TWIST Training With Stakeholders
Applying EU Addiction Research

NEUROSCIENCE TWIST YOUR BRAIN

FERNANDO RODRÍGUEZ DE FONSECA & OLGA VALVERDE

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UNIVERSIDAD DE MÁLAGA

Red de Trastornos Adictivos

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TWIST YOUR BRAIN!
IT DOESN'T HURT

- **LET'S EXPLAIN A FEW HISTORICAL MILESTONES THAT SHOW WHY ADDICTION IS A BRAIN SCIENCE**
- **(the new narcos know more about chemical neuroscience that most of us)**

SCHEME OF THE TRAINING

- **Min 1→25: WHY ADDICTION IS A BRAIN SCIENCE**
  - **(Dr. Fernando Rodriguez de Fonseca)**

  - HISTORICAL VIEW OF SCIENTIFIC THEORIES OF ADDICTION
  - HOW THE MOTIVATIONAL BRAIN EMERGES AS THE CORE OF THE PROBLEM

- **Min 25→70: THE NEUROSCIENCE OF SUBSTANCE USE DISORDER**
  - **(Dr. Olga Valverde)**

  - ADDICTION IS AN ADAPTIVE DISORDER
  - STARRING ROLES: MOLECULAR, CELLULAR AND CIRCUITS

- **Min 70→80: OVERLAPING NEUROSCIENCE OF ADDICTION AND MENTAL DISORDERS.**

- **Min 80→90 GENERAL DISCUSION AND QUESTIONS**

OUR CONCEPT IS:

www.sciencemag.org • SCIENCE • VOL. 278 • 3 OCTOBER 1997

FRONTIERS IN NEUROSCIENCE: THE SCIENCE OF SUBSTANCE ABUSE

Addiction Is a Brain Disease, and It Matters

Alan I. Leshner

YES, IT HAS MEDICAL CONSEQUENCES, BUT THE DEBATE IS STILL OPEN

frontiers in PSYCHIATRY

HYPOTHESIS AND THEORY ARTICLE
published: 11 April 2013
doi: 10.3389/fpsyt.2013.00024

Addiction is not a brain disease (and it matters)

Neil Levy*

Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia

THEORY 1

ADDICTION IS CAUSED BY CHEMICALS

- **ONLY FEW CHEMICALS, LESS THAN 1/100.000, HAVE THE POTENTIAL OF BEING ABUSED BY HUMANS.**
- **WHEN GIVEN THE OPPORTUNITY OF SELF-ADMINISTERING THESE COMPOUNDS, ANIMALS USE, ABUSE AND CAN LOSS CONTROL OVER INTAKE**
- **ALONG HISTORY, WE ISOLATED THESE COMPOUNDS FROM PLANTS AND LEARNT HOW TO SYNTHESIZE THEM, OPTIMIZE ITS CHEMICAL NATURE, AND CREATE NEW PRODUCTS.**

MORPHINE→ 1817
NICOTINE→1828
COCAINE→ 1862
THC→ 1964

→

HEROIN → 1874
AMPHETAMINE → 1887
SPICE HU-210 → 1994
MEPHEDRONE → 1929 (2003)

THEORY 1

ADDICTION IS CAUSED BY CHEMICALS

- **ALL LEGISLATION, INTERNATIONAL TREATS, POLICIES, AND EVEN WARS ARE AROUND THESE CHEMICALS. THINK ABOUT UNO SCHEDULES: JUST CHEMICALS WITH OR WITHOUT MEDICAL INTEREST.**

- **UPON DISCOVERY OF THE TARGETS OF THESE CHEMICALS NEW MEDICINAL CHEMISTRY PROGRAMS LAUNCHED BY PHARMACEUTICAL INDUSTRY AND ACADEMIA PRODUCED HUNDREDS OF NEW STRUCTURES WITH ADDICTIVE POTENTIAL**

- **THOSE NEW CHEMICALS FLOODED THE MARKET IN THE XXI CENTURY. THE EPIDEMICS OF NPS**

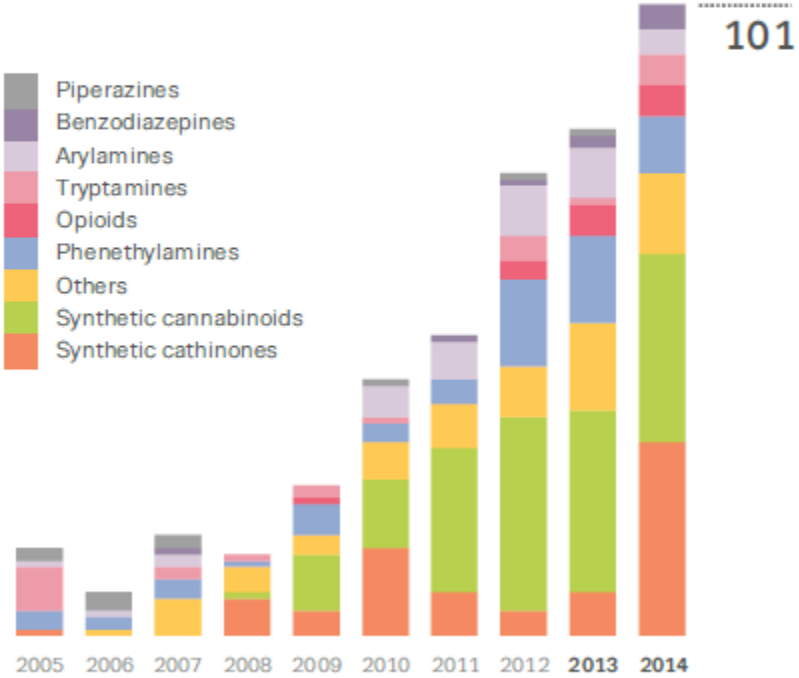
- **IMPORTANTLY: ALL THE TARGETS OF THE PSYCHOATIVE DRUGS ARE IN THE BRAIN. AND THIS WAS KNOWN EARLY IN THE HISTORY. BUT IT DOESN'T CHANGE THE LANDSCAPE: THE IMPORTANT QUESTION FOR THIS THEORY IS TO SUSTAIN THE CHEMICAL NATURE OF ADDICTION.**

THEORY 1

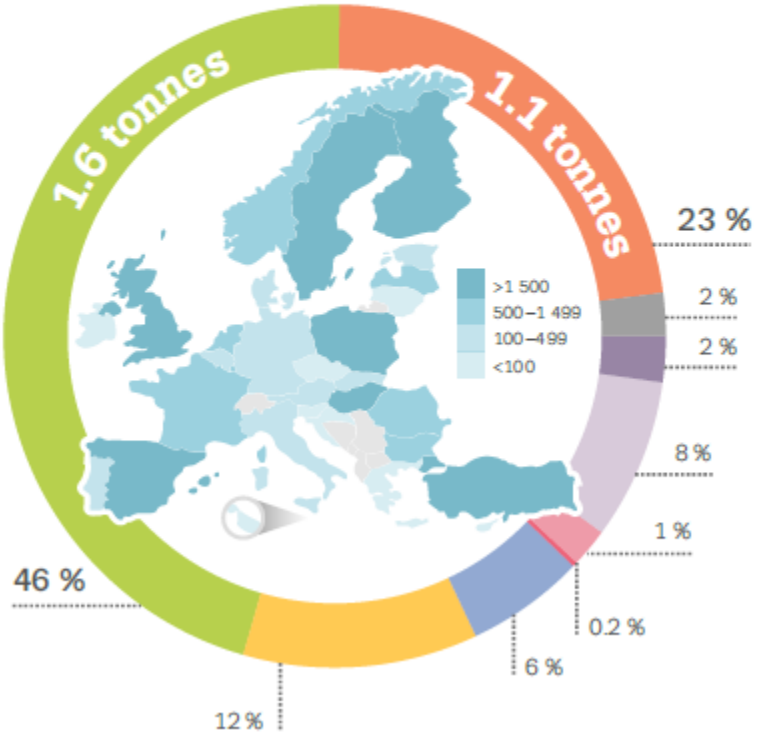
ADDICTION IS CAUSED BY CHEMICALS

New psychoactive substances (NPS) — at a glance

Number of NPS reported to the EU Early Warning System, 2005–14



Number of NPS seizures and proportion of seizures by category of substance, 2013



THEORY 2
THE CONSEQUENCE OF THE ACTIVATION OF A DOPAMINE-BASED BRAIN REWARD SYSTEM

J Comp Physiol Psychol. 1954 Dec;47(6):419-27.

Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain.

OLDS J, MILNER P.

SHARE

REPORTS

Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward

RA Yokel, RA Wise

+ See all authors and affiliations

Science 14 Feb 1975:
Vol. 187, Issue 4176, pp. 547-549
DOI: 10.1126/science.1114313

Science

Vol 187, Issue 4176
14 February 1975

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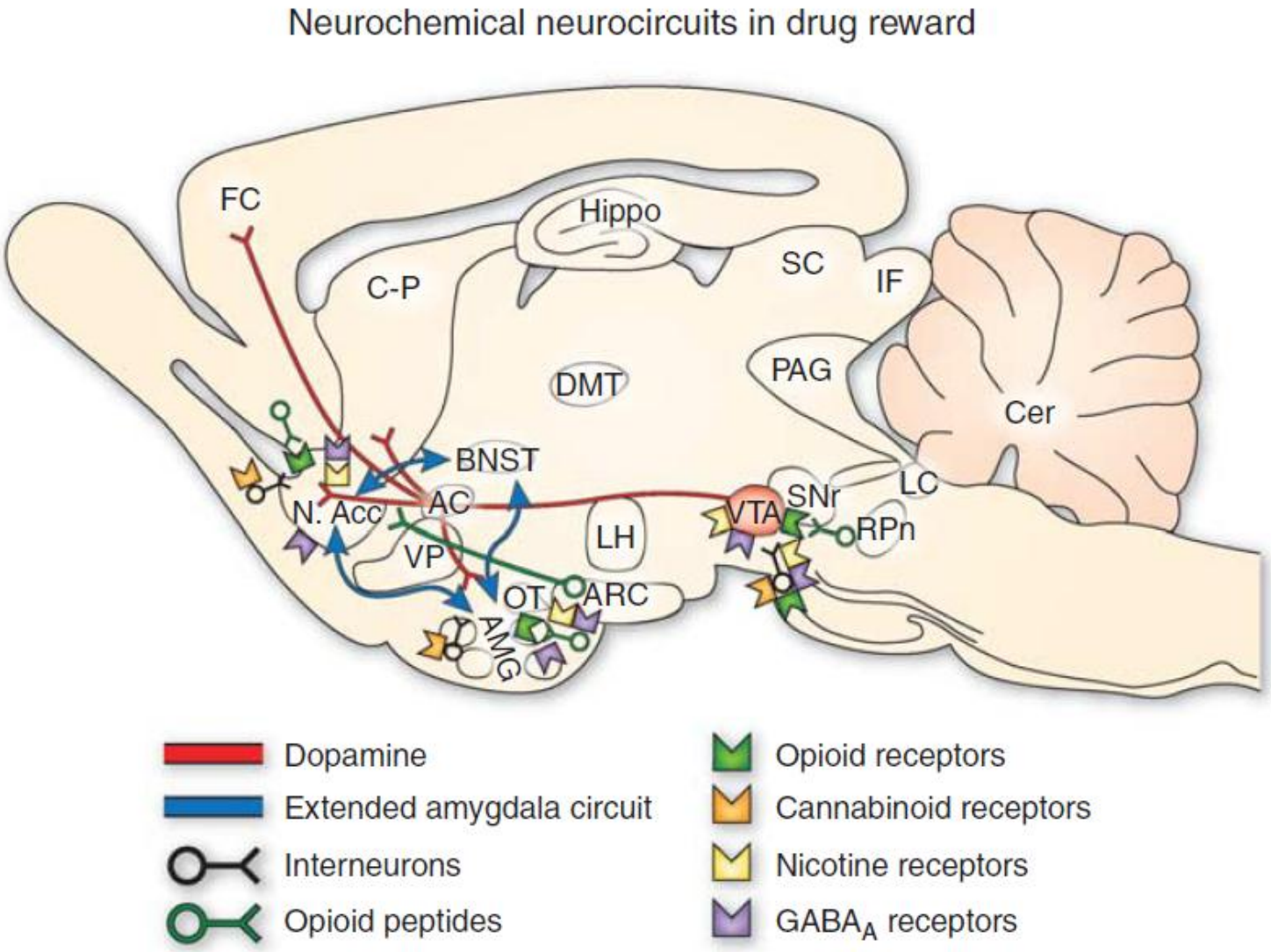
THEORY 2
THE CONSEQUENCE OF THE ACTIVATION OF A DOPAMINE-BASED BRAIN REWARD SYSTEM



