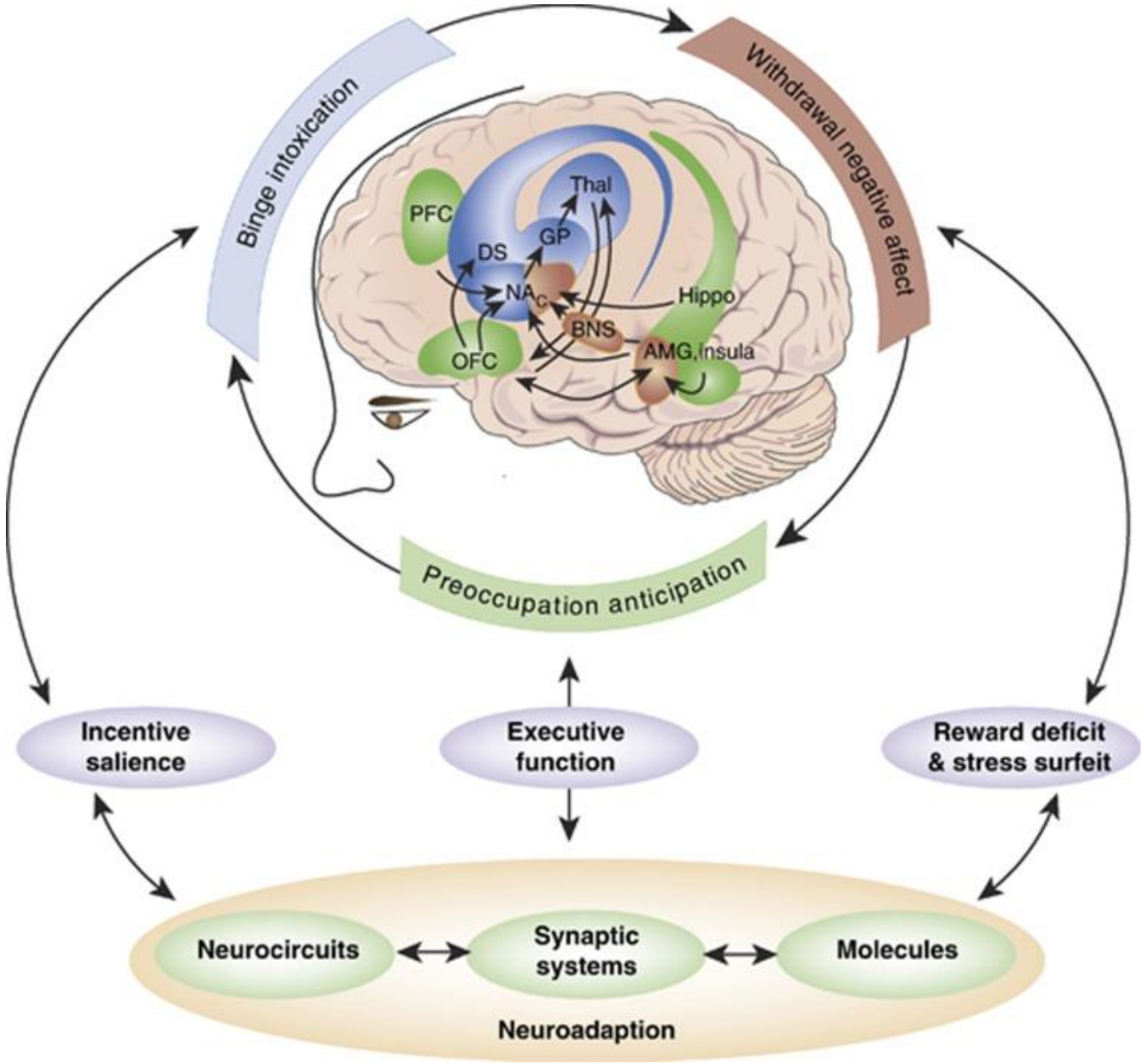
UNODC
United Nations Office on Drugs and Crime

