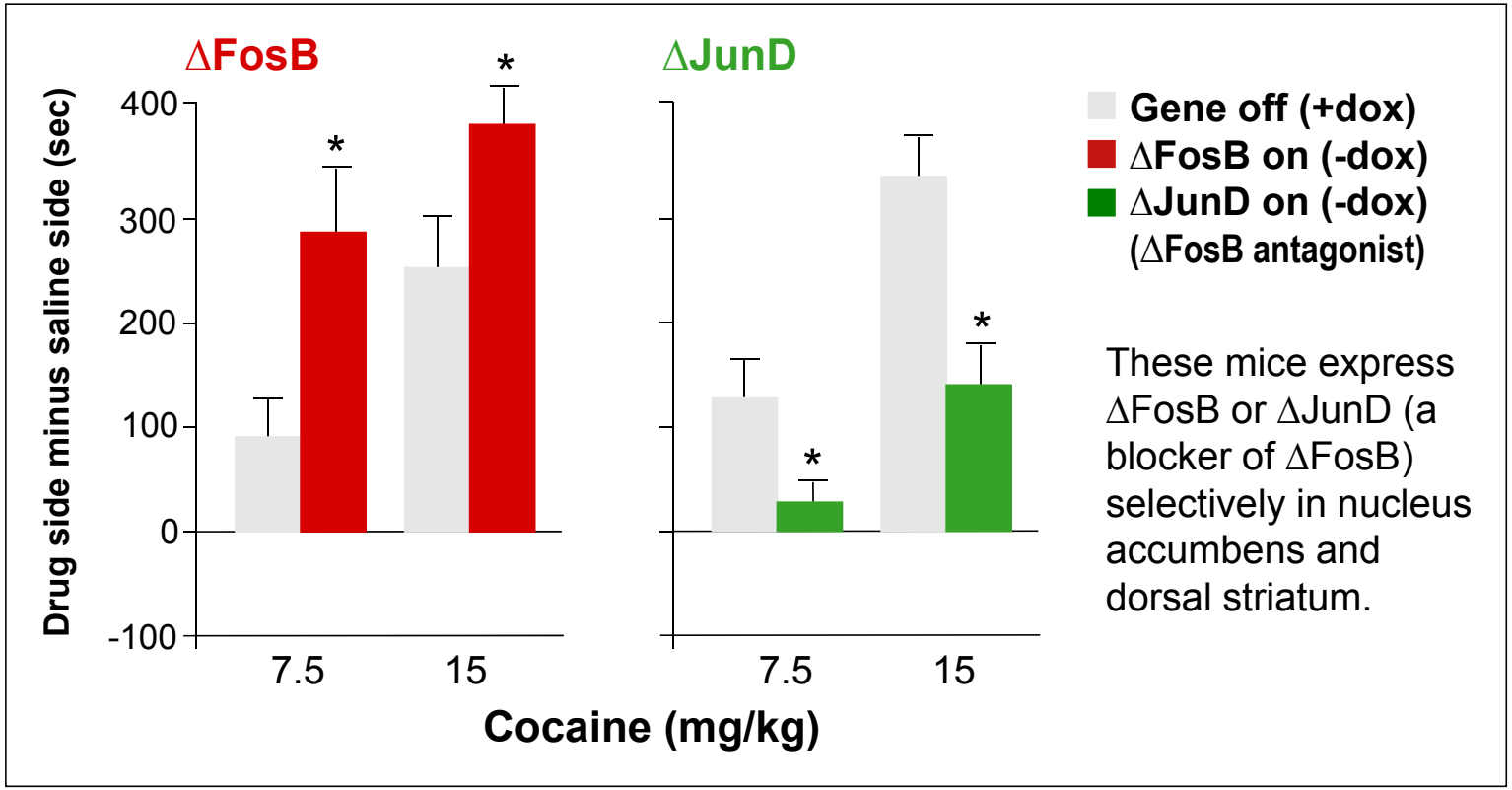
ΔFosB serves this role for every class of abused drug.



Robison and Nestler, *Nat Rev Neurosci,* 2011

ΔFosB Mediates Sensitized Drug Responses

Analysis of inducible bitransgenic mice in place conditioning:



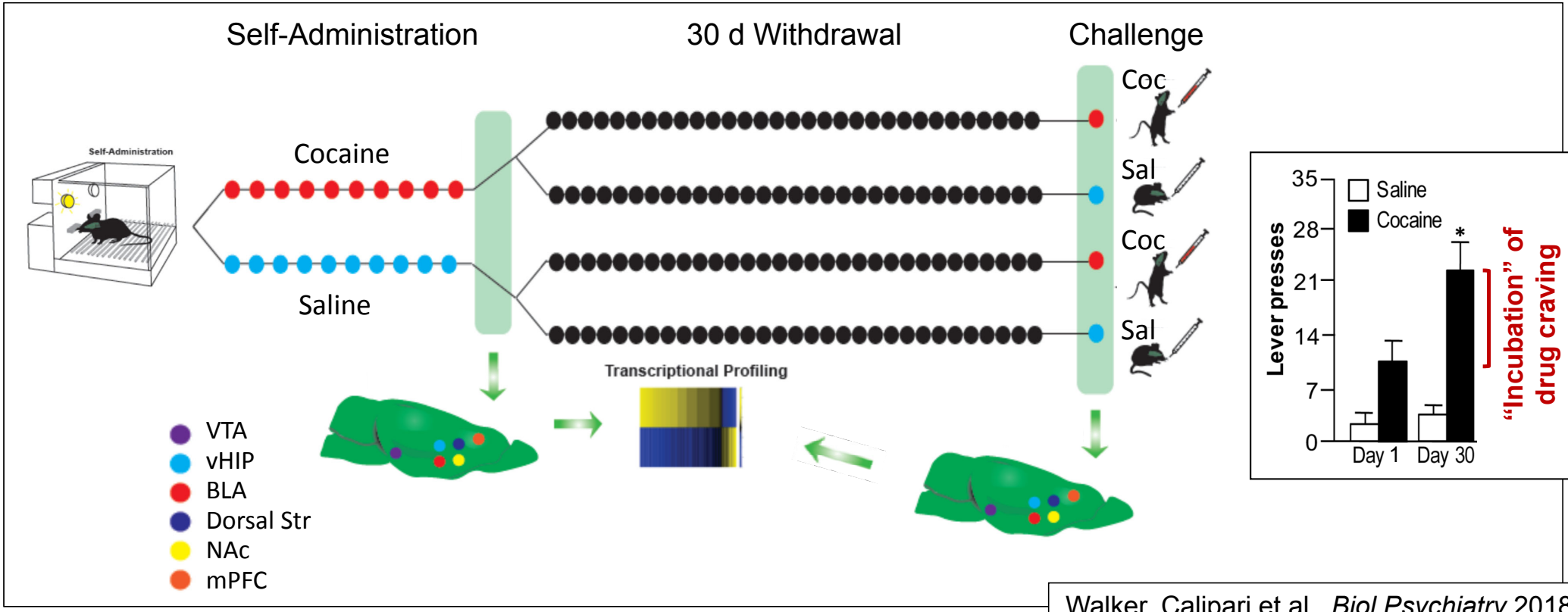
Similar actions are seen for many drugs of abuse, and in drug self-administration assays as well.

A range of target genes for ΔFosB, which regulate synaptic function, have been identified.

Kelz et al., *Nature,* 1999; McClung et al., *Nat Neurosci,* 2003

Identifying Long-Lasting Cocaine-Induced Changes in Gene Expression in Brain Reward Regions

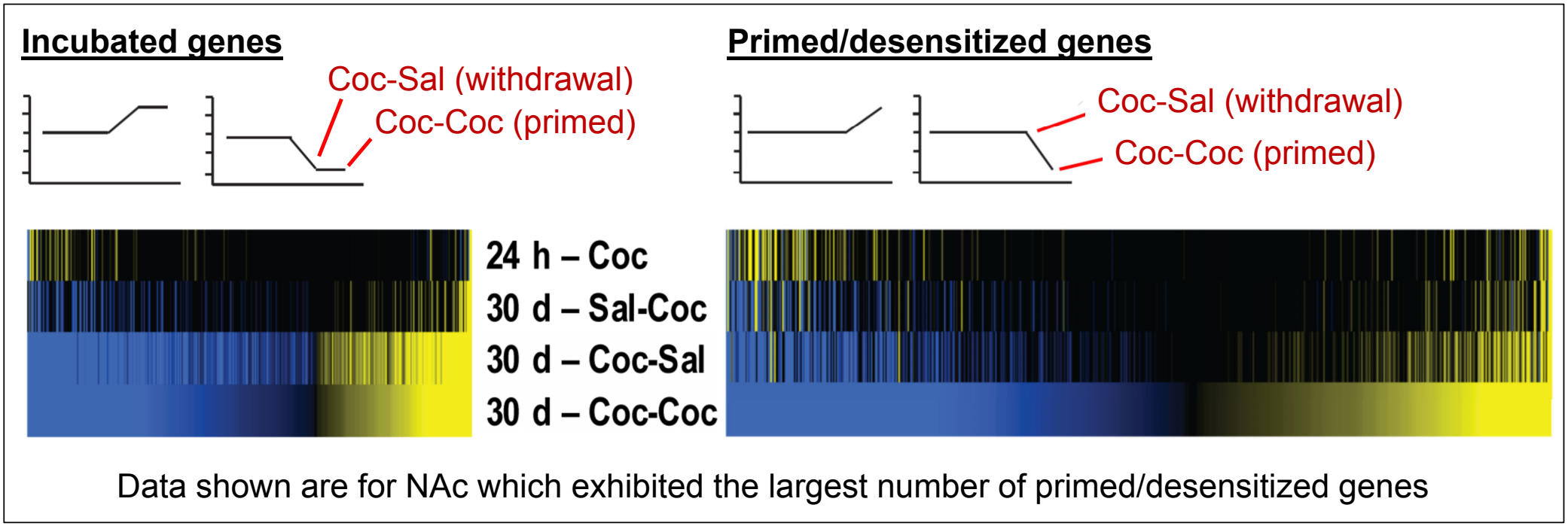
RNA-seq on 6 brain regions after short (1 day) or long (30 days) withdrawal from cocaine self-administration followed by a saline or cocaine challenge:



Walker, Calipari et al., *Biol Psychiatry* 2018

Long-Lasting Cocaine-Induced Changes in Gene Expression in Brain Reward Regions

Identifying genes that show long-lasting changes in gene expression, either altered steady-state expression levels or latent changes in inducibility, in the NAc:

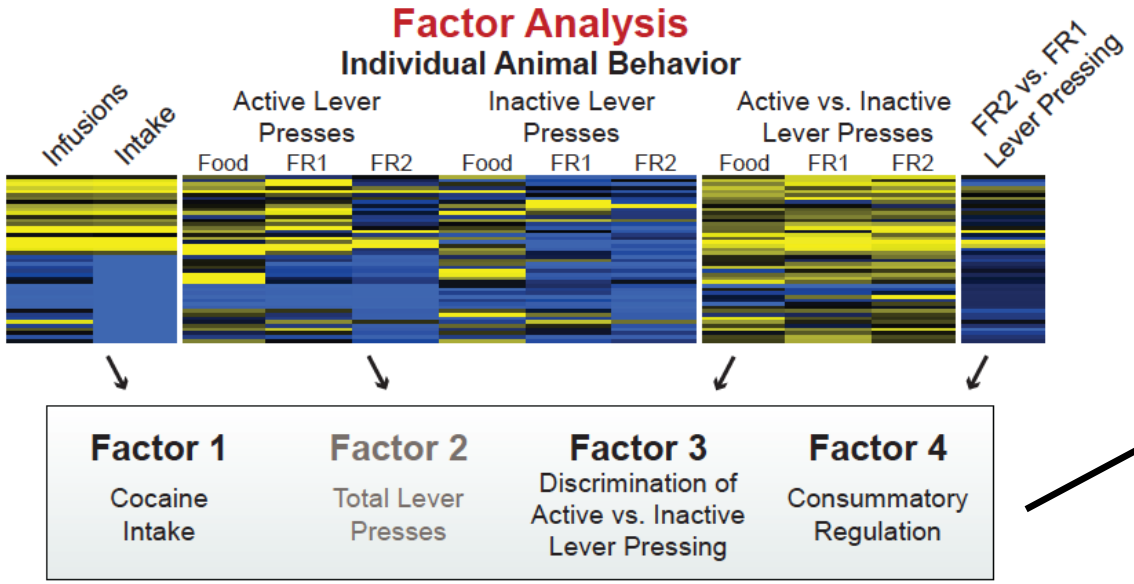


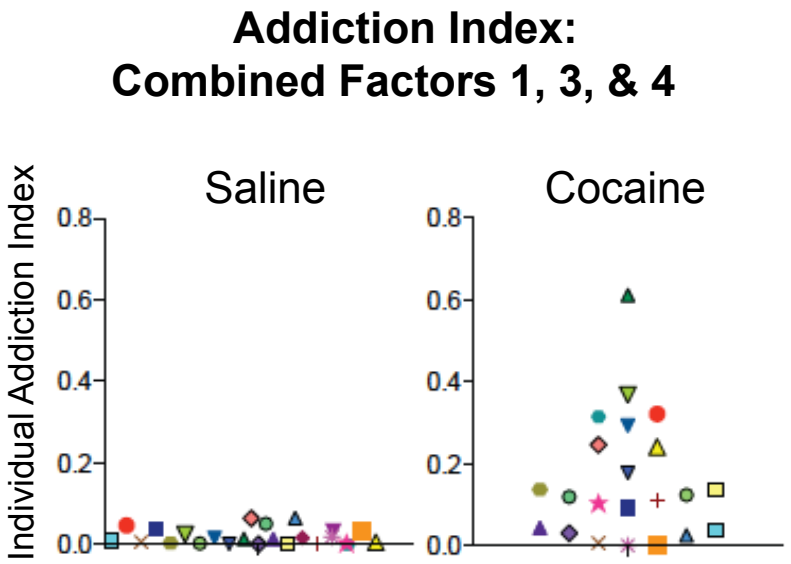
Data shown are for NAc which exhibited the largest number of primed/desensitized genes

Walker, Cates, et al., *Biol Psychiatry* 2018

Creating an "Addiction Index": Associating Gene Expression and Self-Administration Behavior in Individual Mice

Using factor analysis to rate each mouse with respect to the degree to which it self-administered cocaine and became "addicted":