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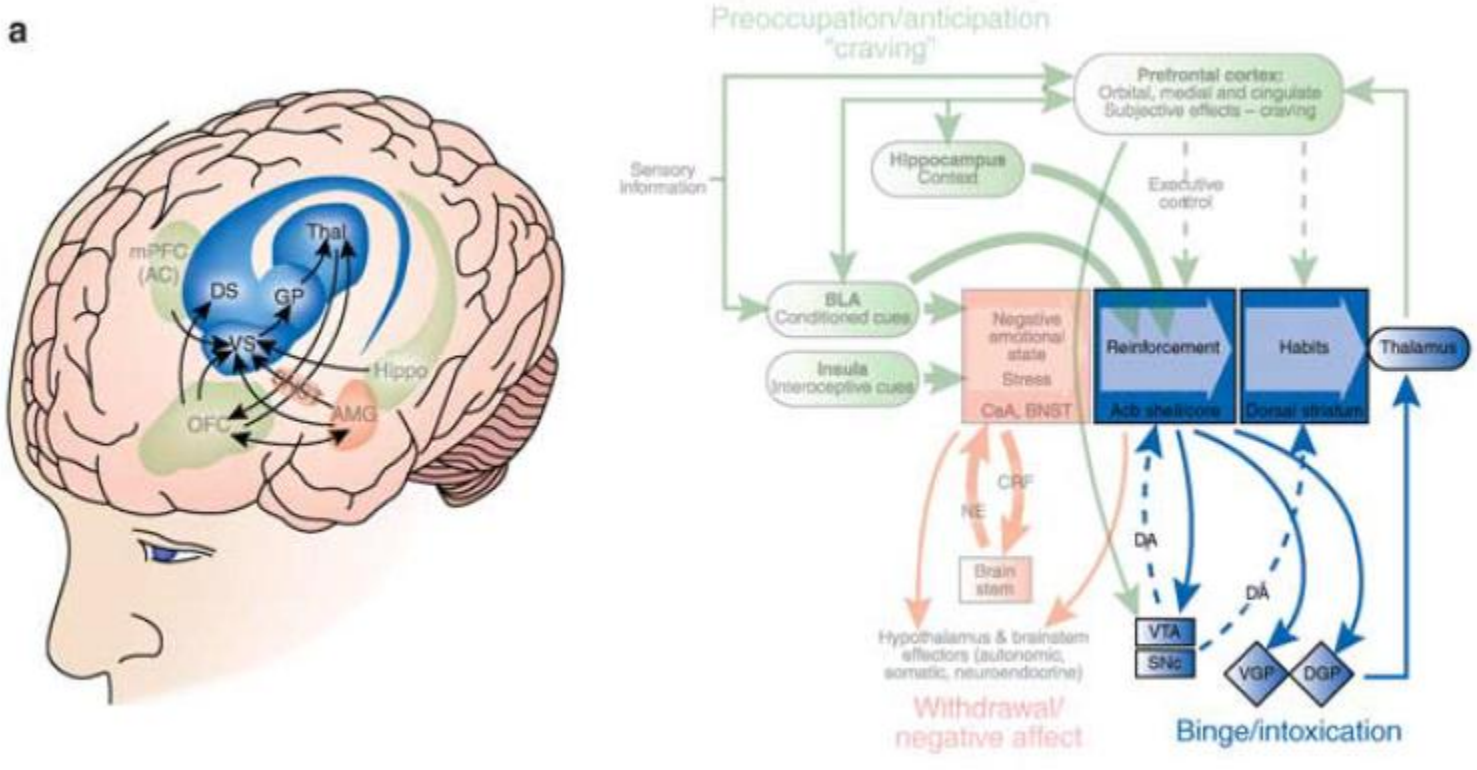
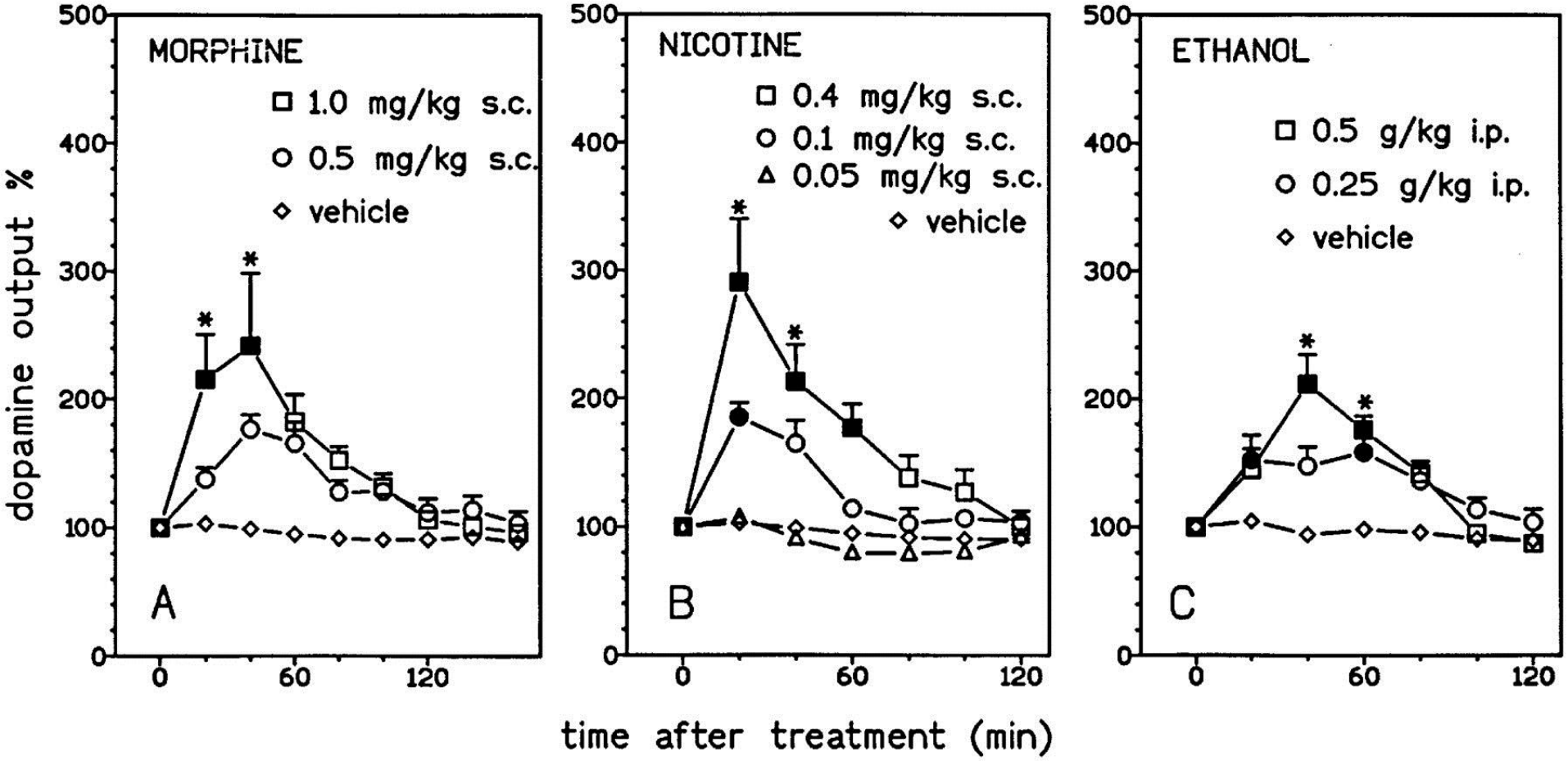




DRUGS OF ABUSE INCREASE DOPAMINE RELEASE IN THE BRAIN

THEORY 3

ADDICTION IS AN ASSOCIATIVE-LEARNING DISORDER WHERE CONTEXTUAL LEARNING PLAYS A ROLE

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

Phil. Trans. R. Soc. B (2008) **363**, 3137–3146
doi:10.1098/rstb.2008.0093
Published online 18 July 2008

Review

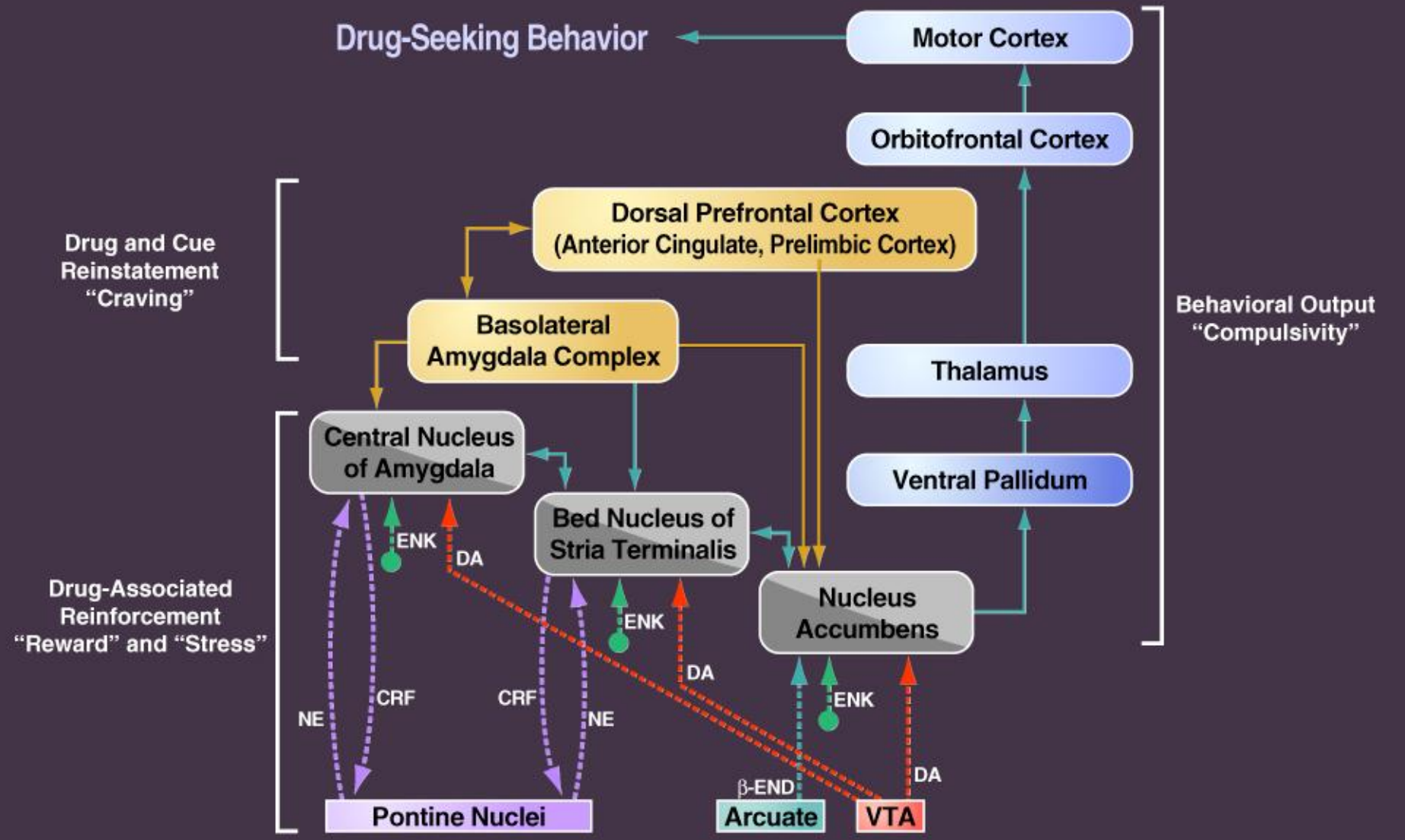
The incentive sensitization theory of addiction: some current issues

Terry E. Robinson* **and Kent C. Berridge**

Department of Psychology (Biopsychology Program), The University of Michigan, East Hall, 530 Church Street, Ann Arbor, MI 48109, USA

Addiction is caused primarily by drug-induced sensitization in the brain mesocorticolimbic systems that attribute incentive salience to reward-associated stimuli. If rendered hypersensitive, these systems cause pathological incentive motivation (‘wanting’) for drugs.