Pathogenesis of Substance Use Disorders

Gilberto Gerra

Chief

Drug Prevention and Health Branch

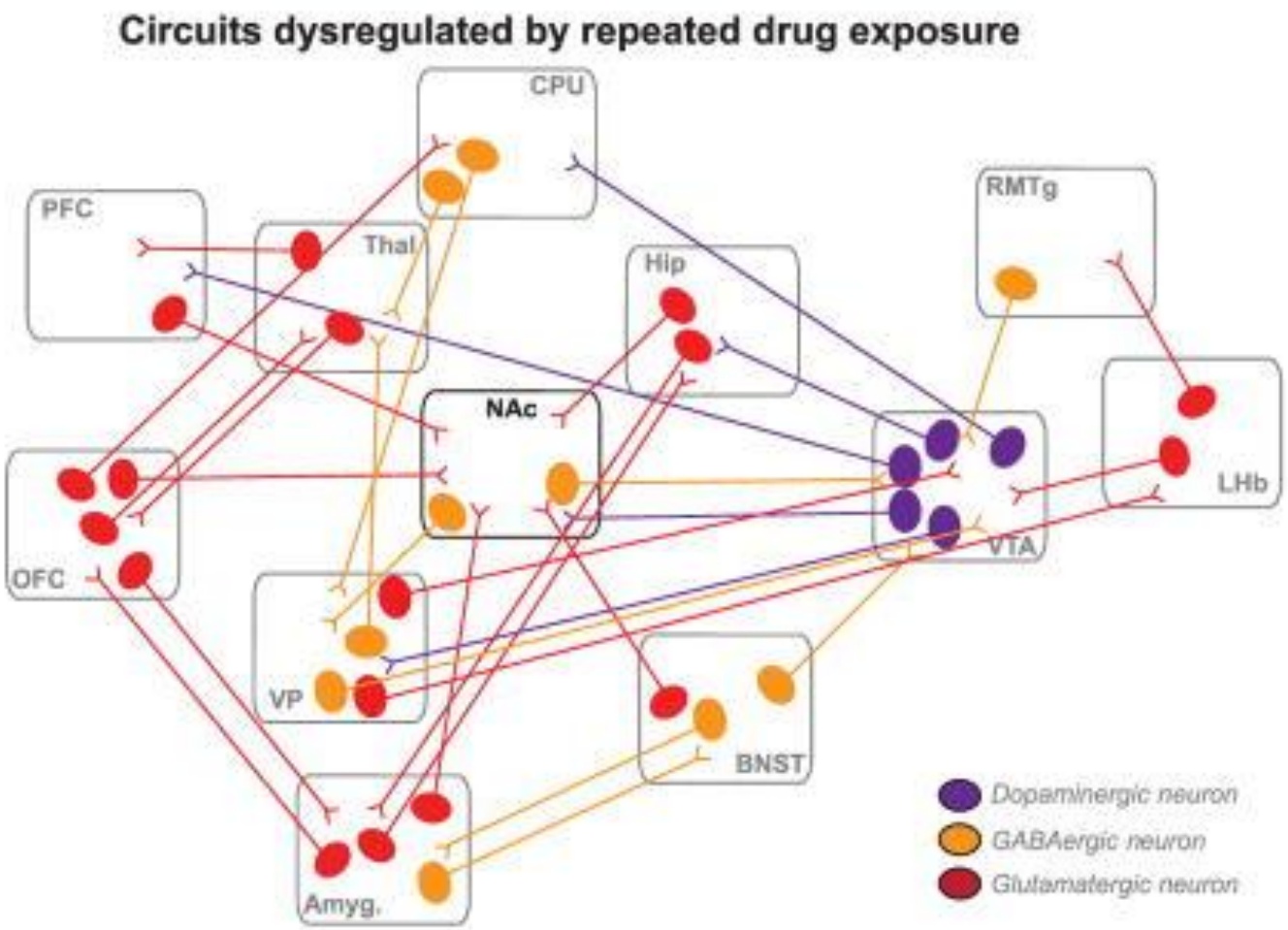


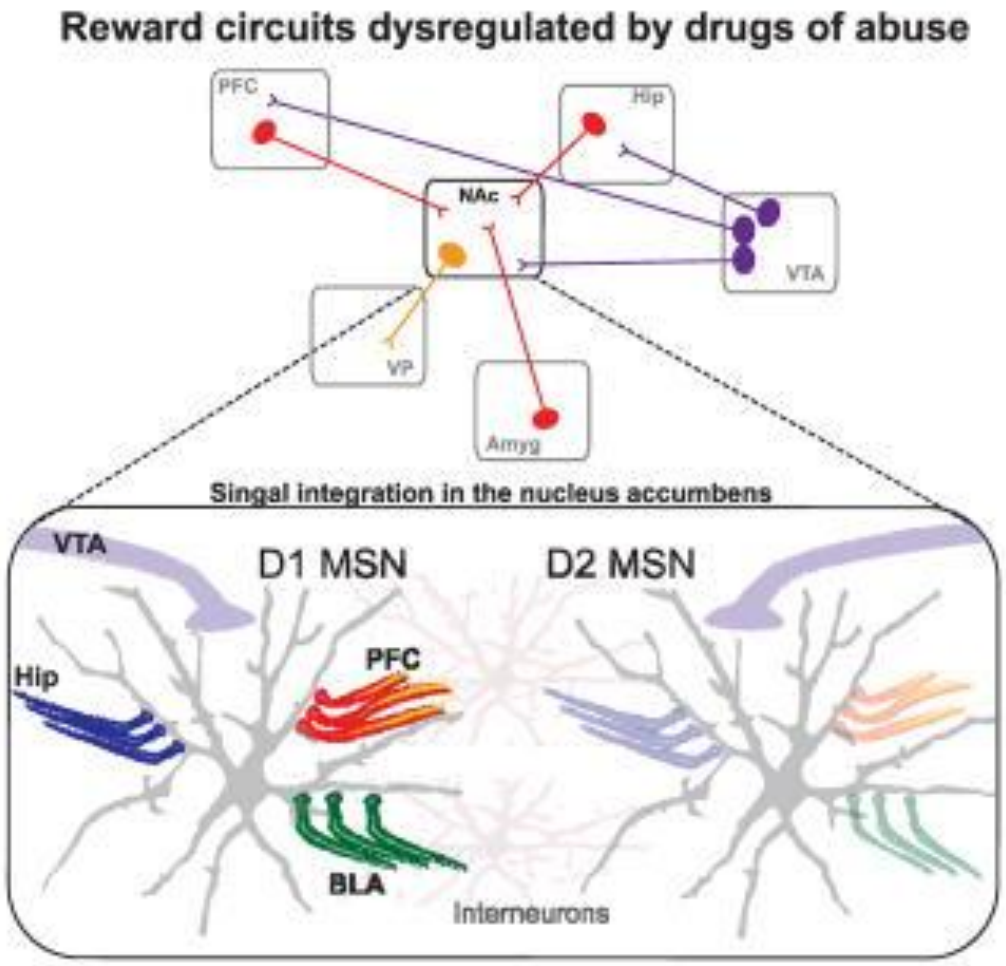
Reward

Aversion

Motivation

Wise and Koob, 2014

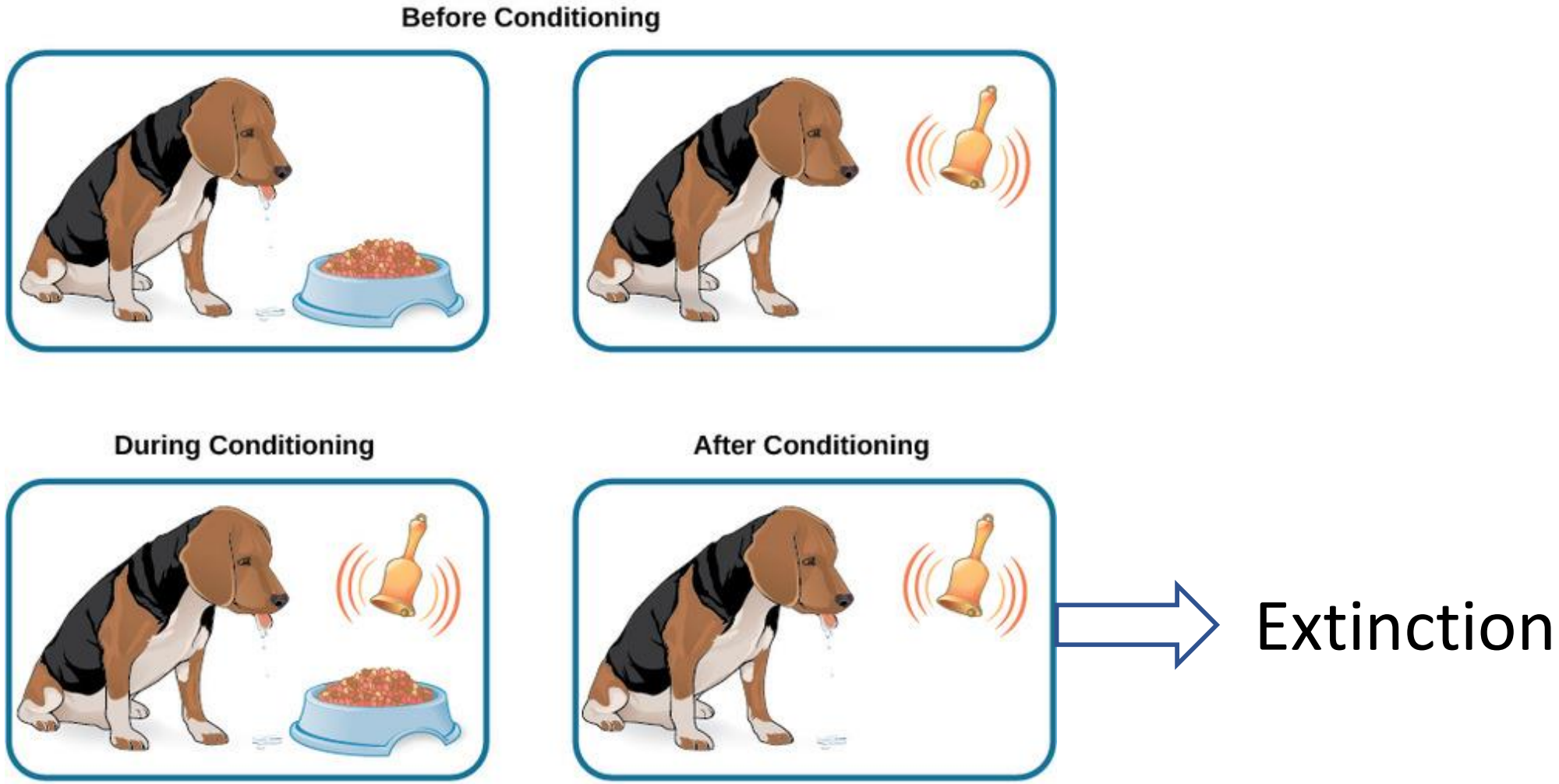




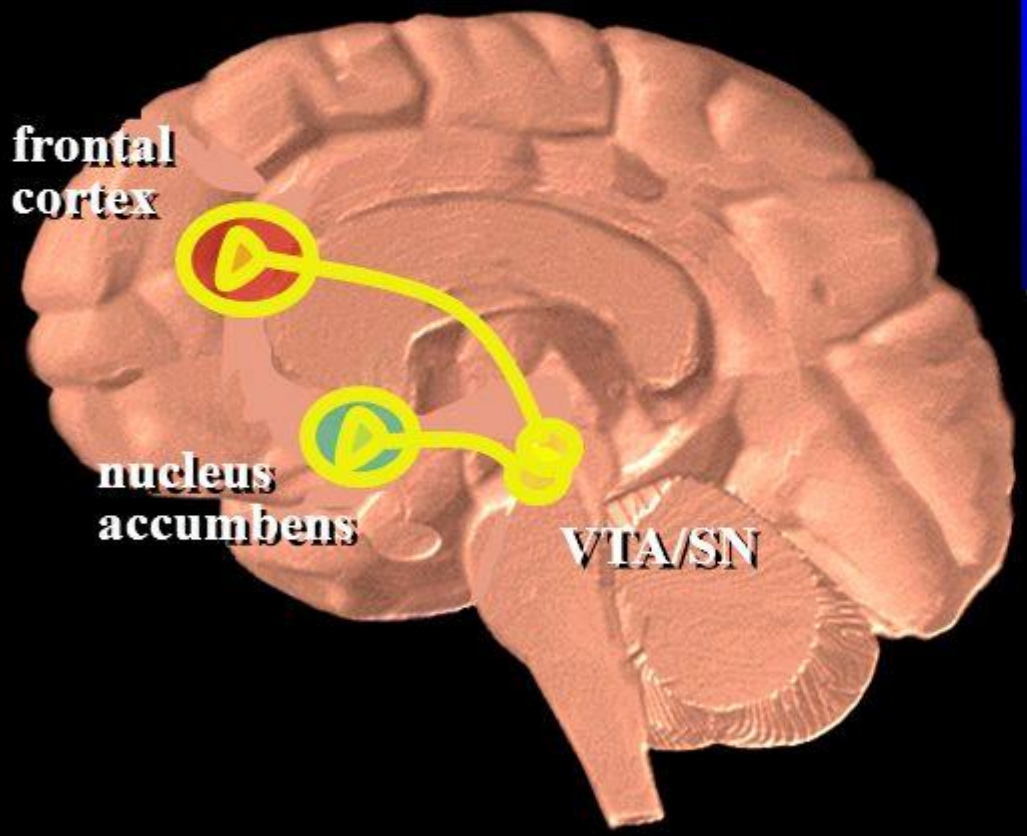
Mews and Calipari, 2017

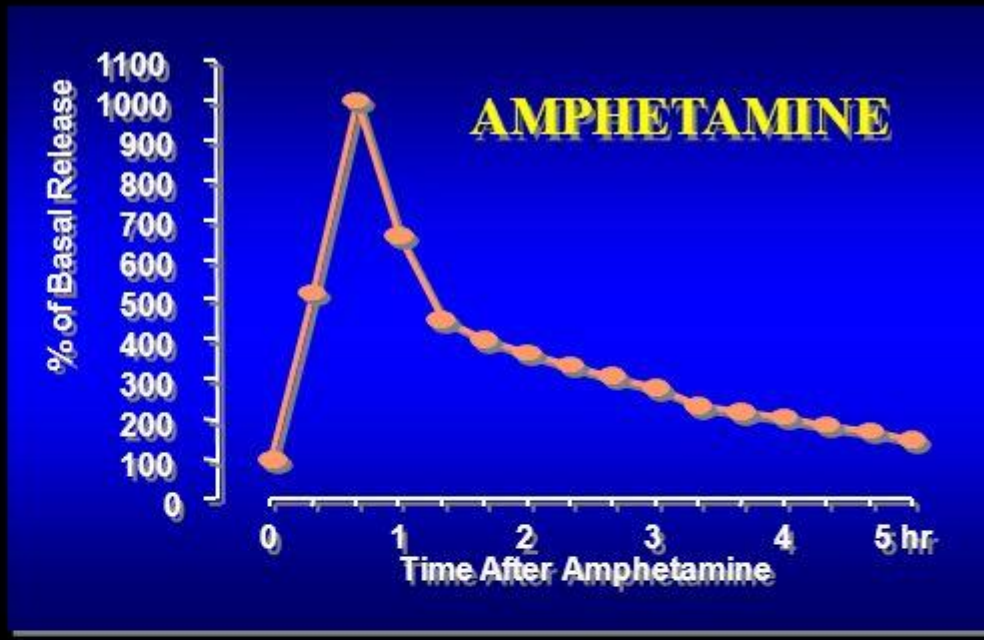
GABAergic projection neurons: Medium Spiny Neurons (MDMs)

Why natural rewards do not create addiction?