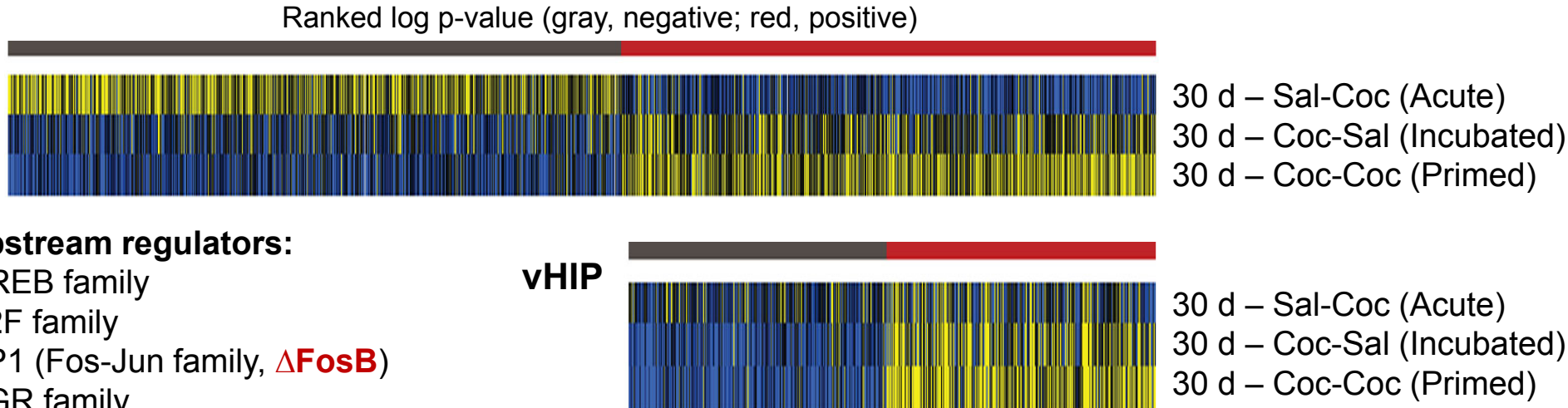




Walker, Cates, et al., *Biol Psychiatry* 2018

Long-Lasting Cocaine-Induced Changes in Gene Expression Associated with Individual Self-Administration Behavior

Identifying genes that show long-lasting changes in gene expression and whose regulation is associated with the "Addiction Index":



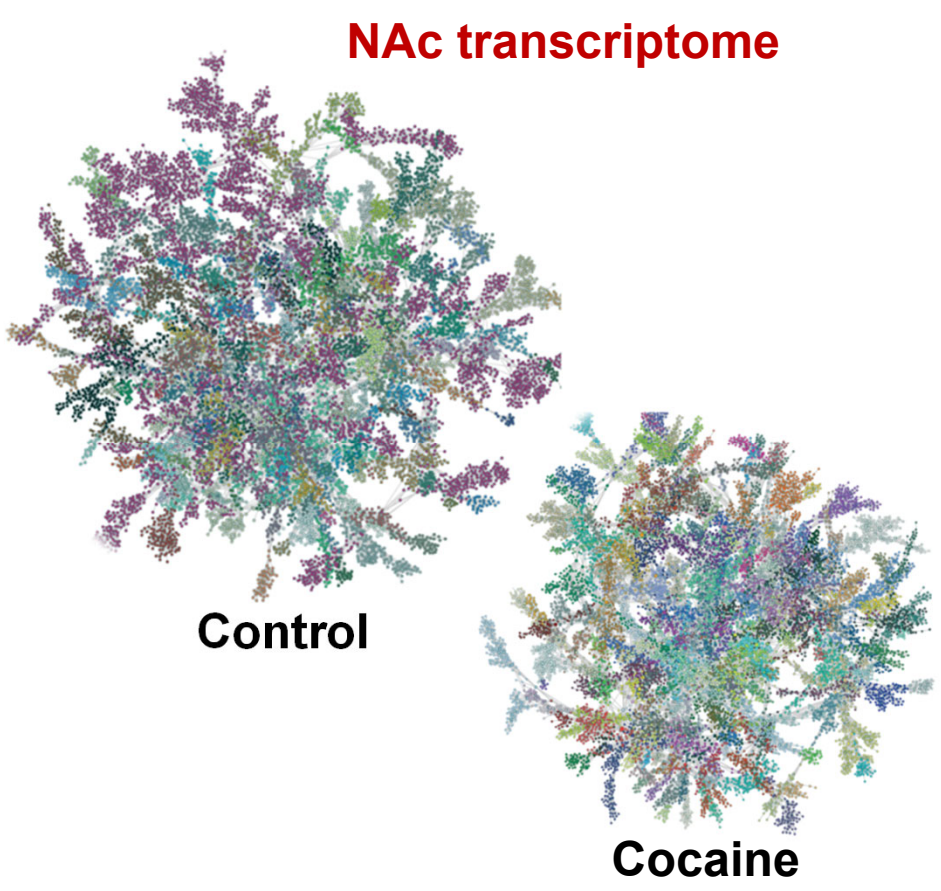
Top upstream regulators:

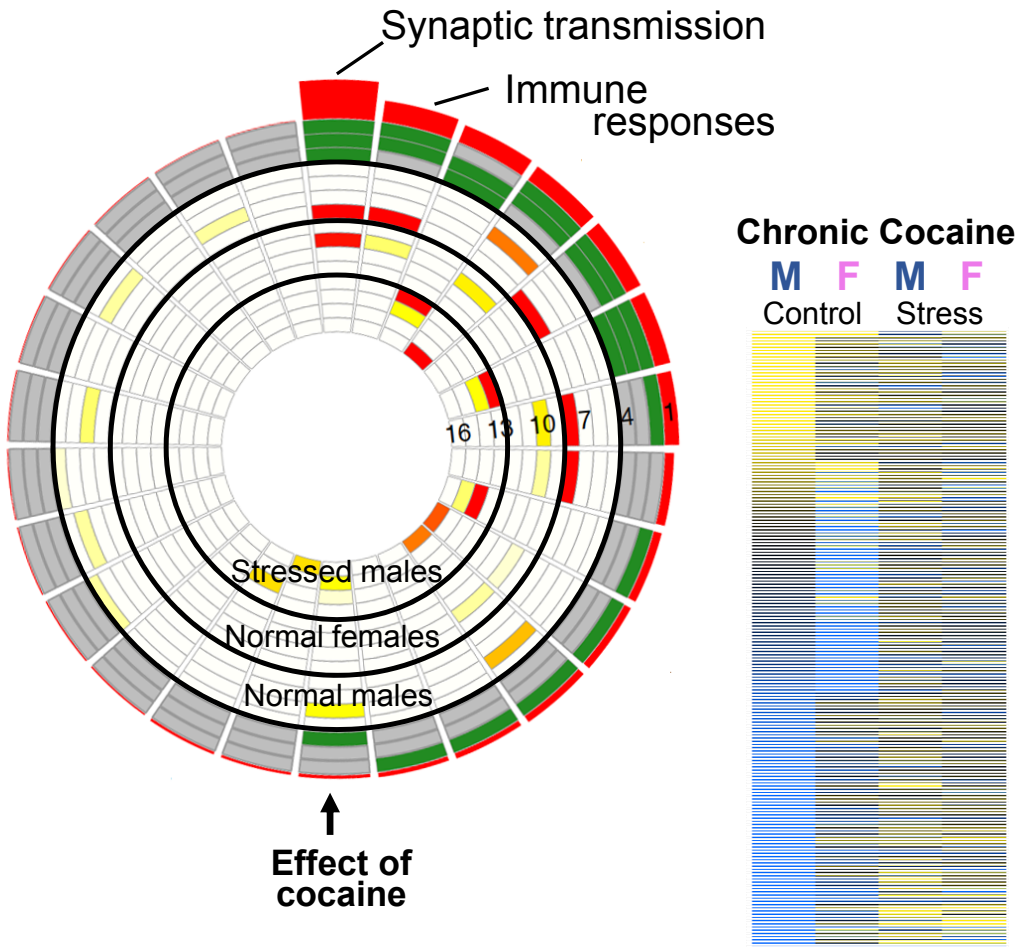
- CREB family
- E2F family
- AP1 (Fos-Jun family, **ΔFosB**)
- EGR family
- SMAD family
- Nuclear receptor family

This work also identifies key biochemical pathways involved in relapse across brain regions.