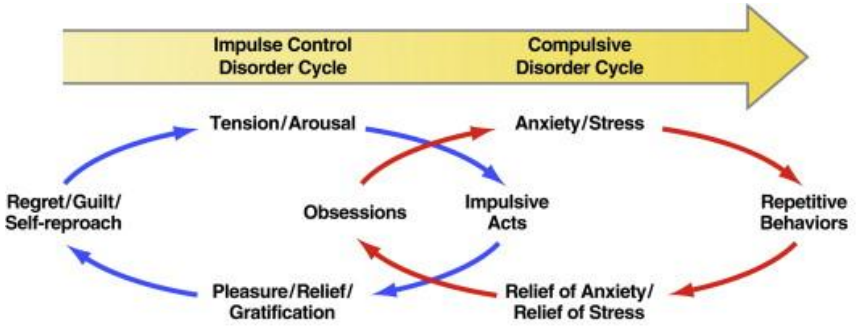
FUNCTIONAL NEUROANATOMY OF DRUG-ASSOCIATED STIMULI



THEORY 4

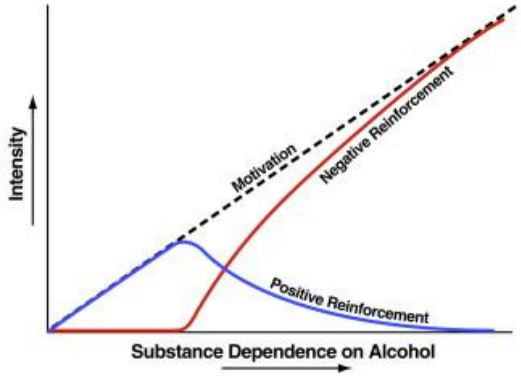
ADDICTION IS AN HEDONIC HOMEOSTASIS DYSREGULATION

- **Addiction = Transition = Plasticity**



Drug Addiction, Dysregulation of Reward, and Allostasis

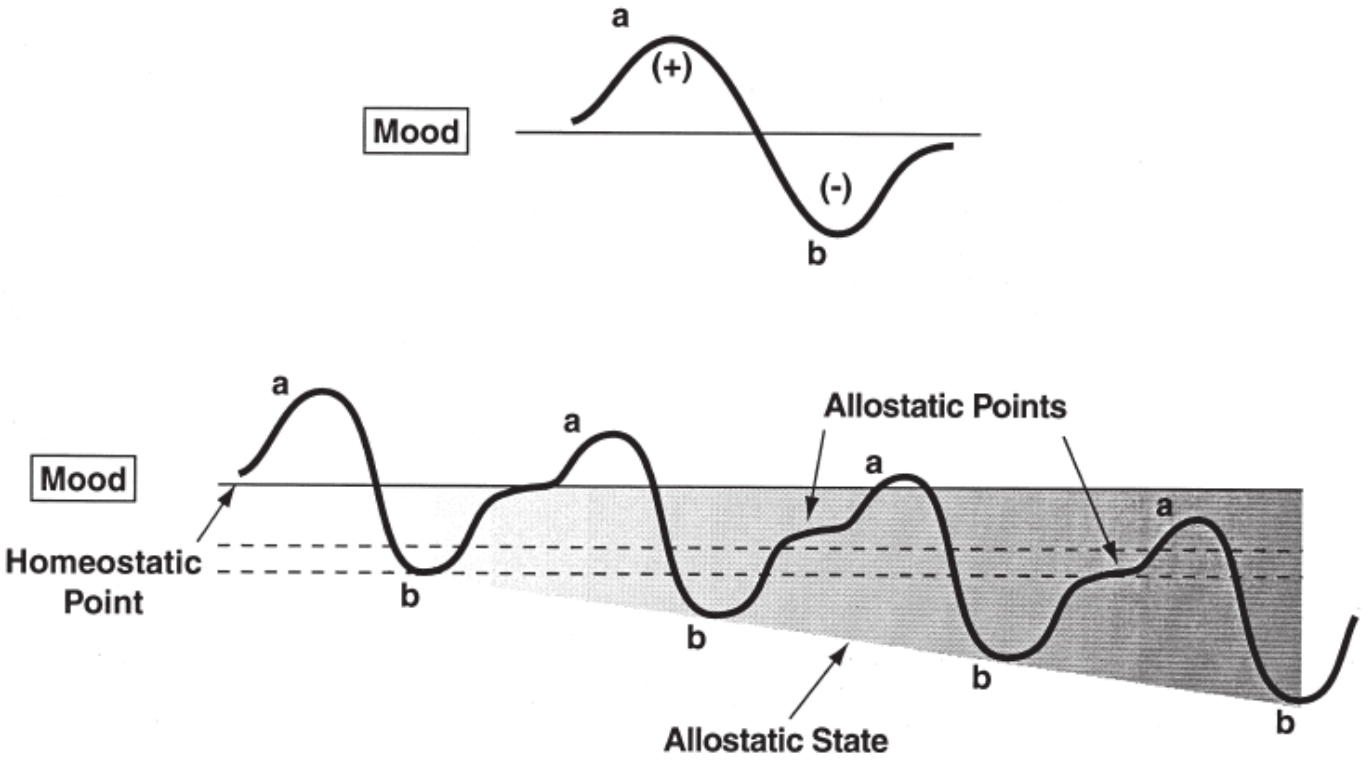
George F. Koob, Ph.D., and Michel Le Moal, M.D., Ph.D.



ADDICTION IMPLIES THE ALLOSTATIC SHIFT IN MECHANISMS CONTROLLING POSSITIVE REINFORCEMENT, LEADING TO DYSPHORIA

THEORY 4

ADDICTION IS AN HEDONIC HOMEOSTASIS DYSREGULATION



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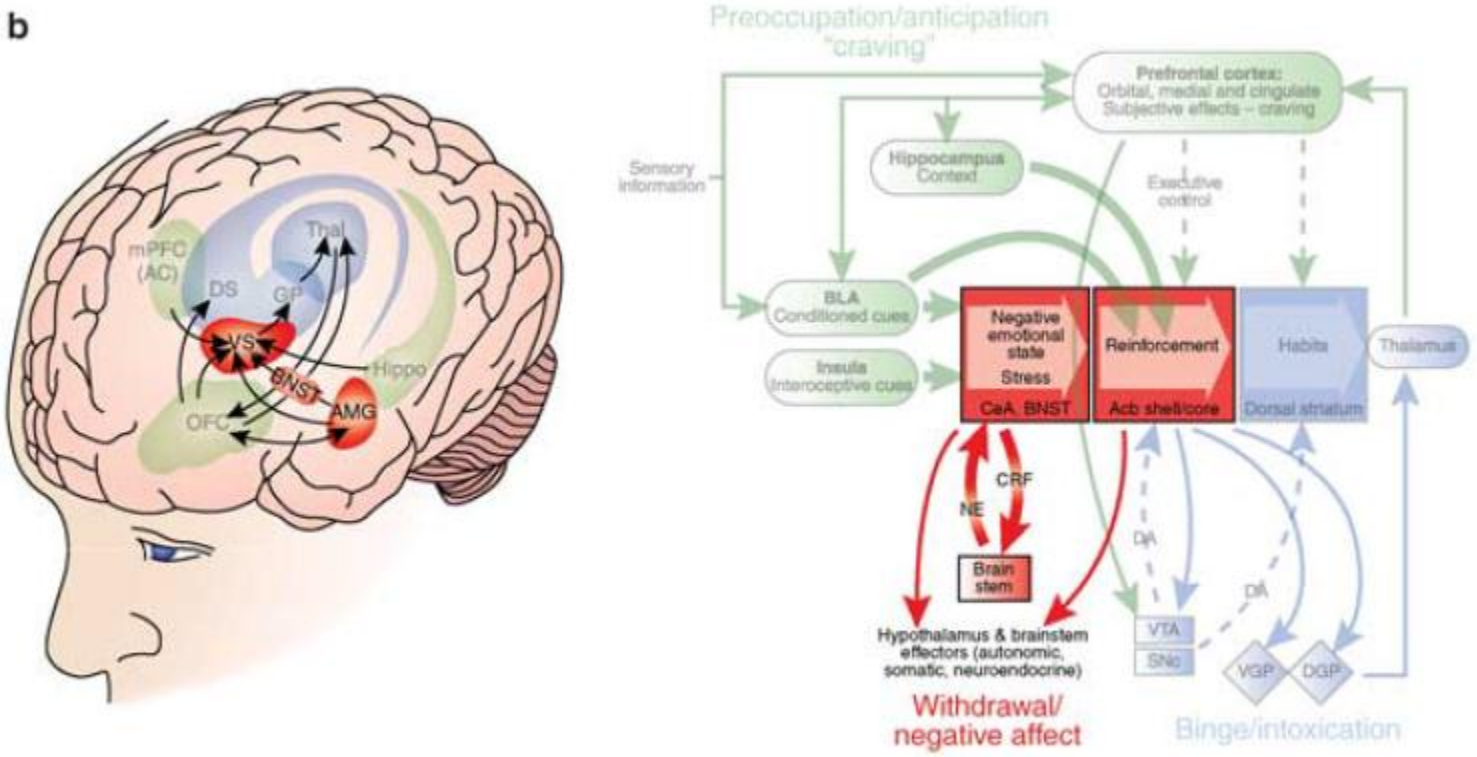

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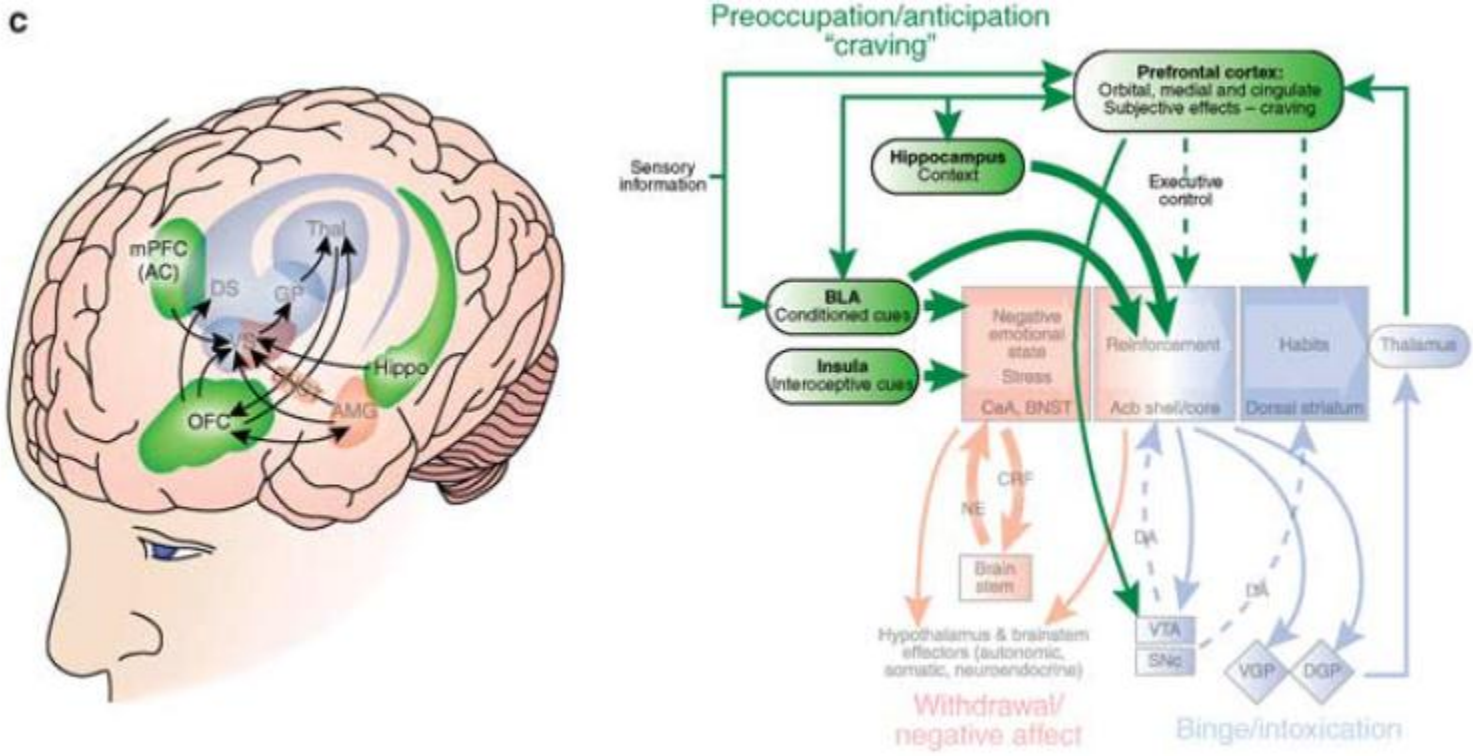

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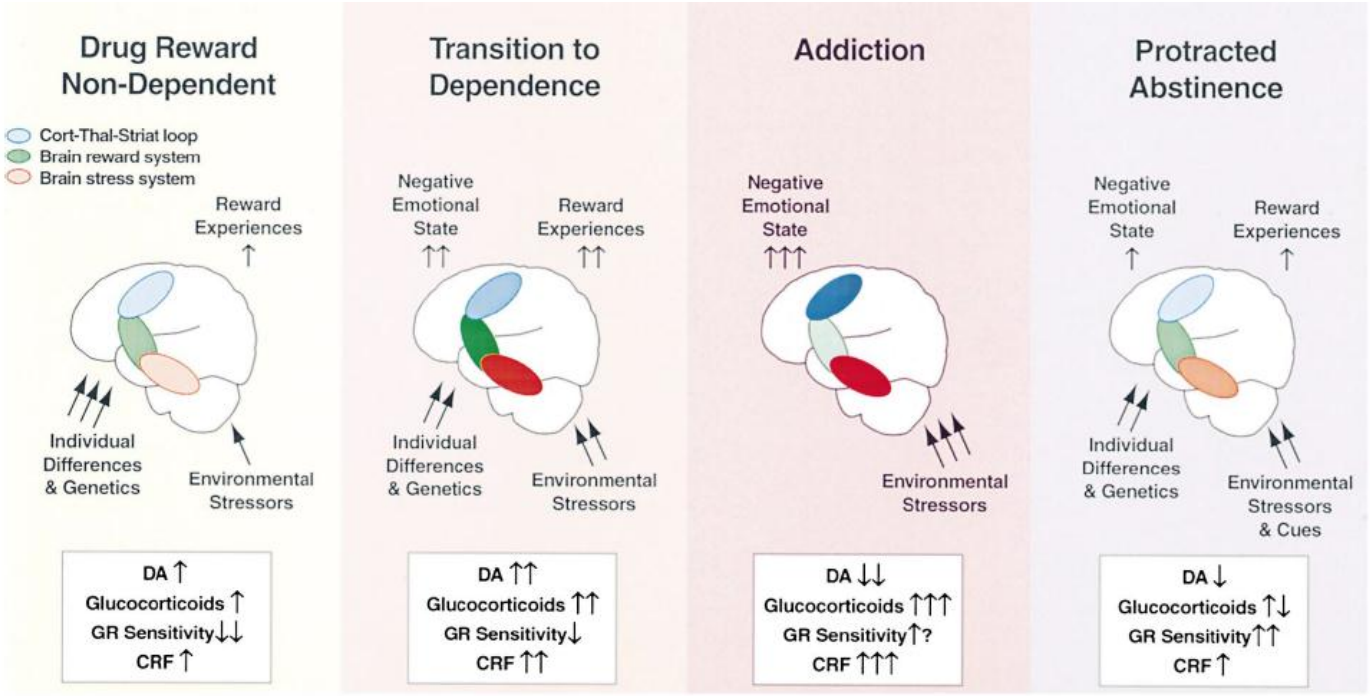
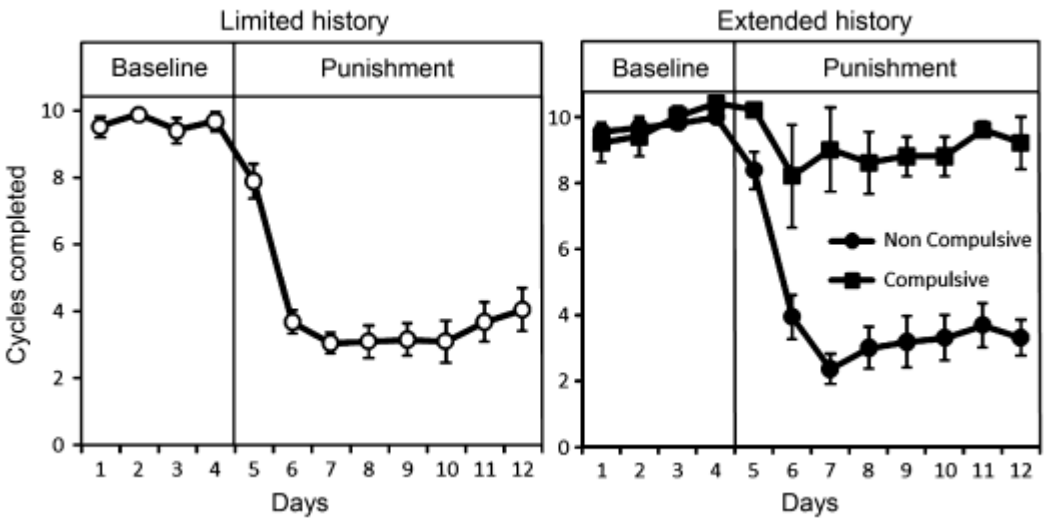