Dopamine Neurotransmission





Behaviour to obtain natural rewards

Easy extinction

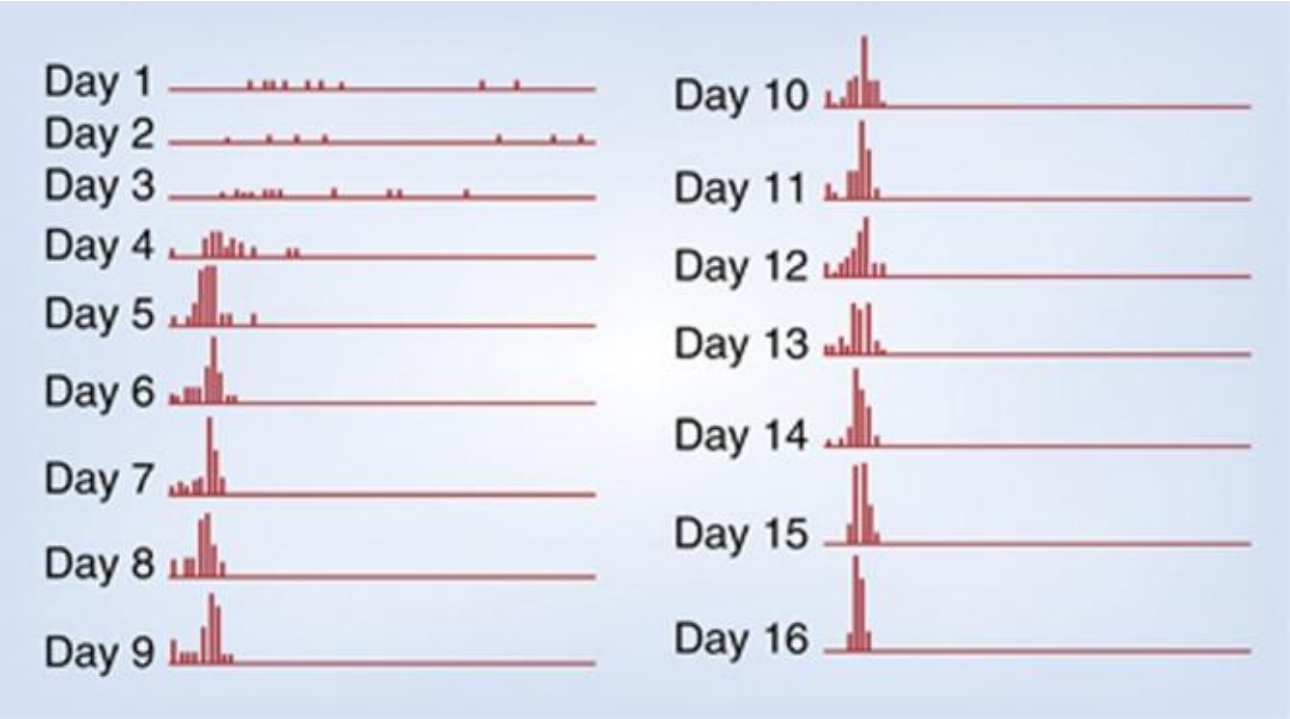
Learn new contingencies

Synaptic remodelling in NAc and PFC

Plasticity: possibility of adaptive mechanism to new rewards

In the case of drug reinforcers
- the process is dysregulated
- inability to update information and extinguish maladaptive behavioural responses
- reduced plasticity

Inter-response intervals from a rat lever-pressing for intravenous cocaine



Narrowing of the distribution of the inter-response times: compulsive cocaine taking

Wise and Koob 2014

In healthy individuals

Association between salient experiences and the related environments

Decision making to guide behaviour toward advantageous outcome

Survival - plasticity

Essential for animals to **successfully navigate their environment**

In addiction, inability to extinguish the associations with cues: dopamine responding only to drugs

- remodelling synaptic connectivity
- **not only neuronal activation**
but transcription epigenetic changes

The ability to increase dopamine levels initially is critical to the reinforcing process

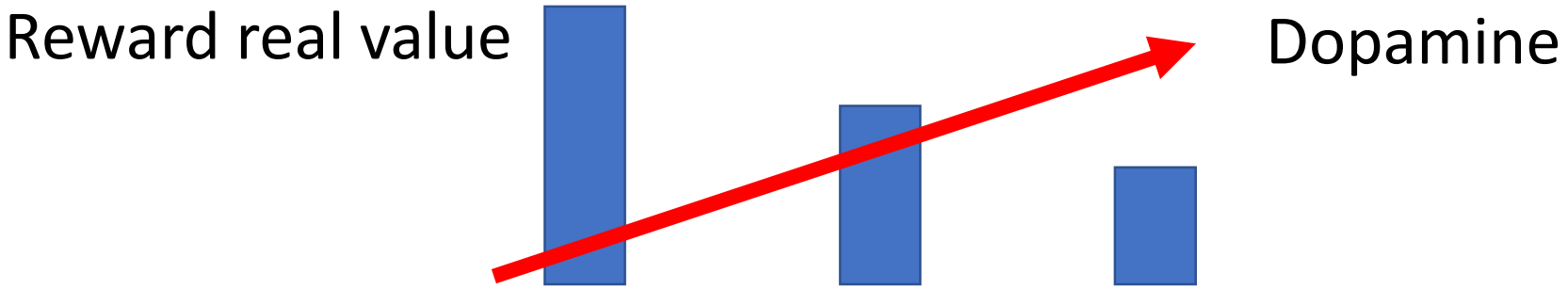
Dopamine acts to predict reward availability and value

For normal individuals, low value of the reward = low dopamine. High reward value = high dopamine

In contrast **drugs: making the neural representation of the reward greater than the value of the reward itself**

The next time the cue is presented the prediction will be that the reward is even bigger

Drugs hijack the reward prediction system, so that they respond maximally do drug predictive cues



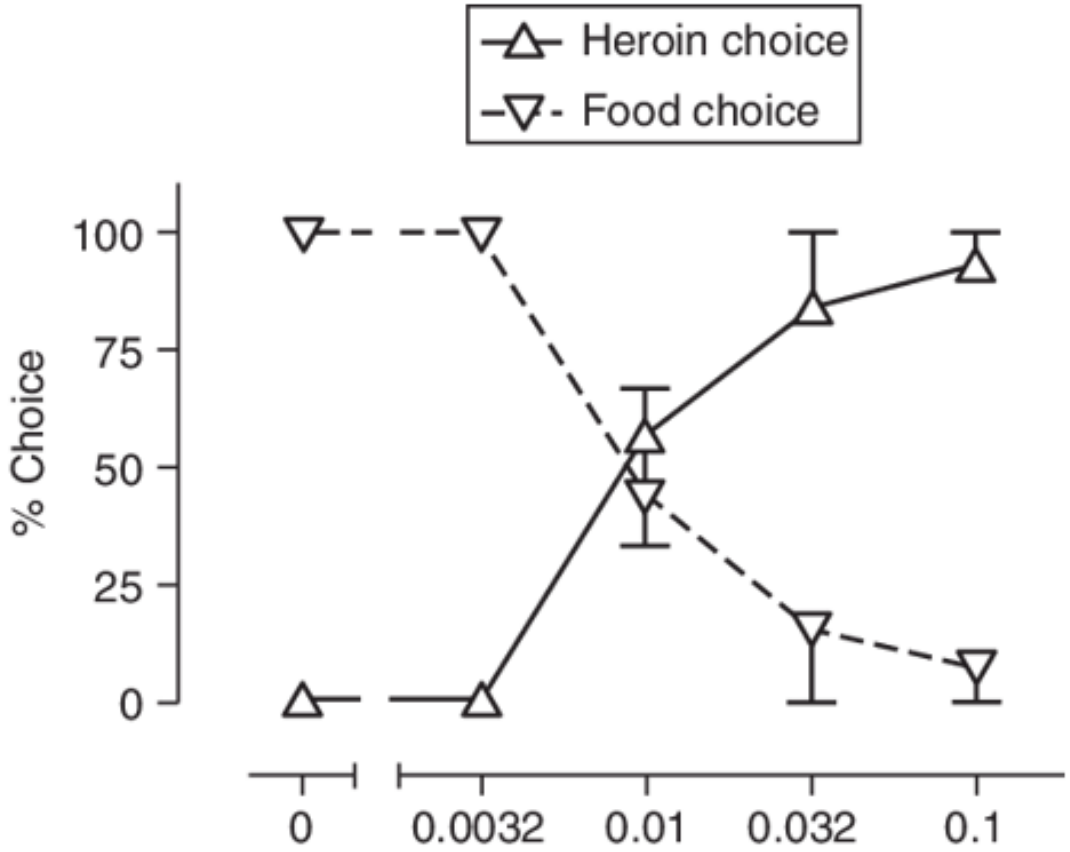
Choose the reward over the others available

Choose heroin over food

Starvation: administer drug to the point of death

After long term abstinence strong memory responsible for relapse

The prediction signal is augmented and guides animals toward bias choices



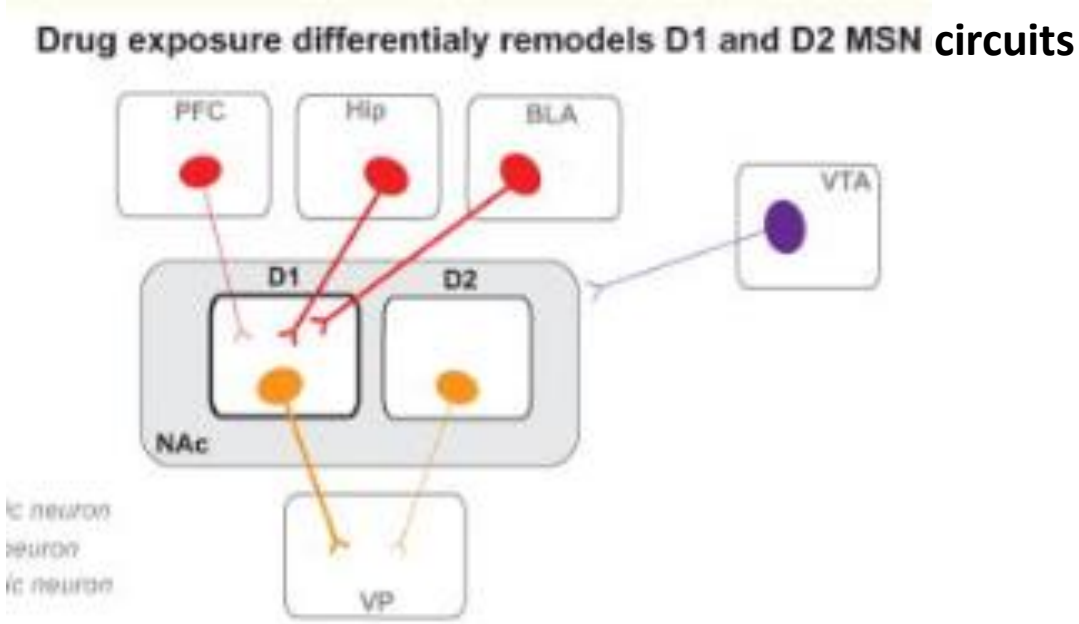
Negus and Rice, 2009

D1 e D2 receptors balance and activation

- D1 signal drug seeking

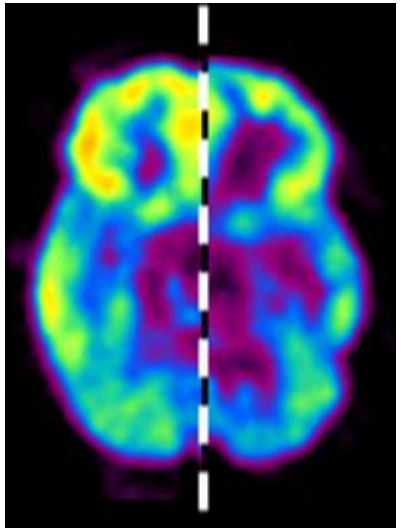
- D1 and D2 signal food self administration