Walker et al., *Biol Psychiatry* 2018

Whole Genome Co-Expression Network Analysis

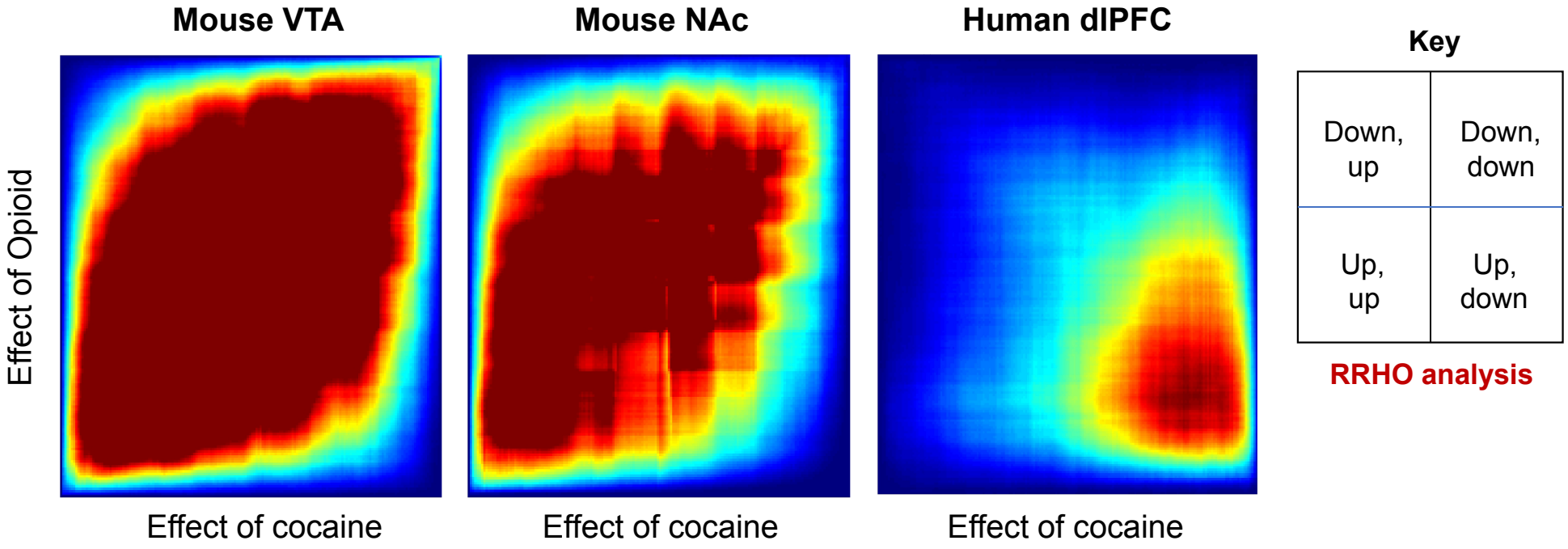




Deena Walker, Xianxiao Zhou, Bin Zhang

Evidence for Both Shared Mechanisms Across Drugs of Abuse As Well As Drug-Specific Addiction Mechanisms

Comparison of RNA-seq datasets show substantial overlap in some brain regions, but strikingly not others:



Feng et al., *Genome Biol* (2014); Ribeiro et al., *Sci Rep* (2017); Mash, Akbarian et al.

Distinct Roles of D1 and D2 NAc MSNs in Drug Addiction

D1 and D2 MSNs (medium spiny neurons) in NAc differ in their patterns of activity and effects on drug reward:

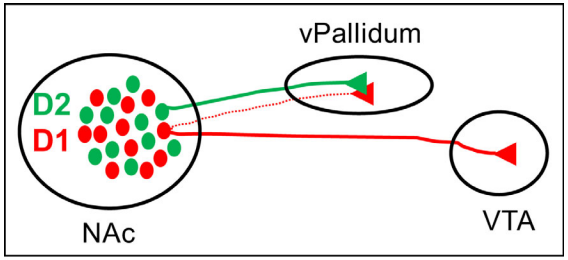
Opposite effects on drug reward:

- **Activation of D1 MSNs in NAc promotes drug reward, while activation of D2 MSNs in NAc attenuates drug reward.**

Opposite effects of cocaine on D1 and D2 MSNs in awake animals:

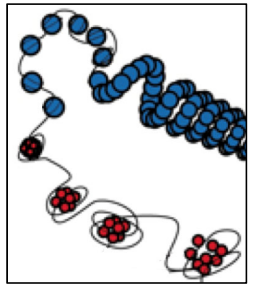
- **Acute drug exposure activates D1 MSNs and suppresses D2 MSNs.**
- **Chronic drug exposure + withdrawal causes a sustained increase in D1 MSN activity, but decreases D2 MSN activity.**

Interestingly, ΔFosB is induced in D1 MSNs by all drugs of abuse except opioids which induce it in D1 and D2 MSNs.