THEORY 5

ADDICTION IS A TRANSITION FROM INCENTIVE LEARNING TO HABITS: THE LOSS OF CONTROL

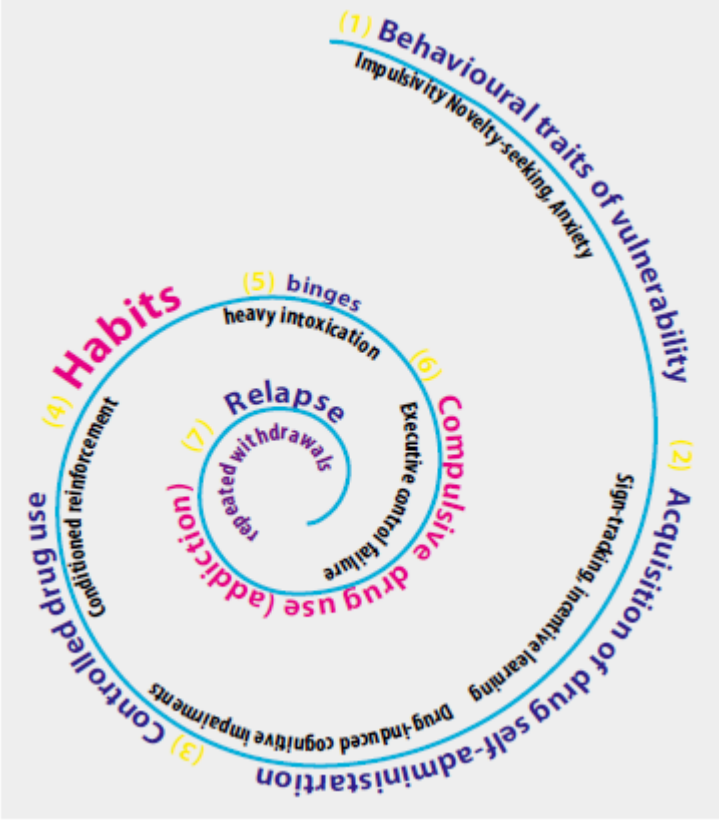


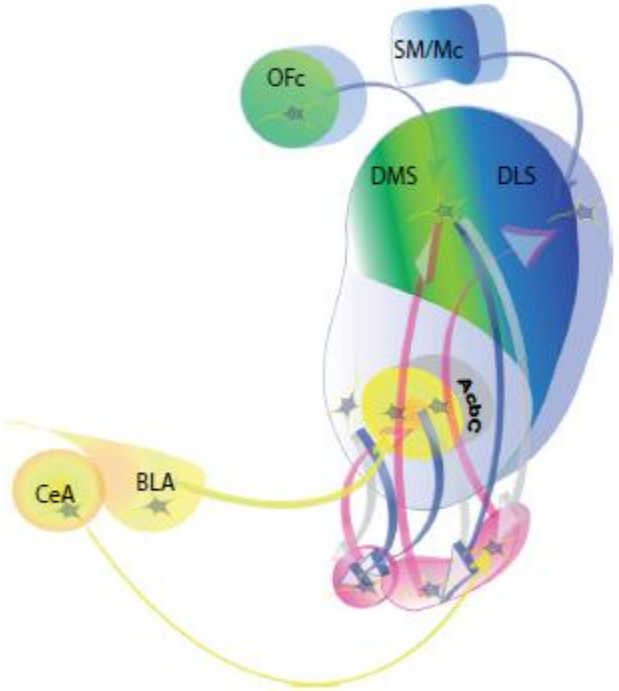
ADICCTION IS A DISORDER RELATED TO THE TRANSITION FROM IMPULSIVE TO COMPULSIVE DRUG USE.