Difference in encoding for food and drugs



Natsubori et al., 2017

Non-addicted brain



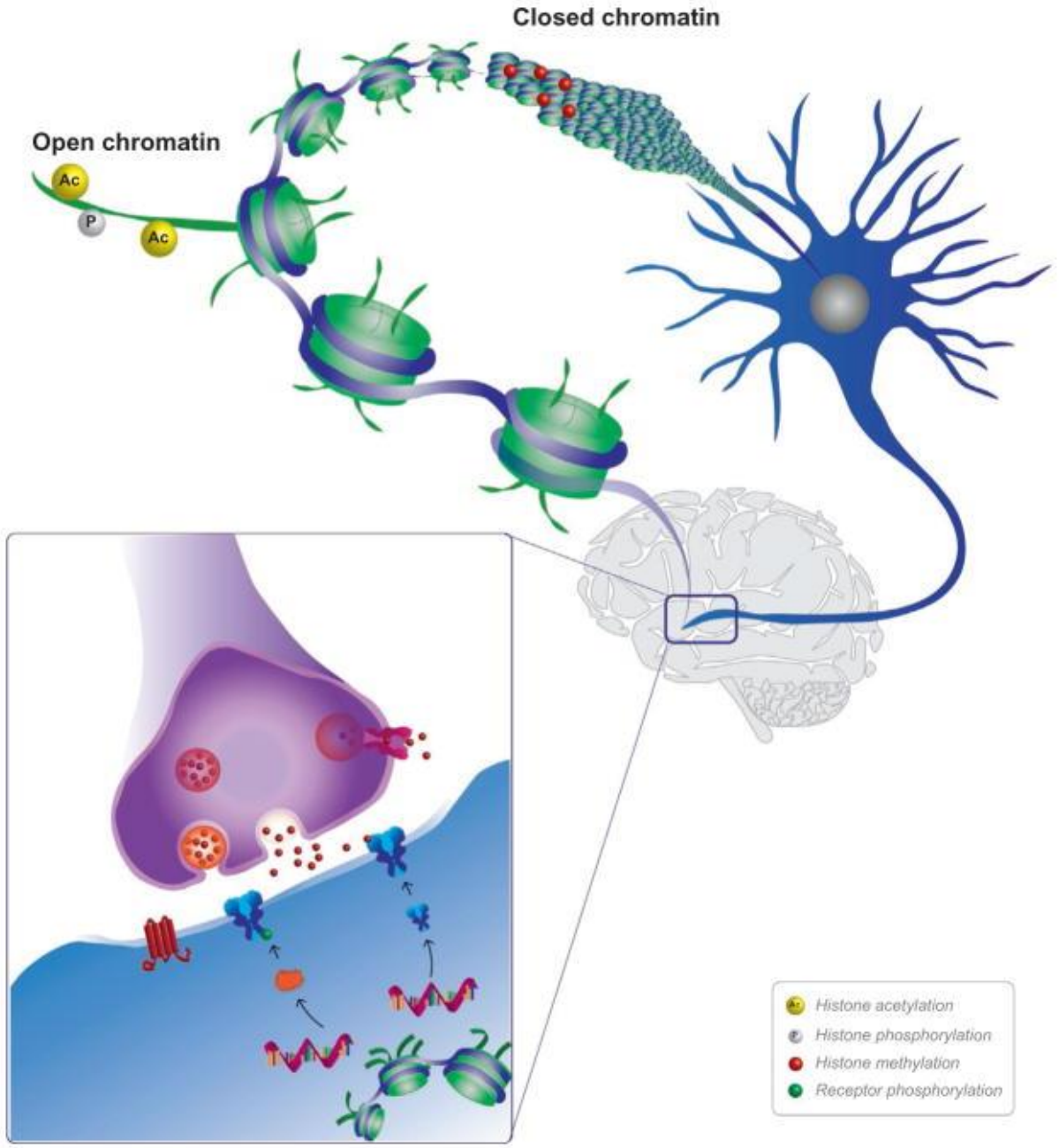
Addicted brain

Adapted: Volkow et al., 2003

Turn genes on - off

The maintenance of
such permanent changes
requires efficient
post-translational
and transcriptional regulation

epigenetic changes
induced by drugs

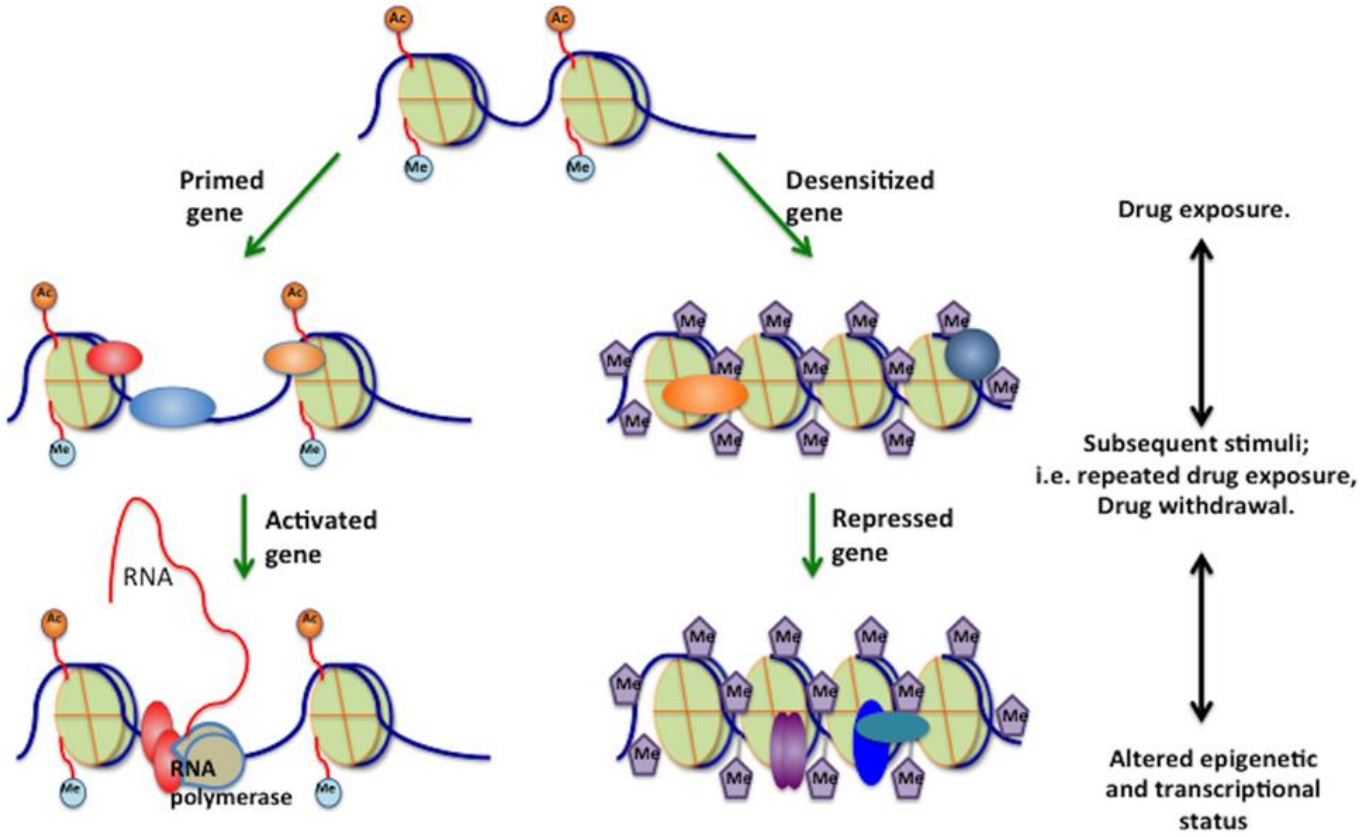


Associative learning about cues and predicted outcome
correlate with increased
acetylation in the hippocampus

Extinction

Reinforcing learning

methylations



Prog Brain Res. Author manuscript; available in PMC 2019 Jan 20.
PMCID: PMC6339819
Published in final edited form as:
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Prog Brain Res. 2017; 235: 19–63.
PMID: 29054289
Published online 2017 Sep 28. doi: 10.1016/bs.pbr.2017.08.012