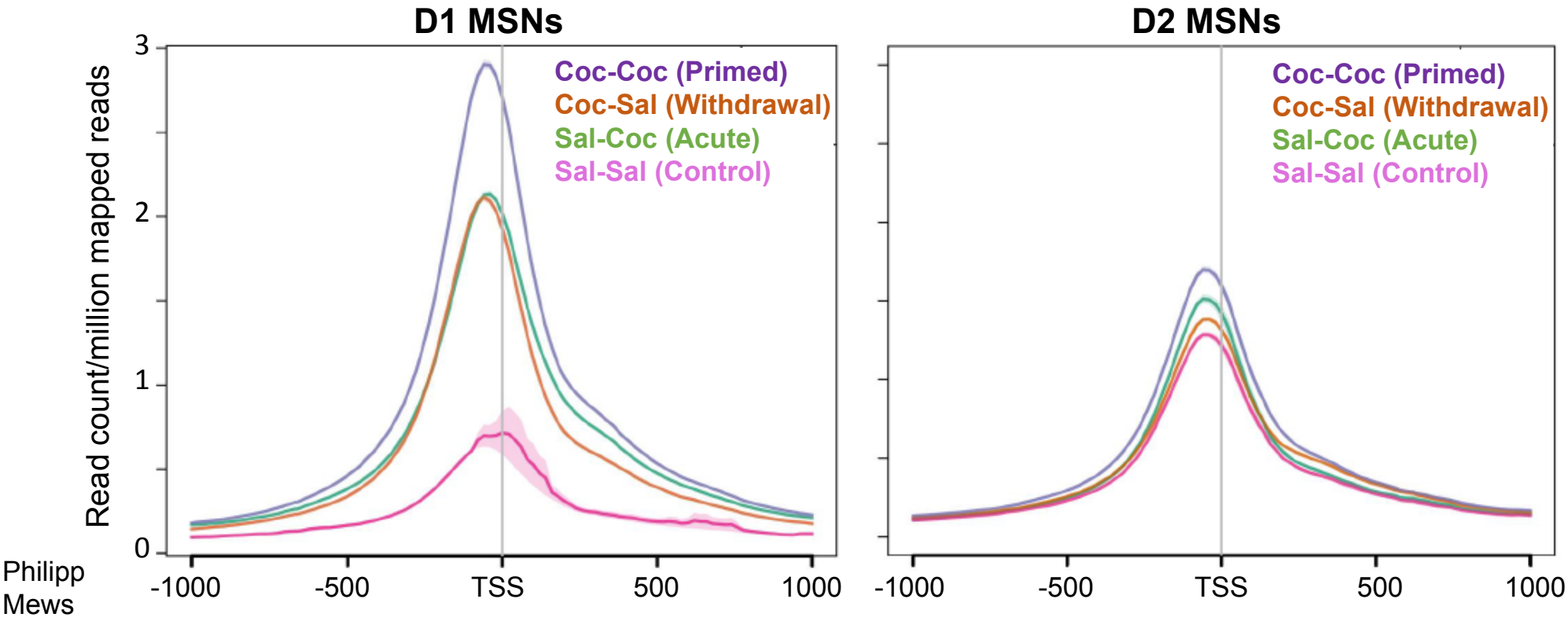


Lobo et al., *Science*, 2010; *J Neurosci*, 2013; Calipari et al., *PNAS*, 2016; other labs

ATAC-seq Reveals Genome-Wide "Opening" of Chromatin Selectively in D1 Medium Spiny Neurons



D1 MSN chromatin is less open at baseline, but shows greater activation during incubation (withdrawal) and priming after chronic cocaine exposure:

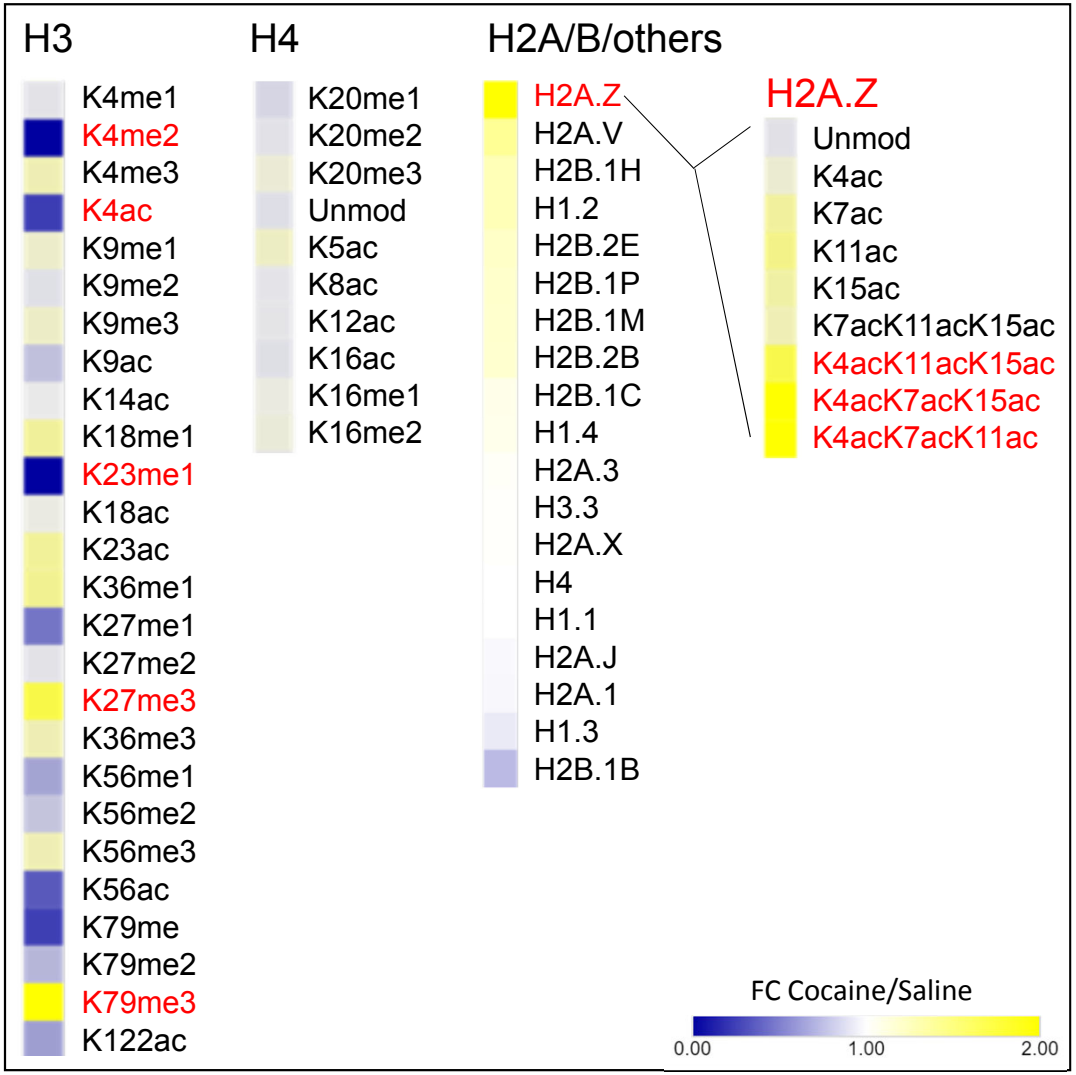


Philipp Mews

Detection of Cocaine-Induced Histone Modifications

Proteomic analysis to identify histone and other modifications associated with gene "priming or desensitization" in NAc in an unbiased manner:

These findings are now guiding ChIP-seq studies to understand the genomic loci and biochemical features of long-lasting "chromatin scars".