THE KEY: HABIT FORMATION

THEORY 5

ADDICTION IS A TRANSITION FROM INCENTIVE LEARNING TO HABITS: THE LOSS OF CONTROL



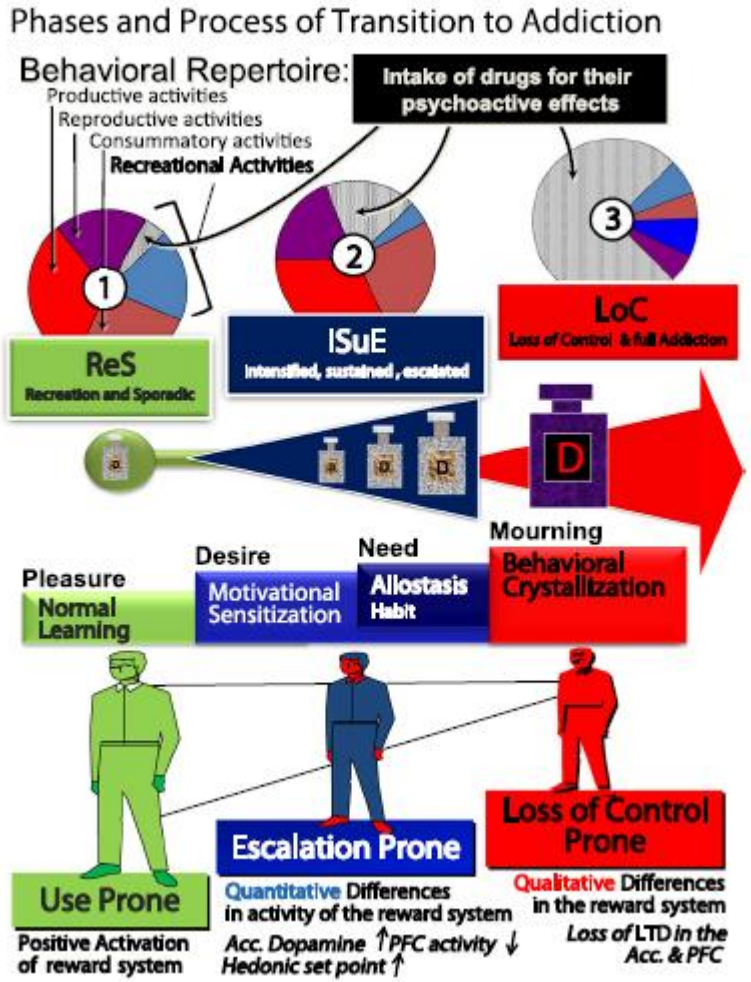


Psychopharmacology (2013) 229:387–413
DOI 10.1007/s00213-013-3224-4

THEORETICAL AND METHODOLOGICAL PERSPECTIVES

A multistep general theory of transition to addiction

Pier Vincenzo Piazza · Véronique Deroche-Gamonet



Universitat Pompeu Fabra Barcelona

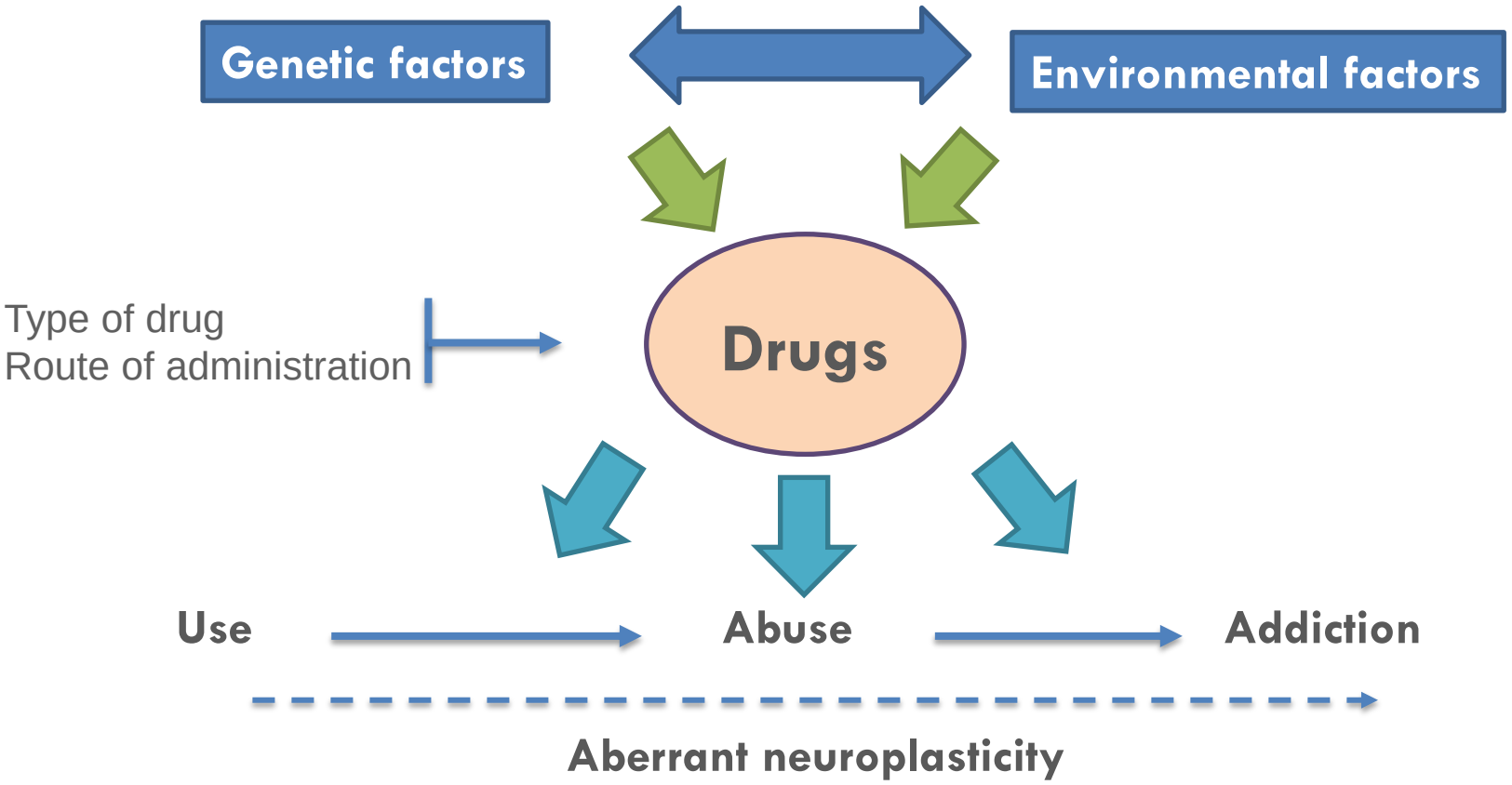
Twist Session

Neuroscience

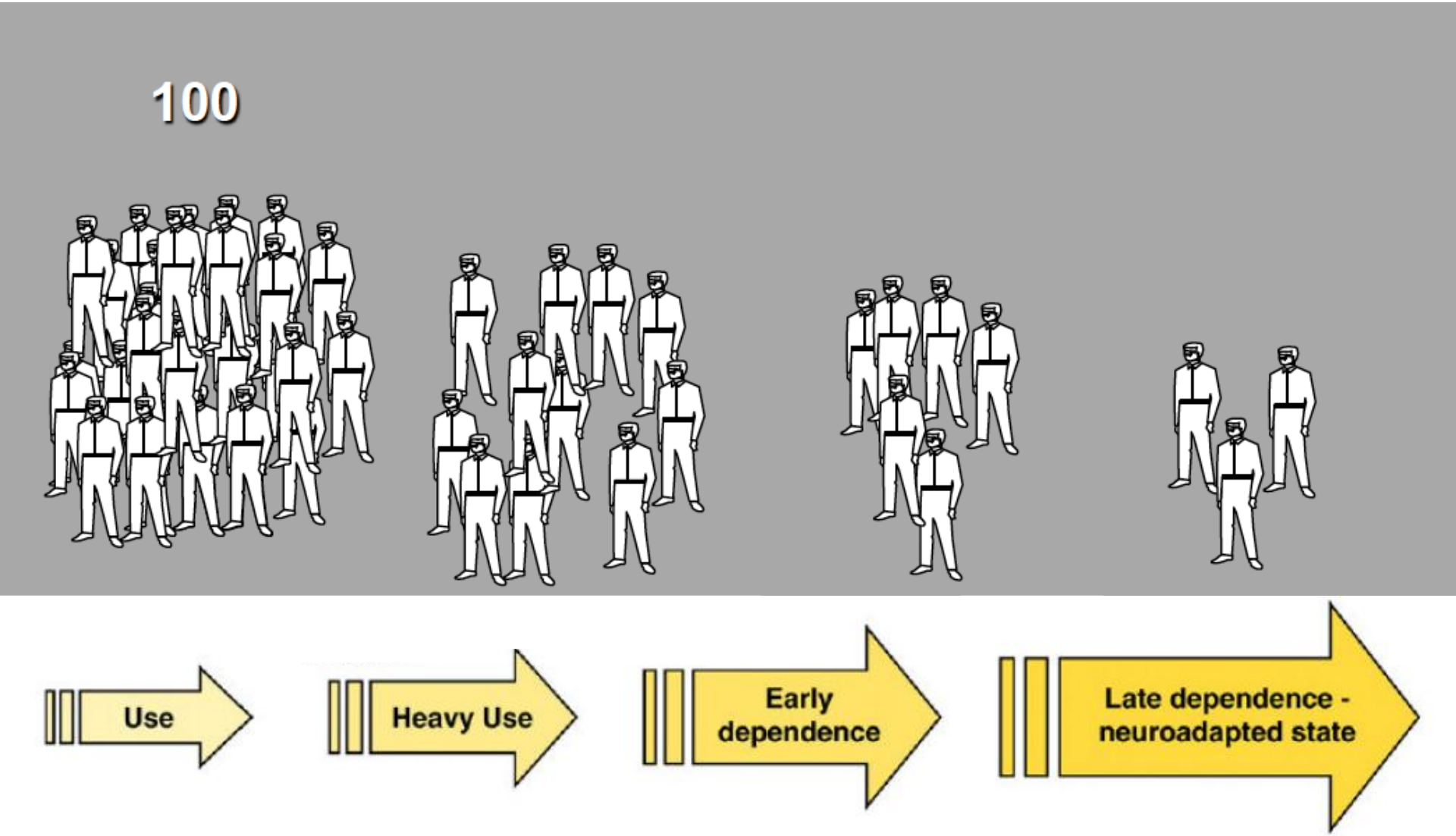
Olga Valverde MD PhD

Neurobiology of Behavior Research Group (NeuroBio-GReNeC)
Department of Experimental and Health Sciences
Universitat Pompeu Fabra