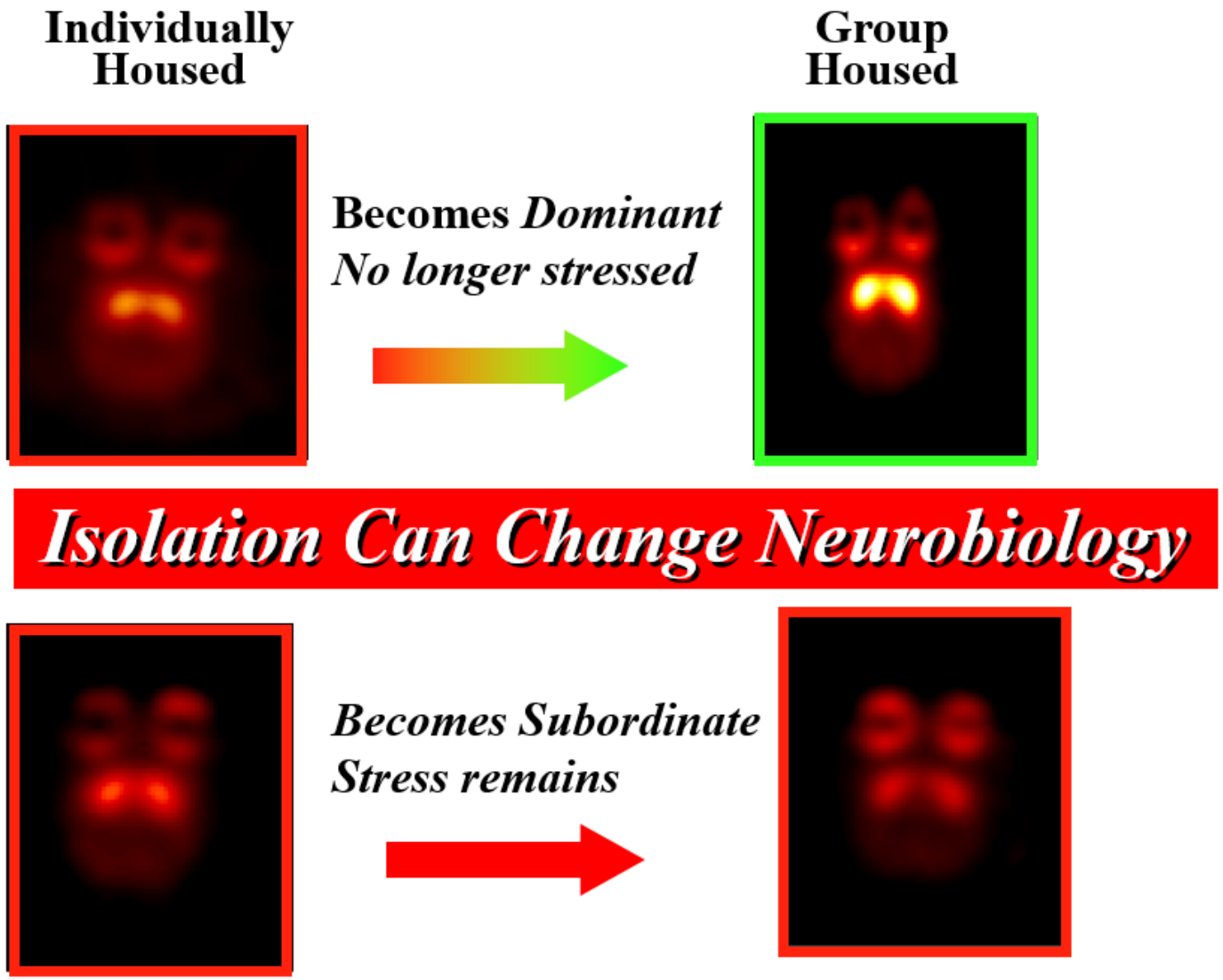
Cross-talk between the epigenome and neural circuits in drug addiction

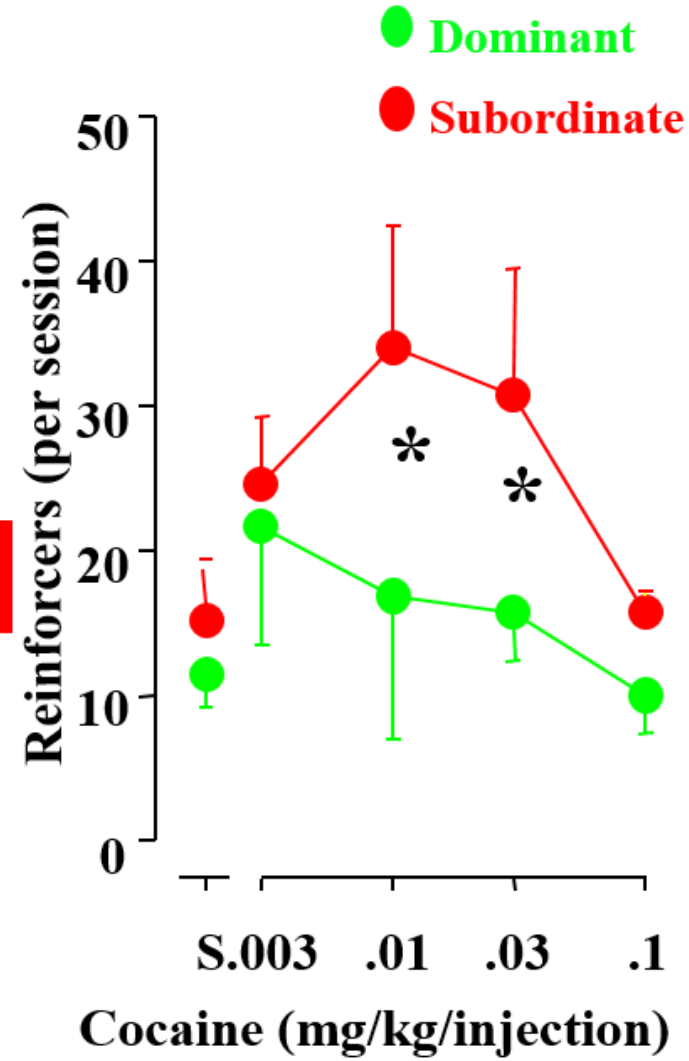
Philipp Mews* and Erin S. Calipari†,1

Who remains trapped in the compulsive cycle?

Reward deficit syndrome Reward delay discount	Dopamine
Maladaptation to Stress/Negative emotions Depression	Glutamate, CRF
Anxiety, obsessive, compulsive planning	GABA, Serotonin

Effects of a Social Stressor on Brain DA D2 Receptors and Propensity to Administer Drugs





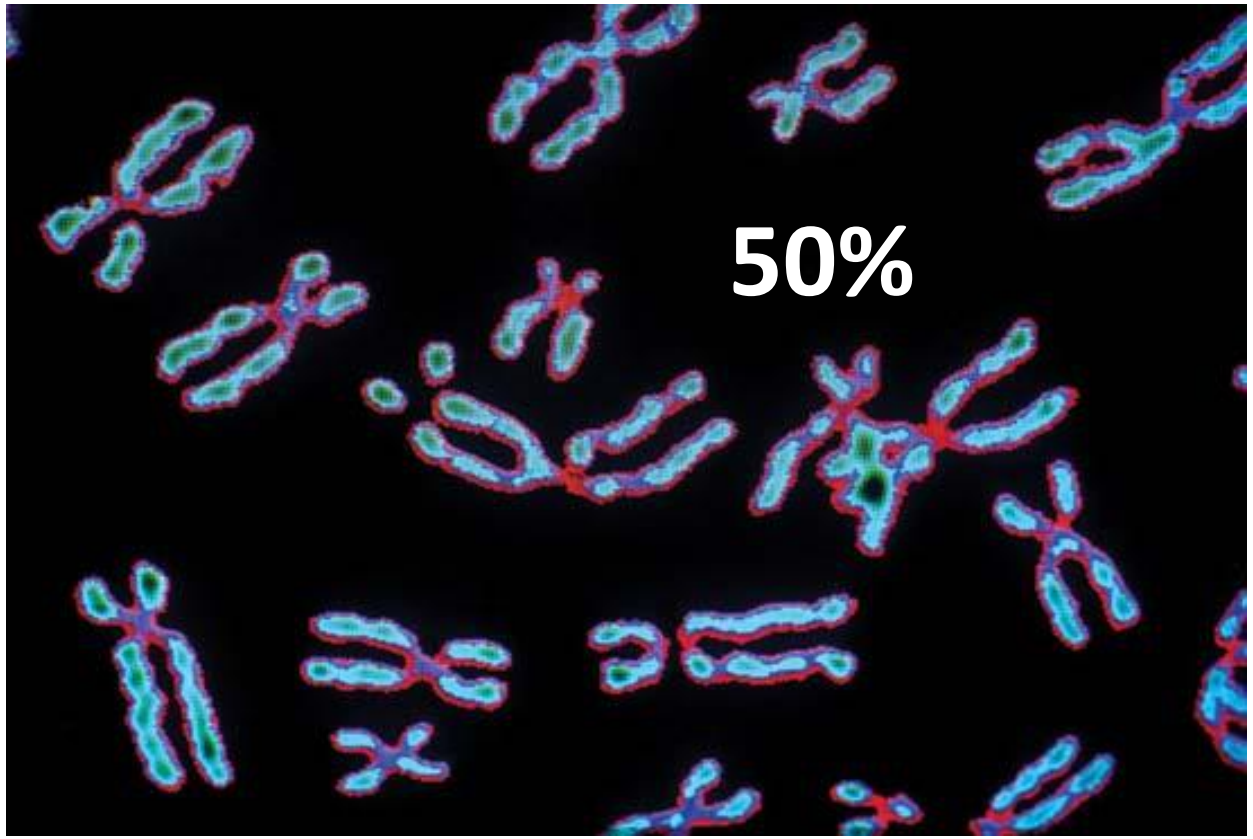
Morgan, D. et al. Nature Neuroscience, 5: 169-174, 2002.

What genes are able to influence?