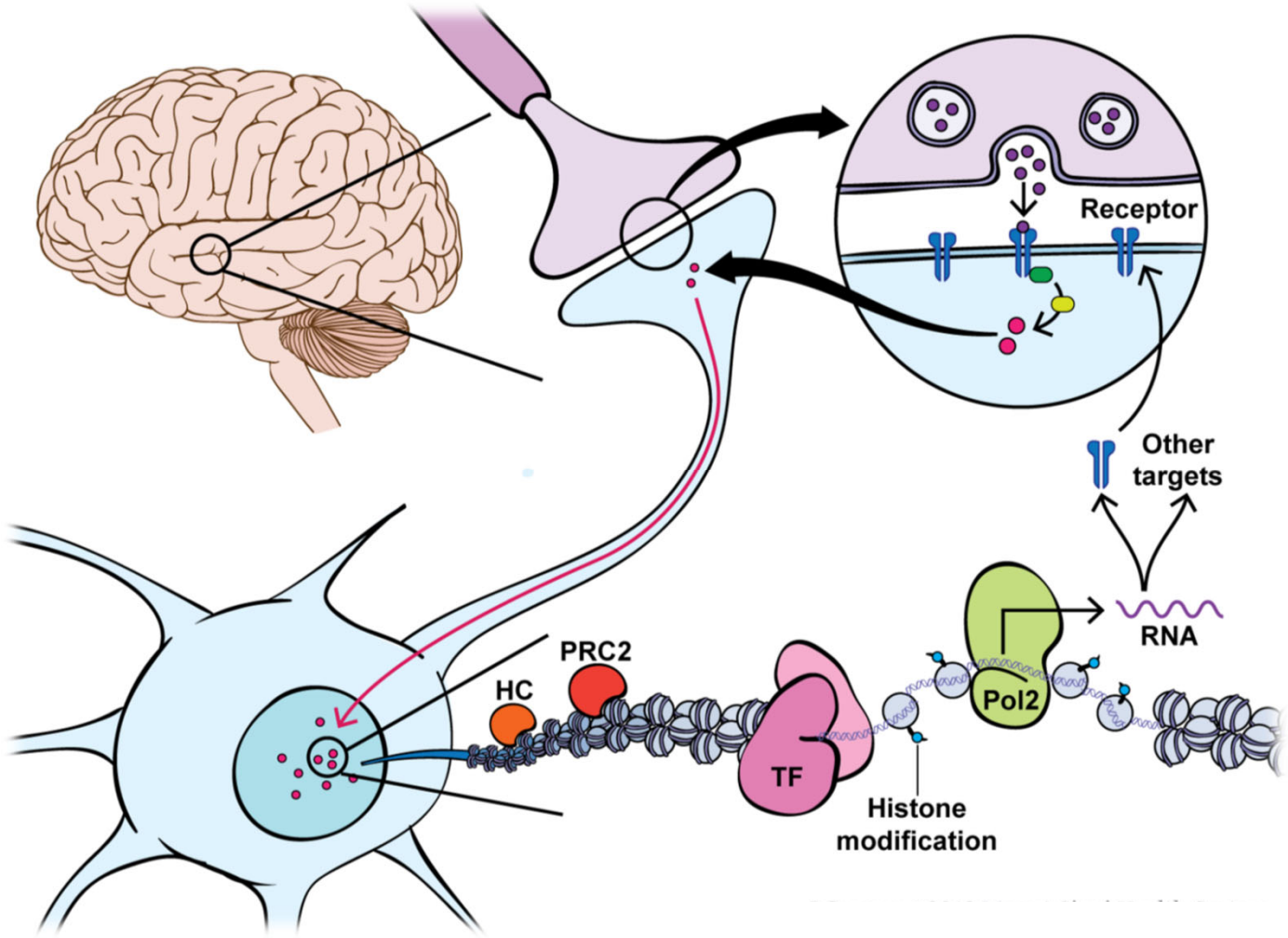


Philipp Mews; Simone Sidoli & Ben Garcia

Template for Drug Discovery

These unbiased studies provide an unprecedented look at genes, proteins, and biochemical pathways that are crucial for the addiction process and will guide drug discovery efforts beyond initial drug targets per se.

It is even conceivable that epigenetic factors underlying addiction could themselves be effective targets.



Summary and Future Directions

1. Despite powerful psychological and social factors, drug addiction is a highly biological phenomenon, and great strides are being made in understanding that underlying biology.

2. The current challenge is to translate these discoveries into improved diagnostic tests, treatments, and prognostic information for human addiction.

3. Unbiased characterization of transcriptional and epigenetic mechanisms, which provide a template for drug discovery.

- **Studies of specific cells in several brain reward regions.**
- **Understanding "chromatin scars" that maintain an addiction for a lifetime.**

Icahn School of Medicine at Mount Sinai

NIH National Institute on Drug Abuse
Advancing Addiction Science