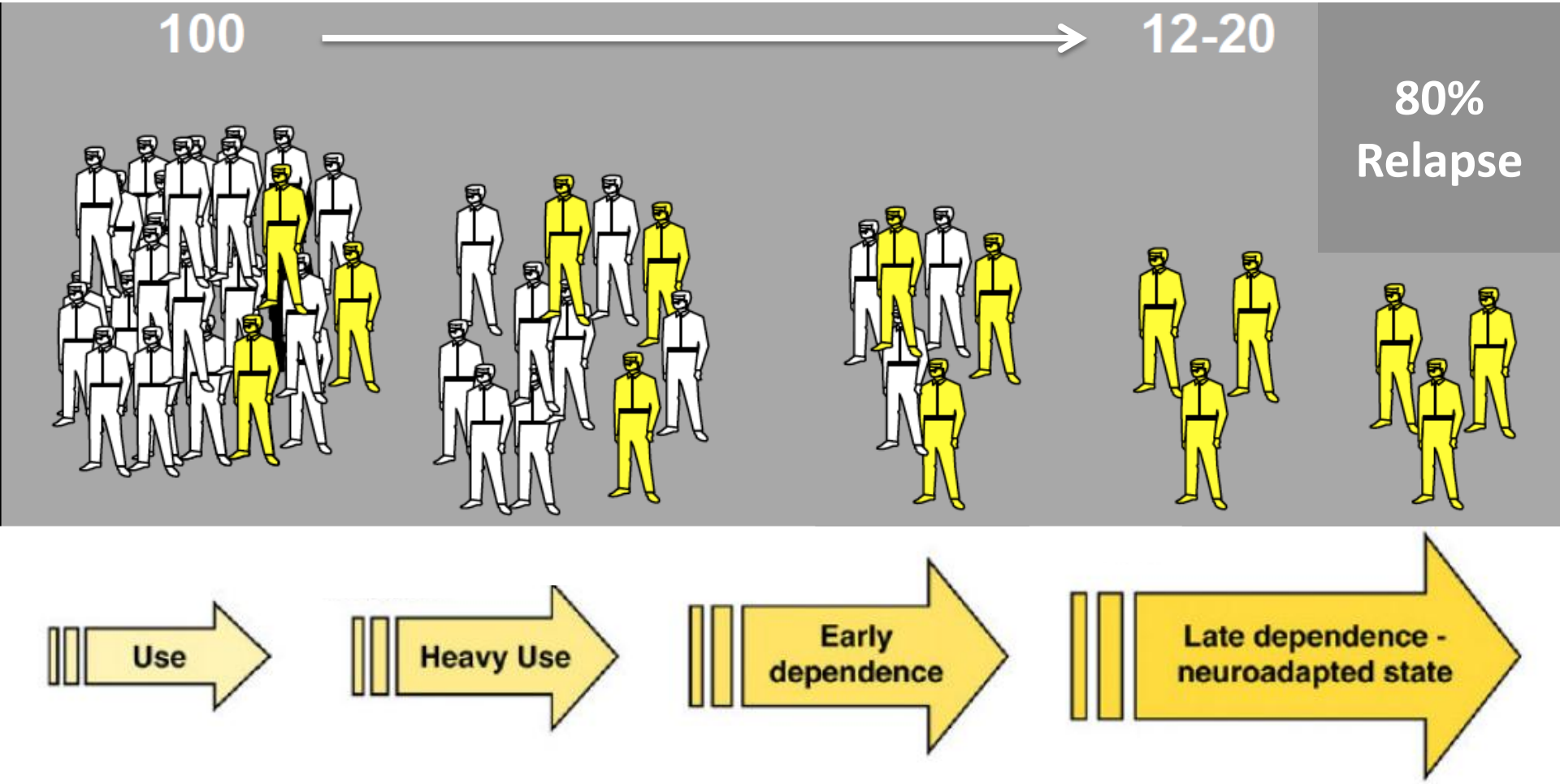
Substance Use Disorders



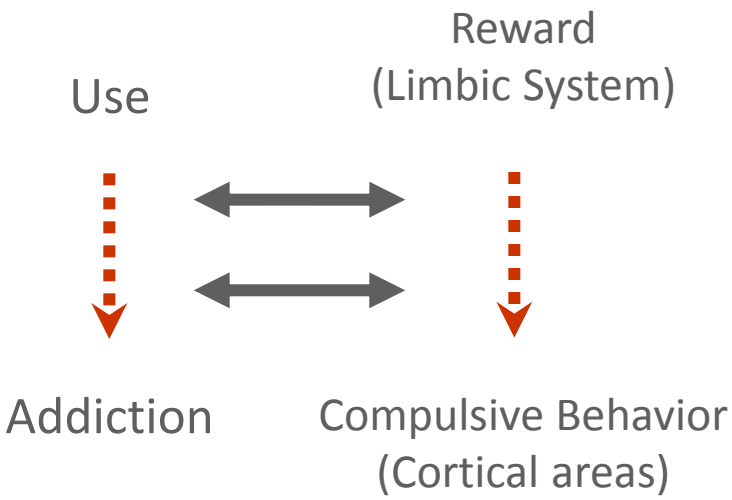
Addiction is a chronic disease



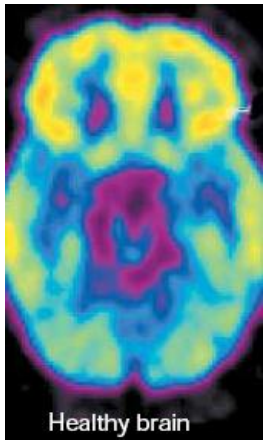
Addiction is a chronic disease



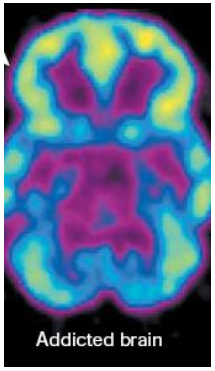
Addiction is a chronic disease



Under control

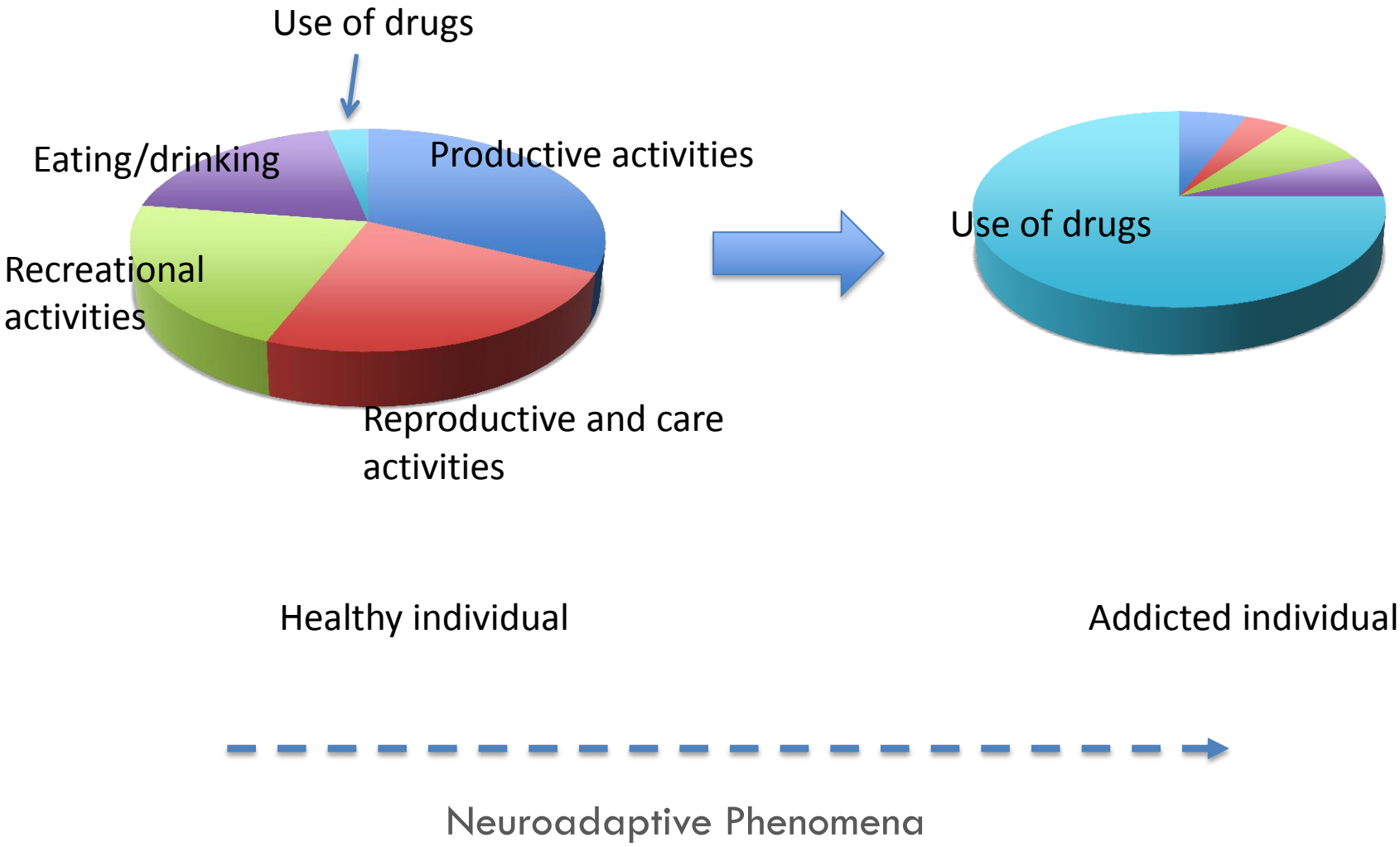


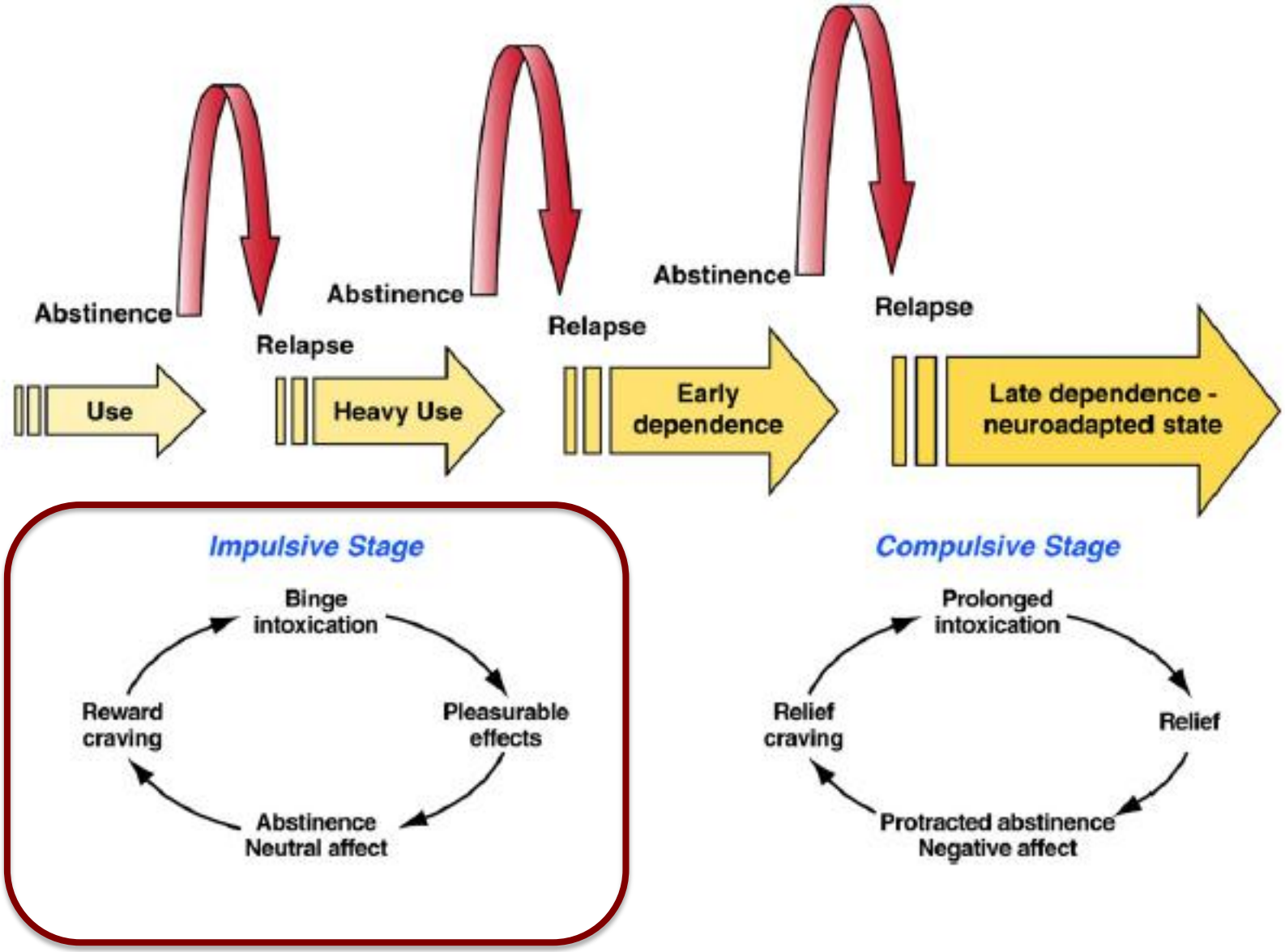
Lost of control



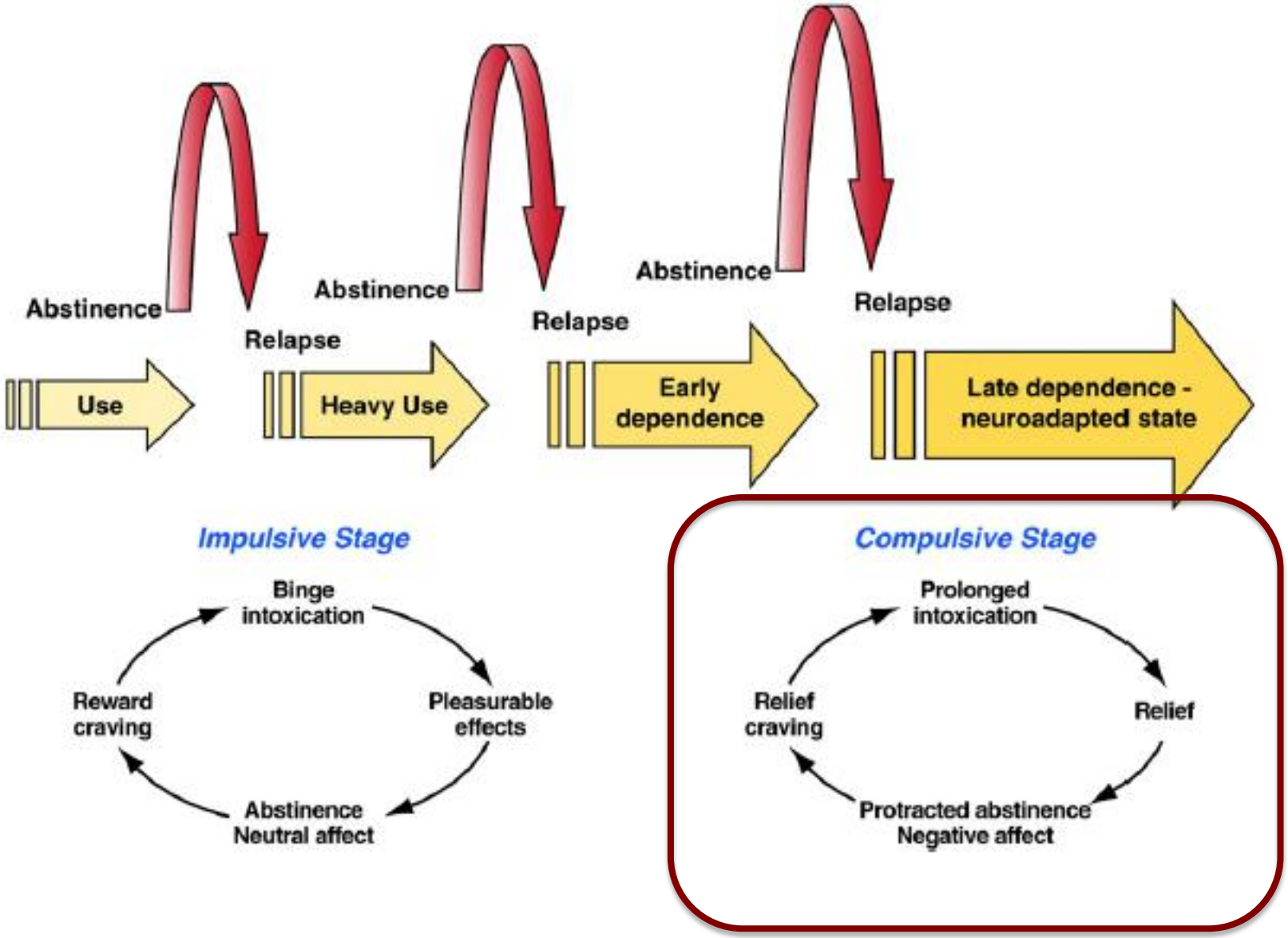
Volkow and Wise, Nature Neurosci. 8: 555, 2005

Behavioral repertoire:





Koob GF, Brain Res, 2009.



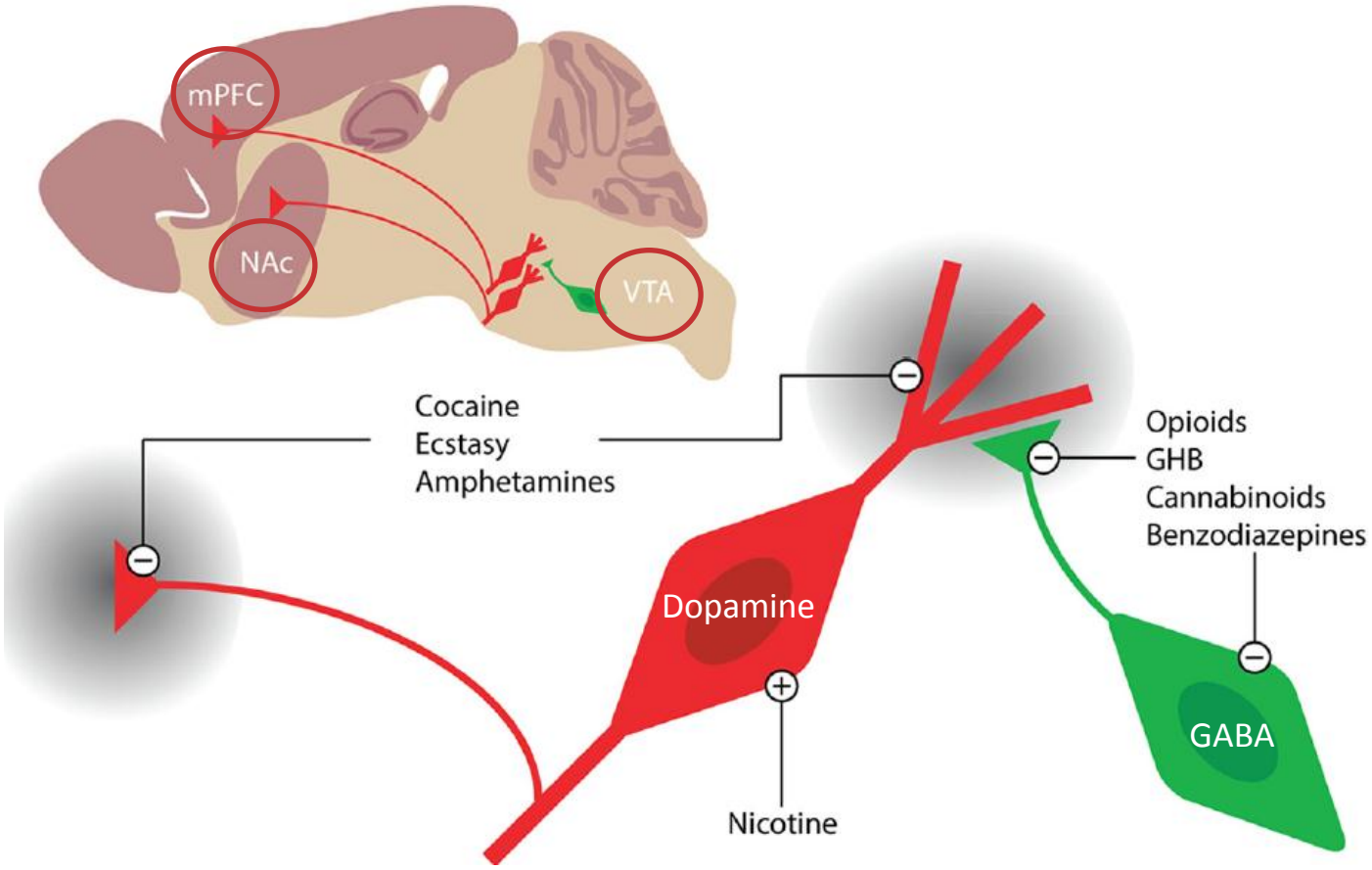
Koob GF, Brain Res, 2009.

A common phenomenon for the different prototypic drugs of abuse

Table 1 | **Acute actions of some drugs of abuse**

Drug	Action	Receptor signalling mechanism
Opiates	Agonist at μ-, δ- and κ-opioid receptors*	G_i
Cocaine	Indirect agonist at dopamine receptors by inhibiting dopamine transporters‡	G_i and G_s§
Amphetamine	Indirect agonist at dopamine receptors by stimulating dopamine release‡	G_i and G_s§
Ethanol	Facilitates $GABA_A$ receptor function and inhibits NMDA receptor function‖	Ligand-gated channels
Nicotine	Agonist at nicotinic acetylcholine receptors	Ligand-gated channels
Cannabinoids	Agonist at CB_1 and CB_2 cannabinoid receptors¶	G_i
Phencyclidine (PCP)	Antagonist at NMDA glutamate receptors	Ligand-gated channels
Hallucinogens	Partial agonist at $5\text{-}HT_{2A}$ serotonin receptors	G_q
Inhalants	Unknown	