Variants in genes
codifying for drugs/alcohol
metabolic enzymes

Variants in genes
codifying for drugs/
alcohol effects on the brain

Variants in genes
codifying for risky
temperament and
personality traits

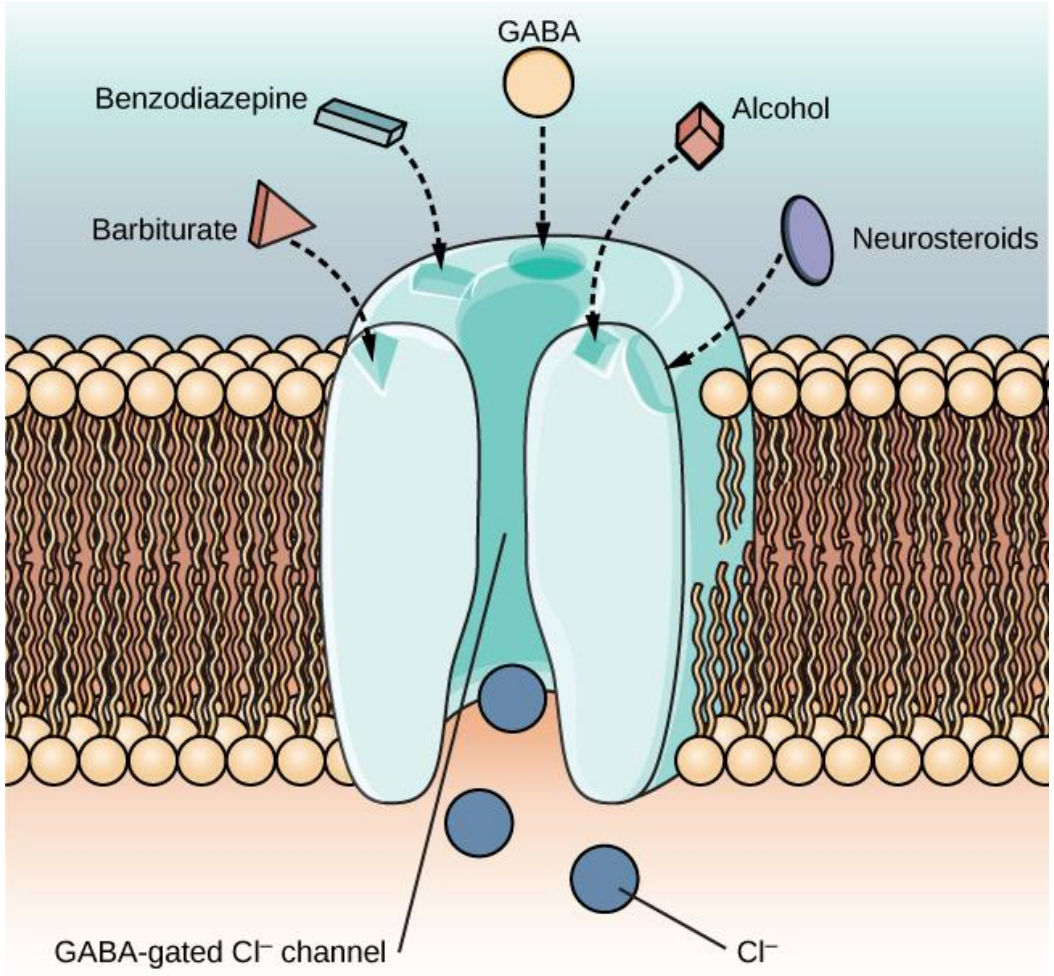


Agrawal and Lynskey, 2008
Pinto and Ansseau, 2009
Iyer-Eimerbrink and Nurnberger , 2014

Neuropsychopharmacology

Several behavioral traits relevant for alcoholism are controlled by ɣ2 subunit containing GABAA receptors on dopamine neurons in mice.

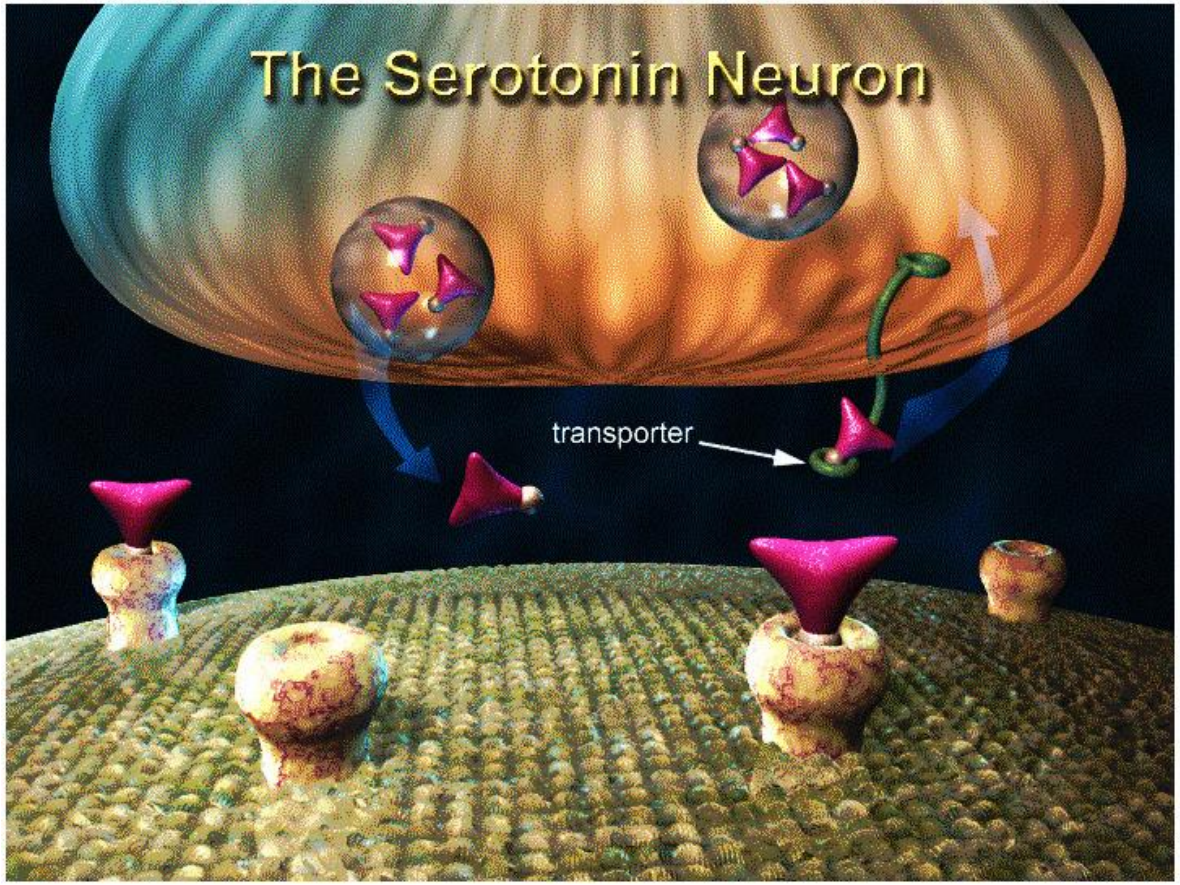
Stojakovic et al., 2018



- Impulsive behaviour
- Less sensitive to the sedative effects
- More dopamine firing / more reward

Genetic variation in $GABA_A$ receptor subunits, including the ɣ2 subunit (Gabrg2), affects the risk for developing alcoholism.

Behav Brain Res. **Association between DRD2, 5-HTTLPR, and ALDH2 genes and specific personality traits in alcohol- and opiate-dependent patients.** Wang et al., 2013



Short allele: low-functional

Addiction

The genetic epidemiology of cannabis use, abuse and dependence.

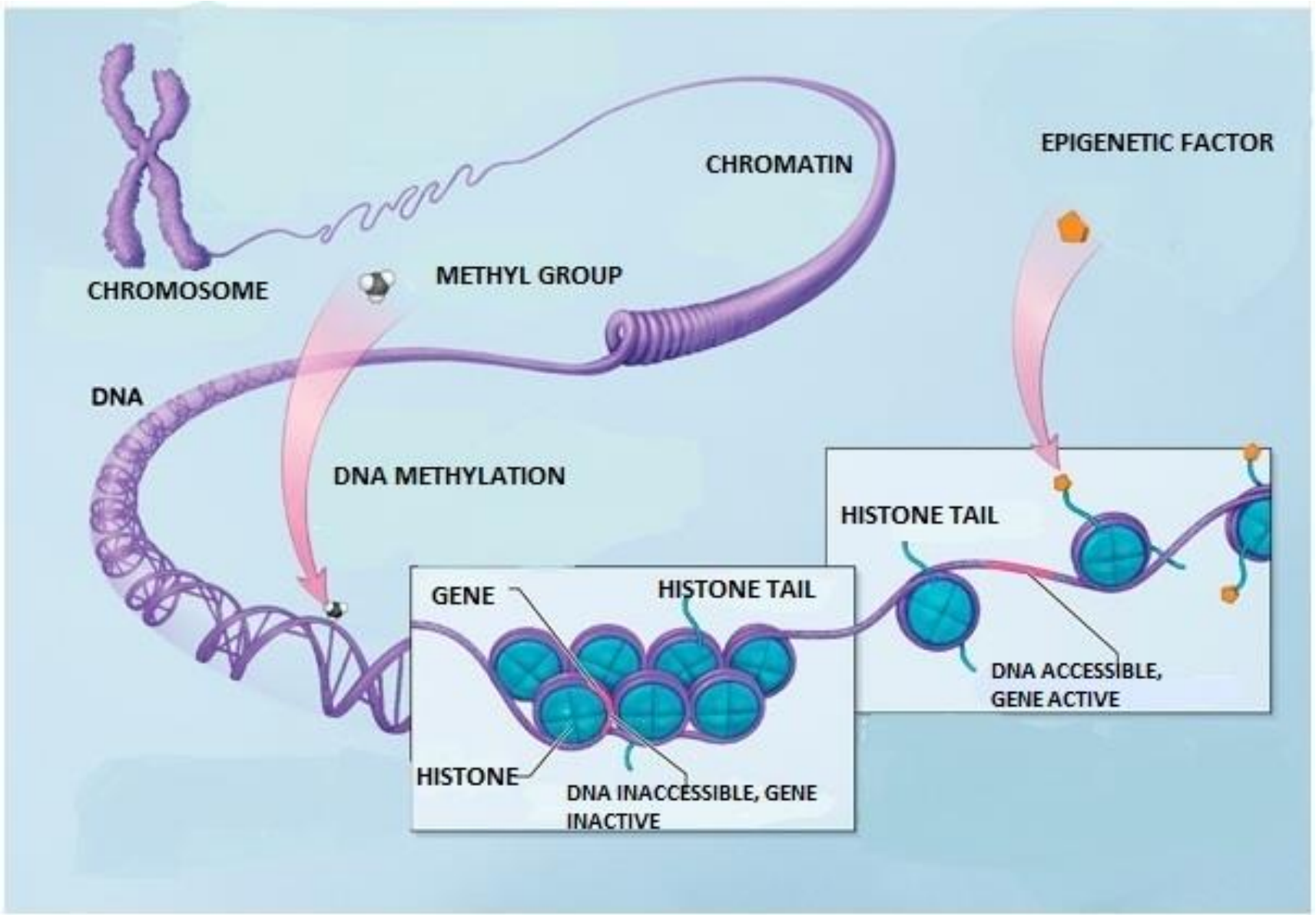
Agrawal and Lynskey, 2006

The substantial evidence for the heritability of …

- cannabis use,
- abuse
- dependence

Genetic basis
to each stage
of cannabis involvement

Epigenetics and environmental factors



Neurotox Res.
Unravelling the Link Between Prenatal Stress, Dopamine and Substance Use Disorder.
Pastor et al., 2017