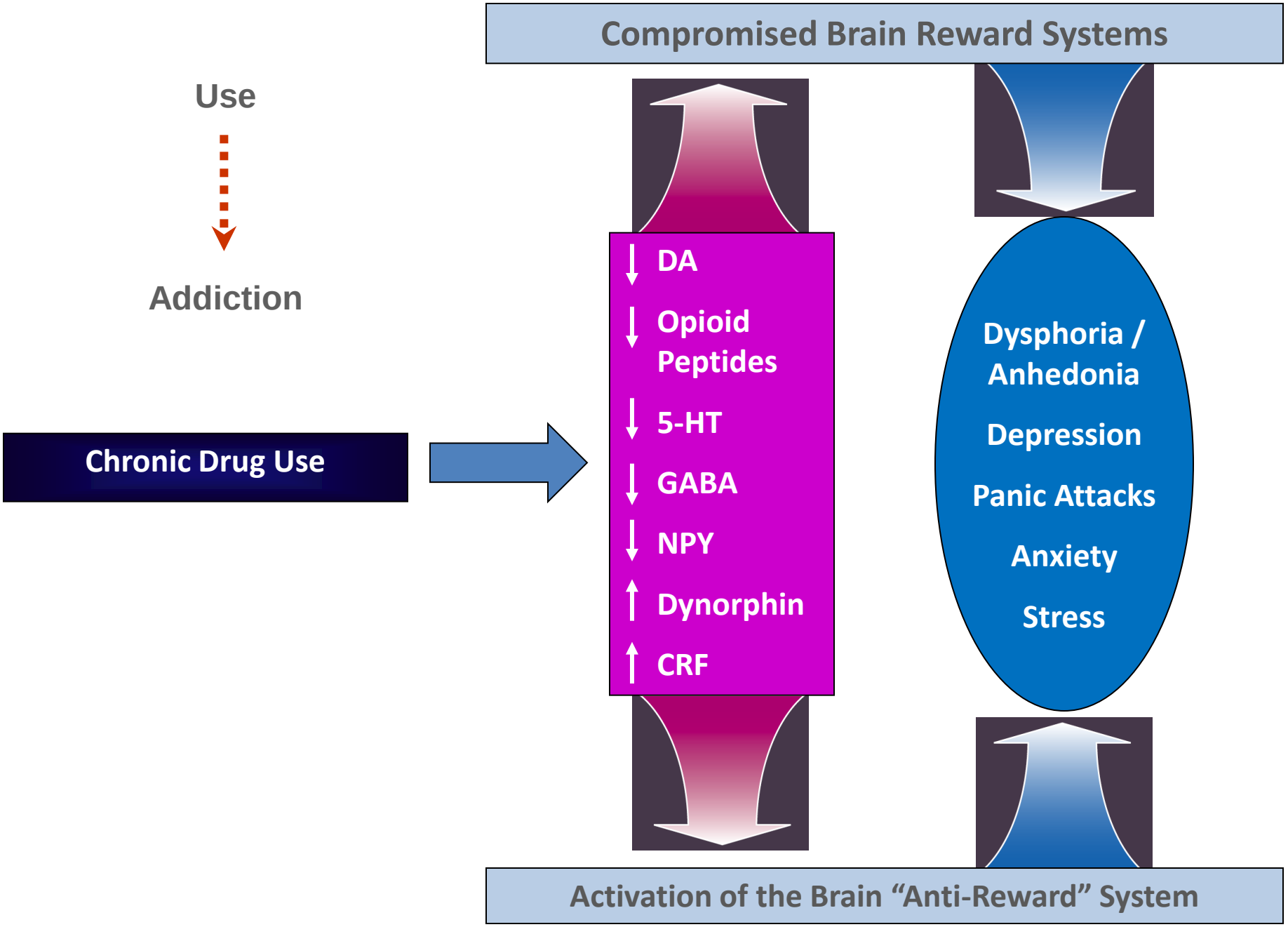
The mesocorticolimbic dopamine system



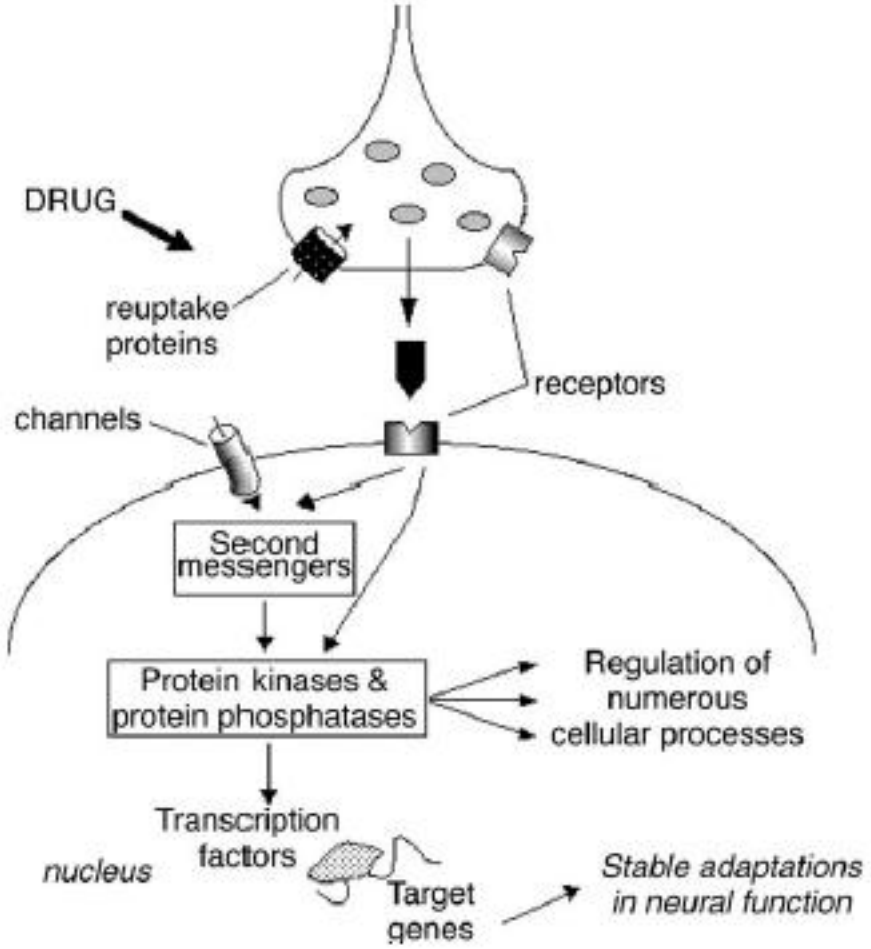
Lüscher and Malenka, 2011

Drug addiction is an adaptive phenomenon

Long-term cellular and molecular effects are developed during drug exposure


Compromised Brain Reward Systems
Use
Addiction
Chronic Drug Use
DA
Opioid Peptides
5-HT
GABA
NPY
Dynorphin
CRF
Dysphoria / Anhedonia
Depression
Panic Attacks
Anxiety
Stress
Activation of the Brain "Anti-Reward" System

Molecular players



Short-term

Long-term

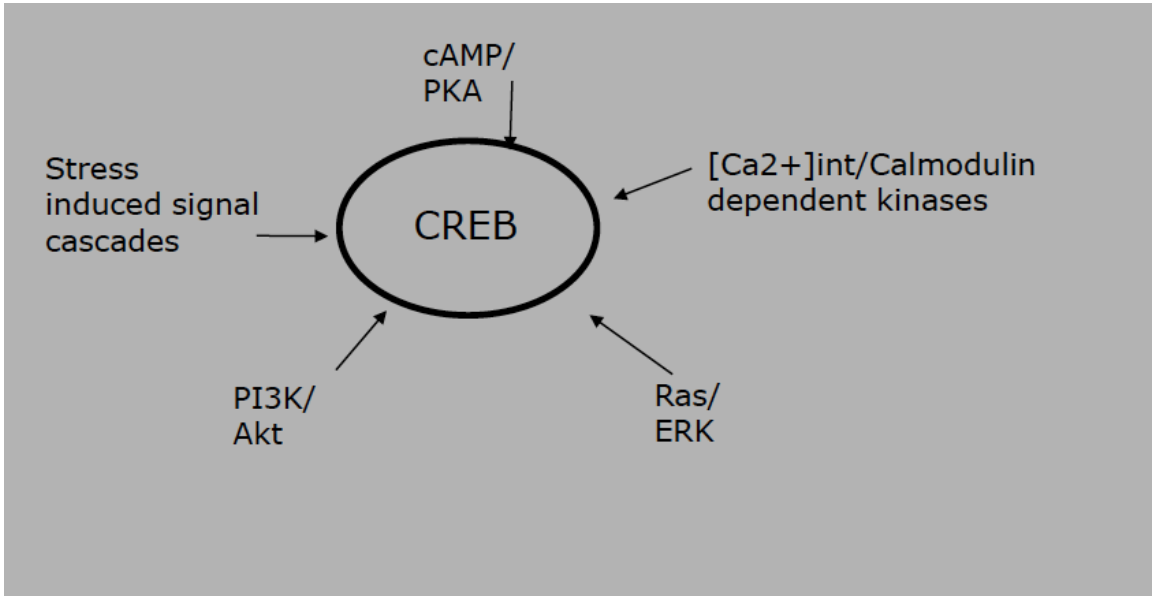
CREB → BDNF
ΔFosB → DYN
MEF2 → Glu
Epigenetic modifications

Nestler E. Neuropharmacology, 2004

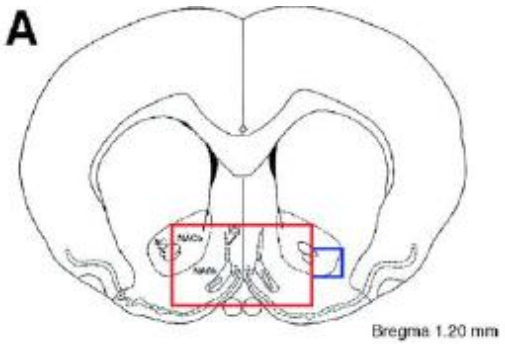
Transcription factors

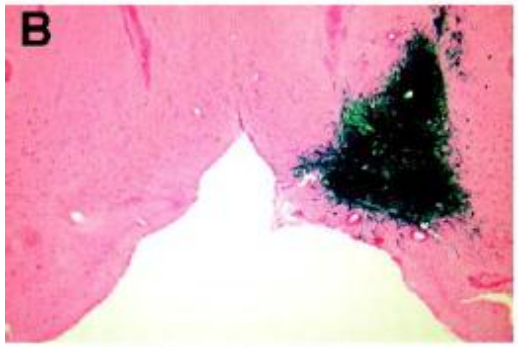
CREB: cAMP response element binding protein.

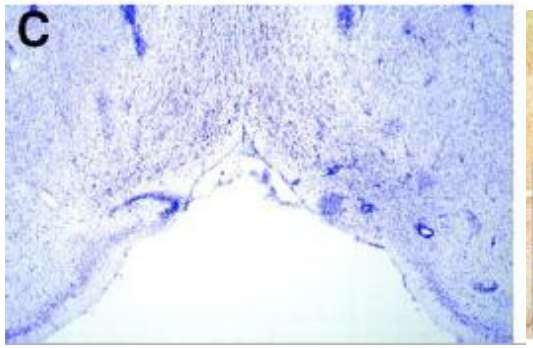
- Superfamily of transcriptor factors (bZIP)
- Dimerization and binding to CRE sequences
- Activated by fosphorilation at S133
- CREB binding protein (CBP) link to transcription initiation complex (HAT activity)

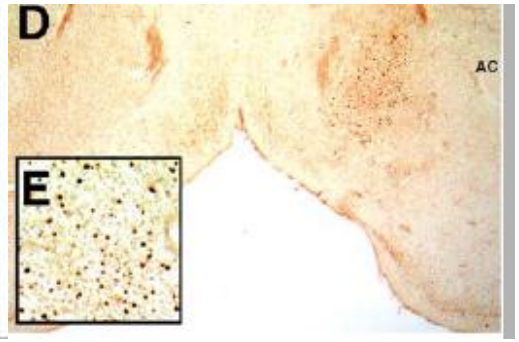


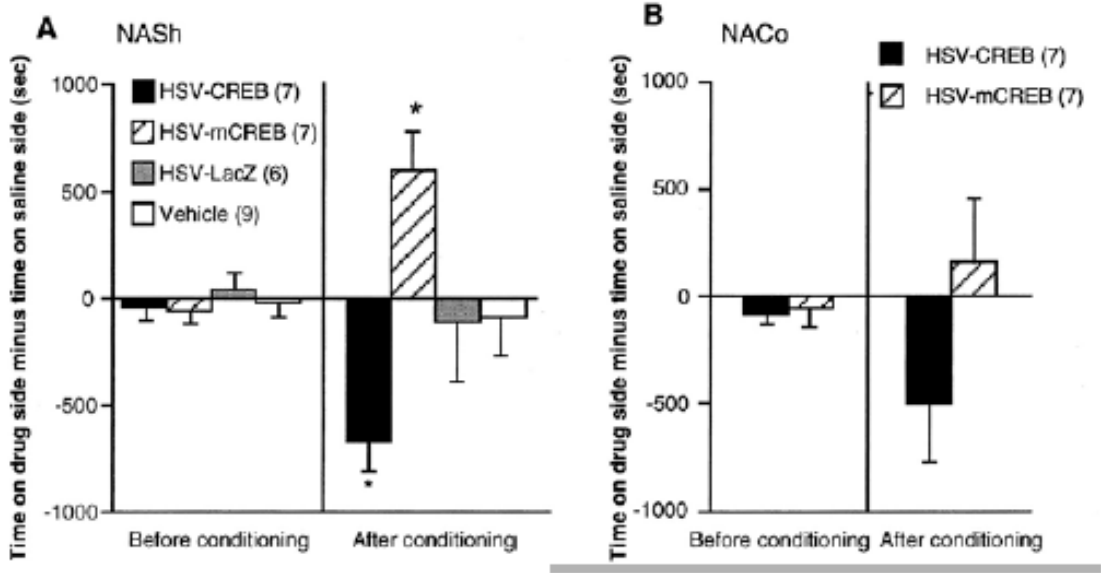
CREB: cAMP response element binding protein