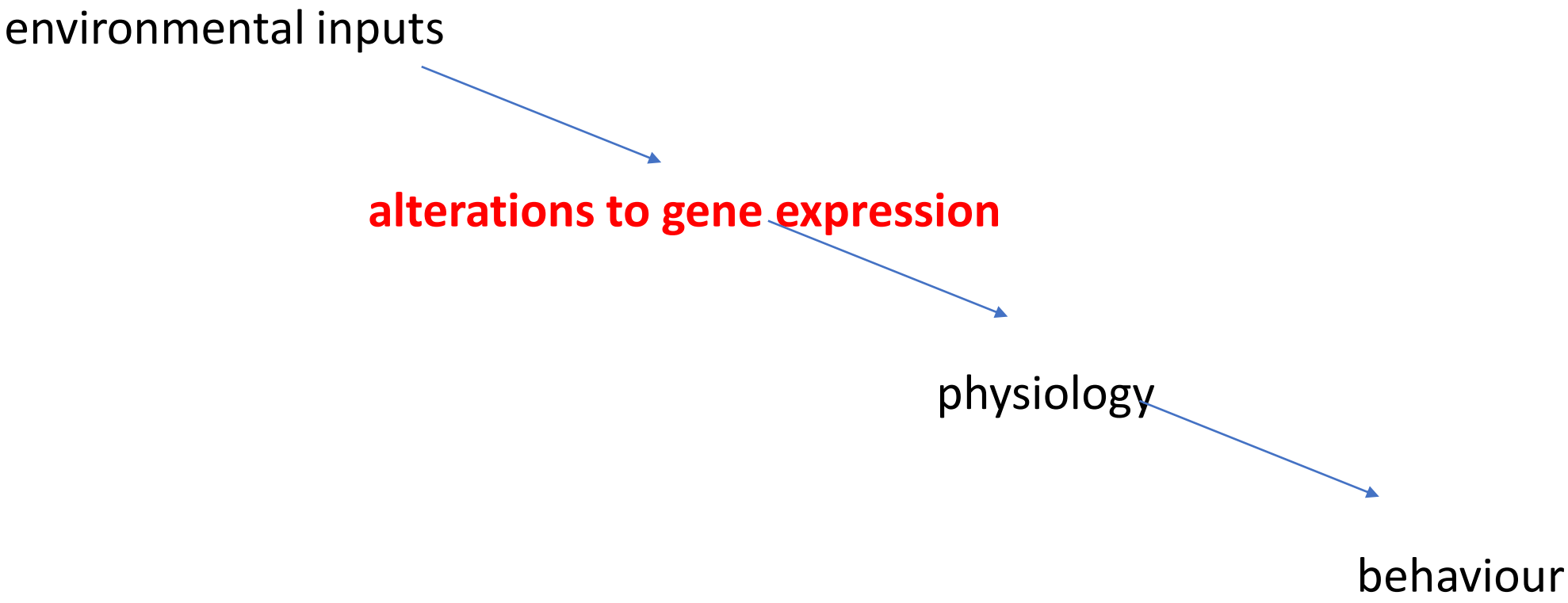
The development of meso-corticolimbic dopaminergic system is disrupted by prenatal stress

Prenatal stress as a candidate to explain SUD vulnerability

Dev Psychopathol.

Prenatal influences on temperament development: The role of environmental epigenetics.

Gartstein and Skinner, 2017.



Molecular mechanism of how environmental factors impact development and subsequent health and disease, including early brain and temperament development.

Nervenarzt.
Addiction as an attachment disorder.
Unterrainer et al., 2017

Substance Use Disorders
as a possible expression
of parent-child attachment
disorder

Disorganized, insecure, poor

Psychiatr Enfant.
The development of attachment according to the temperament of the newborn
Balleyguier, 1991

Infant Behav Dev.
Infant and parent factors associated with early maternal sensitivity: a caregiver-attachment systems approach.
Mills-Koonce et al., 2007

- irritable babies develop an anxious attachment

- avoidant children reduce maternal sensitivity

temperament at birth influences mother's attitude

Adverse Childhood Experiences (ACEs)

Physical/sexual abuse
Physical neglect
Emotional abuse
Emotional neglect
Household dysfunction

affect the brain through epigenetic changes

Neuron

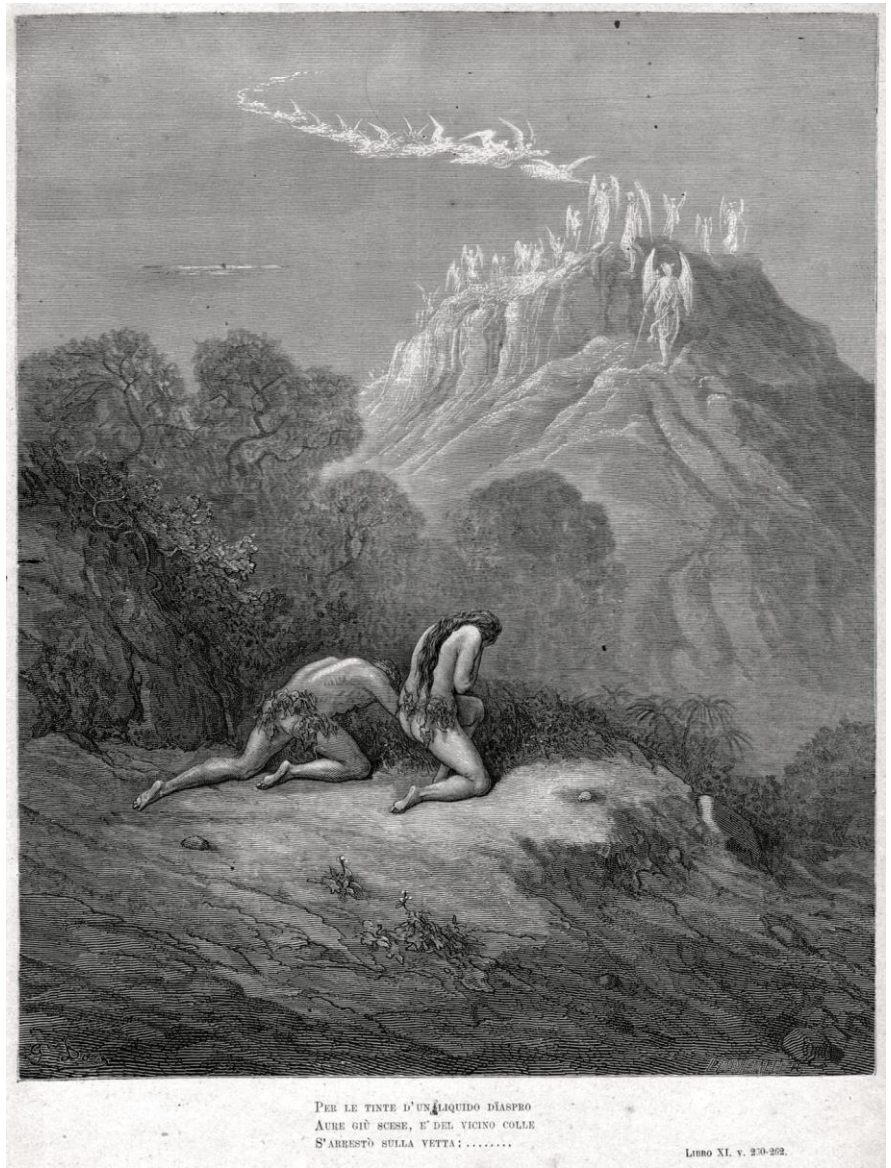
Paradise Lost: The Neurobiological and Clinical Consequences of Child Abuse and Neglect.

Nemeroff, 2016

child abuse and neglect is associated with a marked increase in risk for major psychiatric, **substance use disorders** and medical disorders

persistent biological alterations associated with childhood maltreatment

epigenetic mechanisms thought to transduce environmental stressors into disease vulnerability

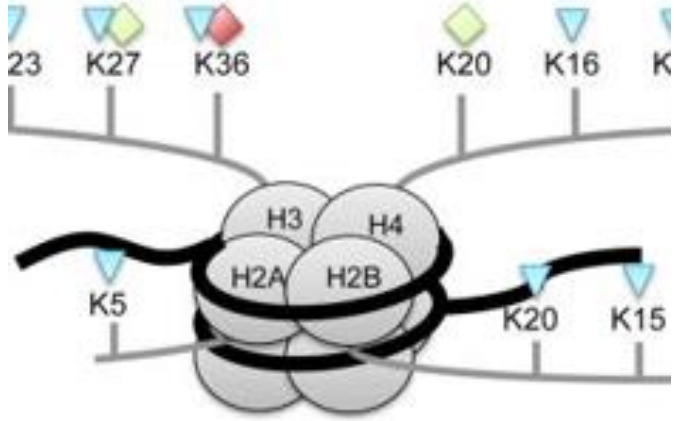


Dev Psychopathol.
Exploring genetic moderators and epigenetic mediators of contextual and family effects: From Gene × Environment to epigenetics.
Beach et al., 2016

the association between family context
and mental and physical health outcomes

early environments may influence epigenetic
motifs that potentially serve as mediators
of long-term effects of early family and
community environments

genotype may sometimes influence epigenetic outcomes



Biol Psychiatry.

Methylation matters: interaction between methylation density and serotonin transporter genotype predicts unresolved loss or trauma.

van Ijzendoorn et al., 2010

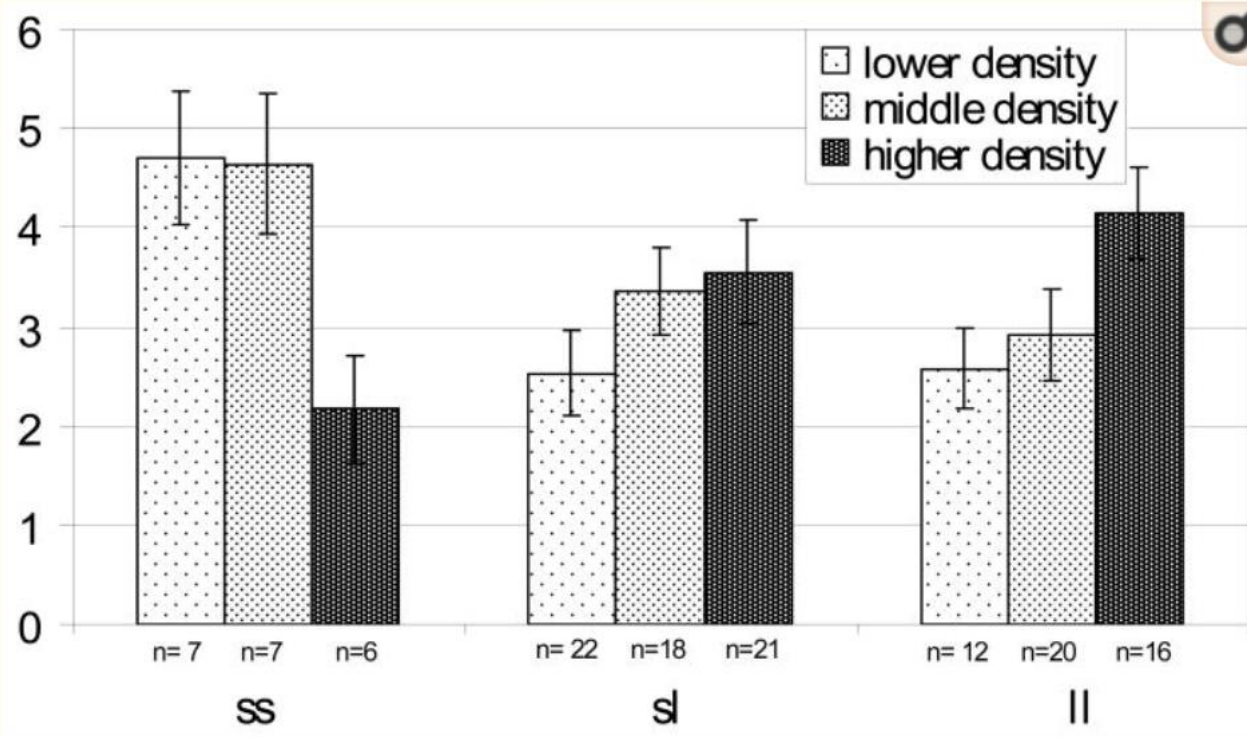


Figure 1

Scores for unresolved loss and trauma (M, SE) as related to 5HTTLPR genotype (*ss, sl, ll*) and methylation density (lower third, middle third, higher third).

Psychol Med.
The rearing environment and risk for drug abuse:
a Swedish national high-risk adopted and not adopted co-sibling control study.
Kendler et al., 2016

Although drug abuse is strongly familial, with genetic influences, we need to know more about the role of rearing environment.

High-quality rearing environments
can substantively reduce risk for substance abuse in those at high genetic risk

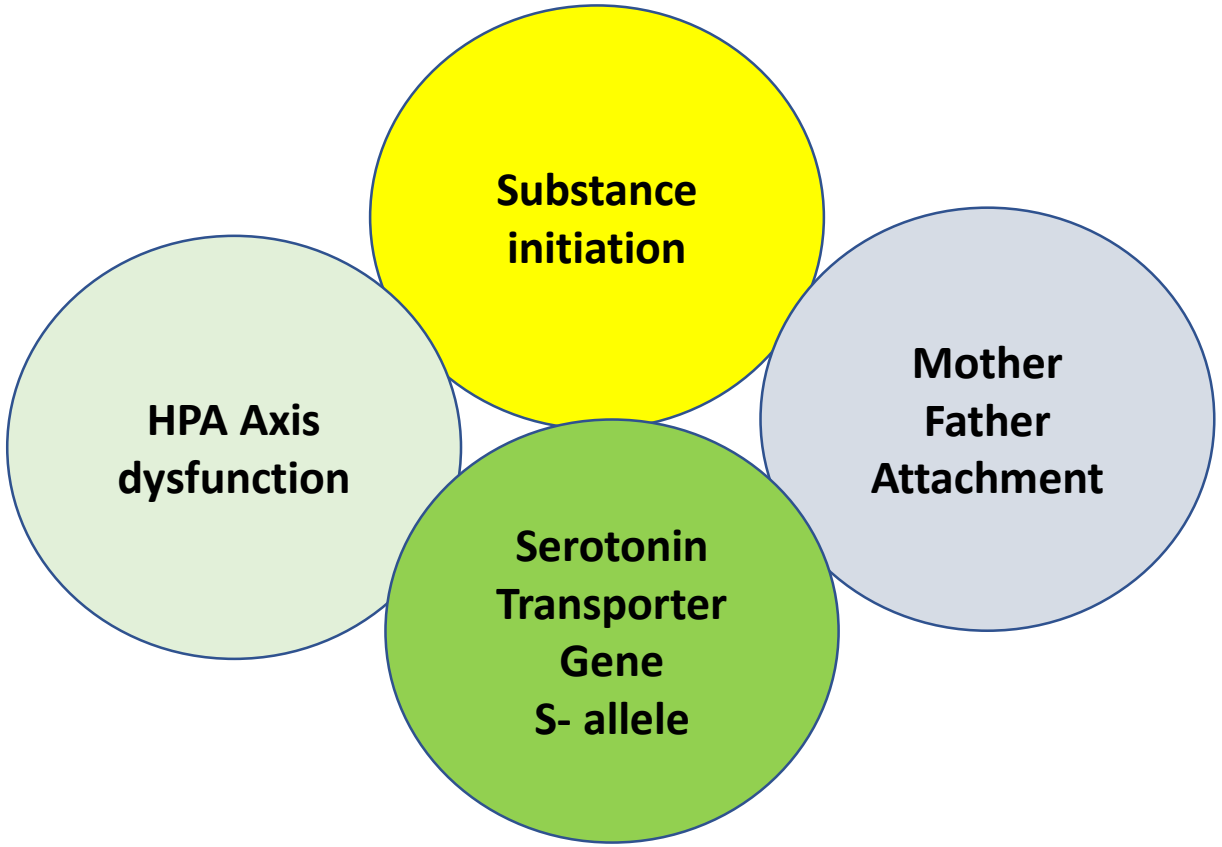
J Consult Clin Psychol. 77(1):1-11.
Parenting moderates a genetic vulnerability factor in longitudinal increases in youths' substance use.
Brody et al., 2009

5-HTTLPR status SS linked with increases in substance use over time

the association was greatly
reduced by **involved-supportive parenting**

- Am. J. Med Genet Part B
Perceived Parenting Behaviour in the Childhood of Cocaine Users:
Relationship With Genotype and Personality Traits. Gerra et al., 2007

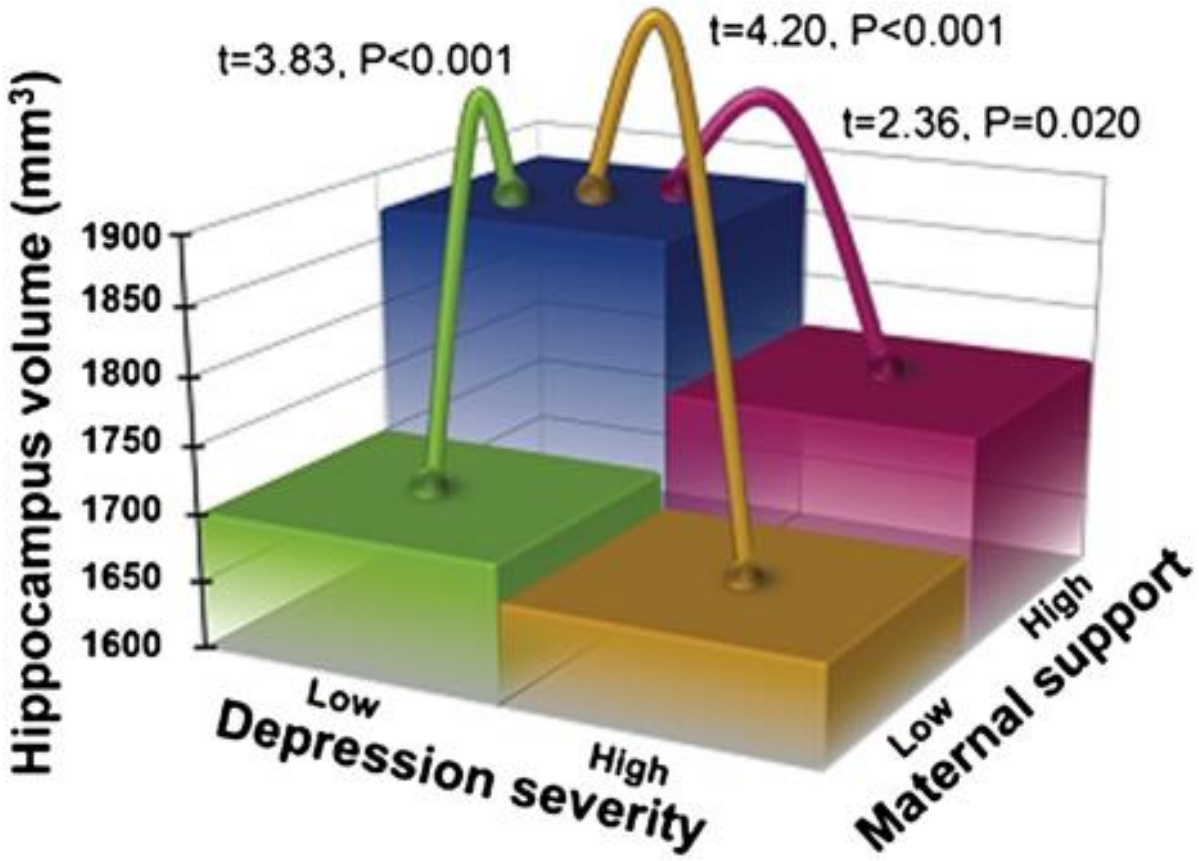
the association between 5-HT transporter polymorphism and psycho-stimulant use may be mediated by mother-child relationship and parental attachment perception, both being environmental and genetic factors involved in the proneness to substance use disorders



Proc Natl Acad Sci U S A.

Maternal support in early childhood predicts larger hippocampal volumes at school age.

Luby et al., 2012



Maternal support has been shown to promote specific gene expression and neurogenesis

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Dysregulated responses to emotions among abstinent heroin users: Correlation with childhood neglect and addiction severity☆

Childhood neglect

Altered response to emotions

HPA axis dysfunction

Addiction Severity

Gerra et al., 2013

Half of those who experience a mental illness during their lives will also experience a substance use disorder and vice versa

NIDA 2018
Ross *Clin Neuropharmacol*. 2012.
Kelly and Daley *Soc Work Public Health*. 2013.

Psychosocial and behavioural interventions

The large framework of health, welfare and wellbeing (UNGASS, 2016)

- Children social protection
- Improving parental skills
- School connectedness

E-mail
gilberto.gerra@un.org

Twitter
@gilbertogerra