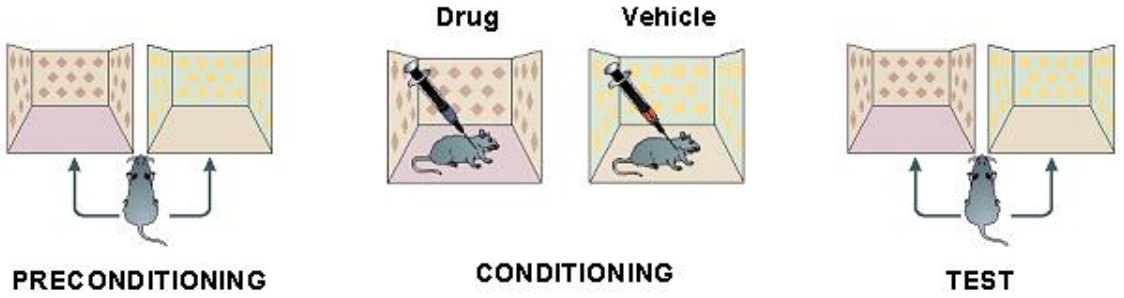










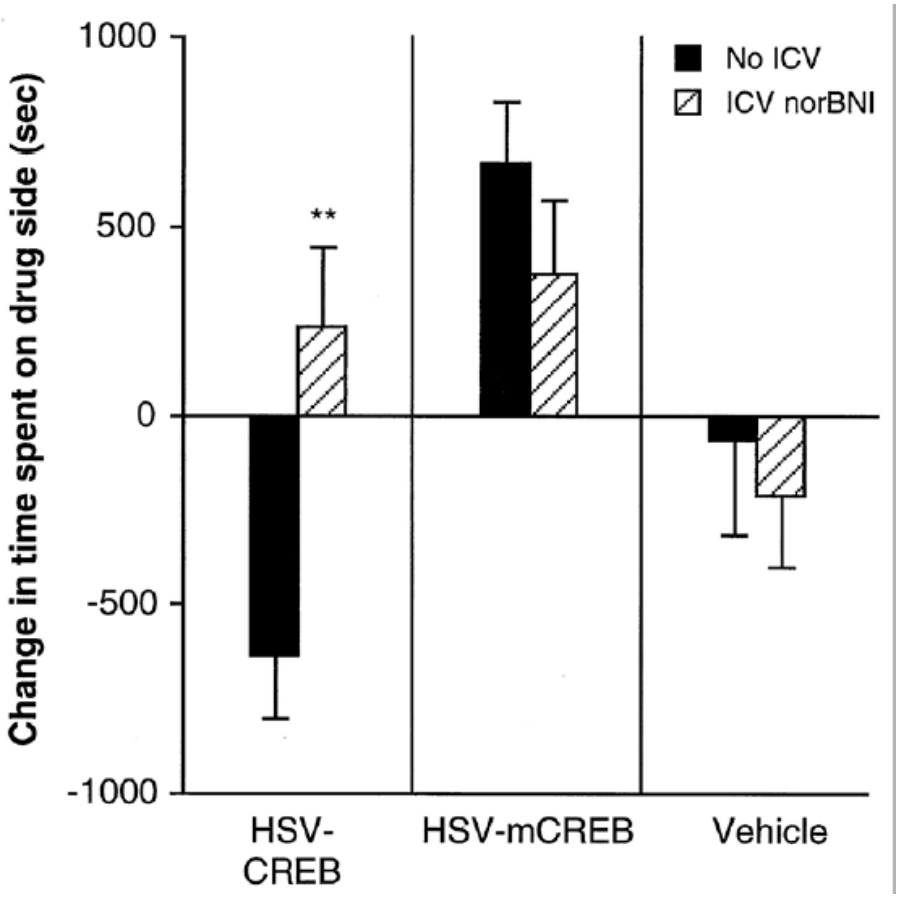


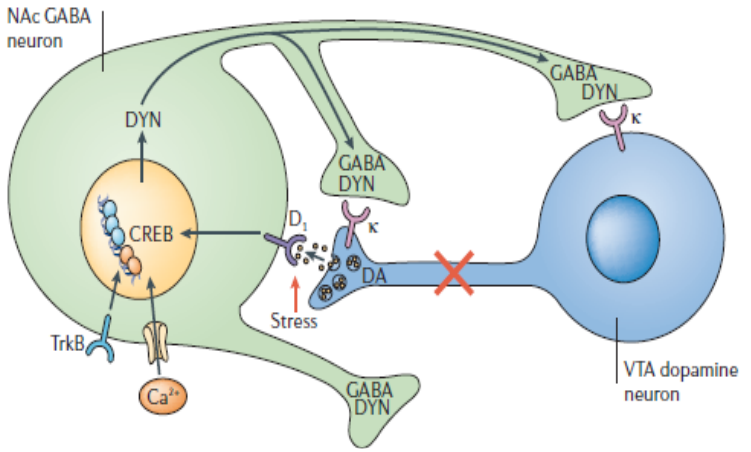
Viral over-expression

CREB over-expression produces aversion
CREB blockade increses reward

Carlezon et al., Science, 1998

CREB: cAMP response element binding protein

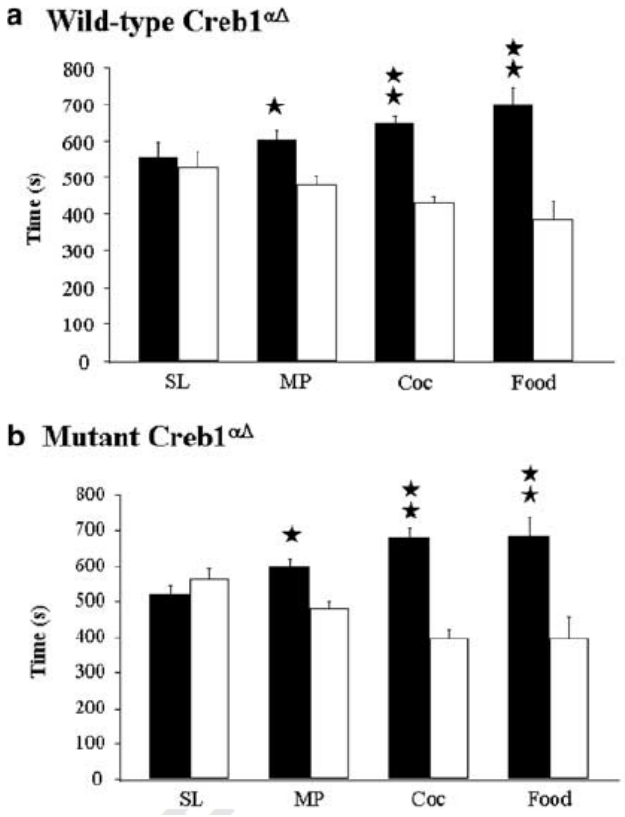


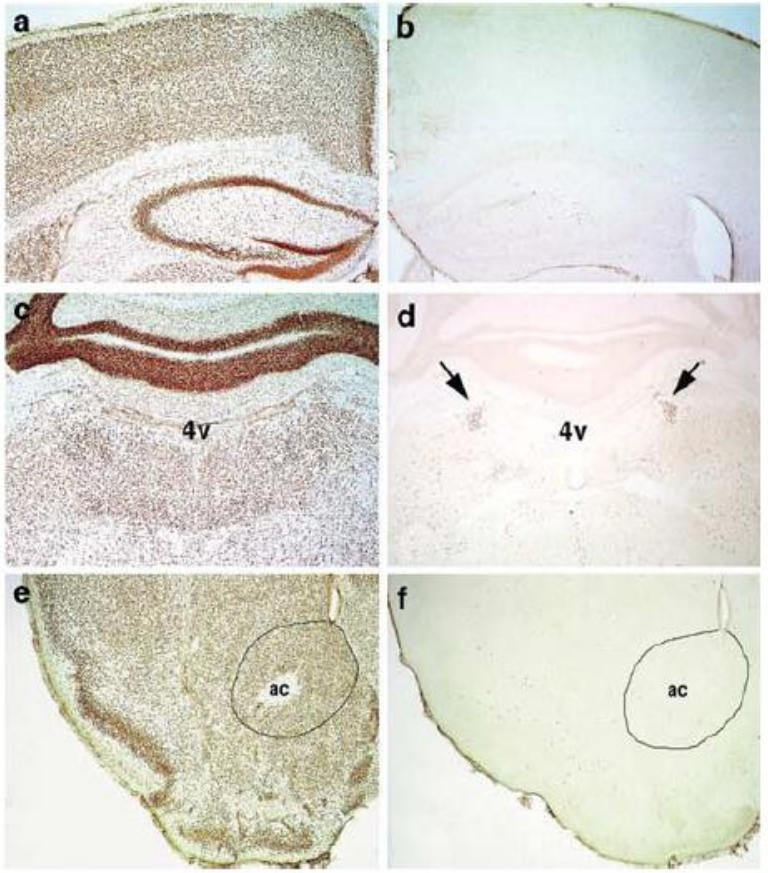


- ↓ DA
- ↓ Opioid Peptides
- ↓ 5-HT
- ↓ GABA
- ↓ NPY
- ↑ Dynorphin
- ↑ CRF

Carlezon et al., Science, 1998

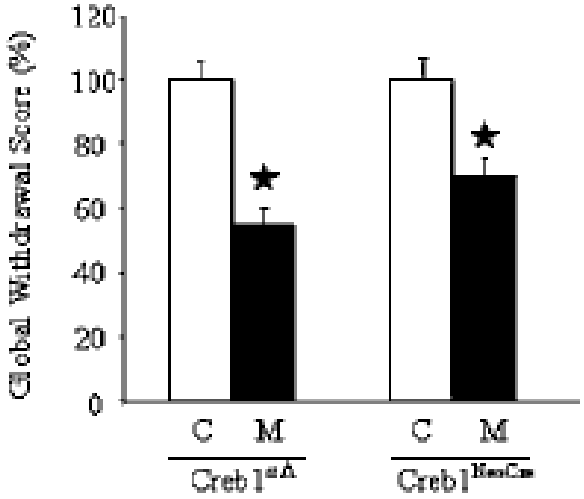
CREB: cAMP response element binding protein

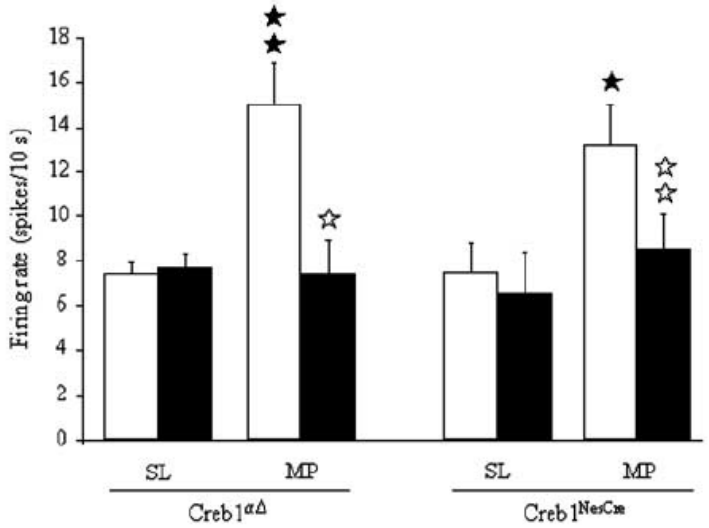


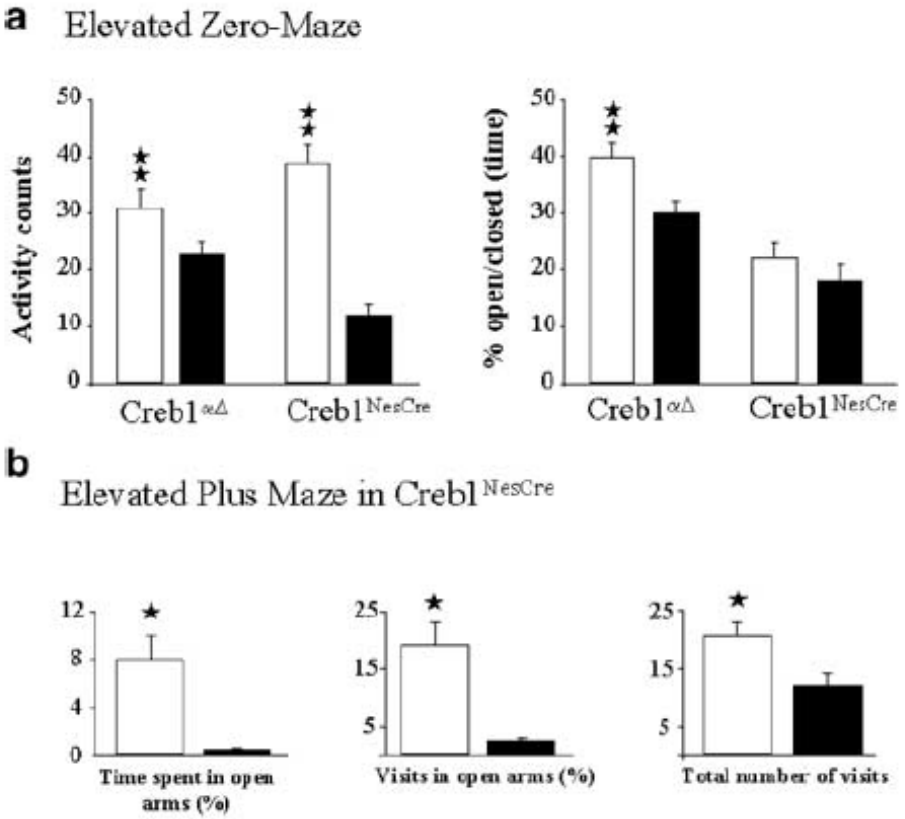


Valverde et al., Neuropsychopharmacology, 2004

CREB: cAMP response element binding protein

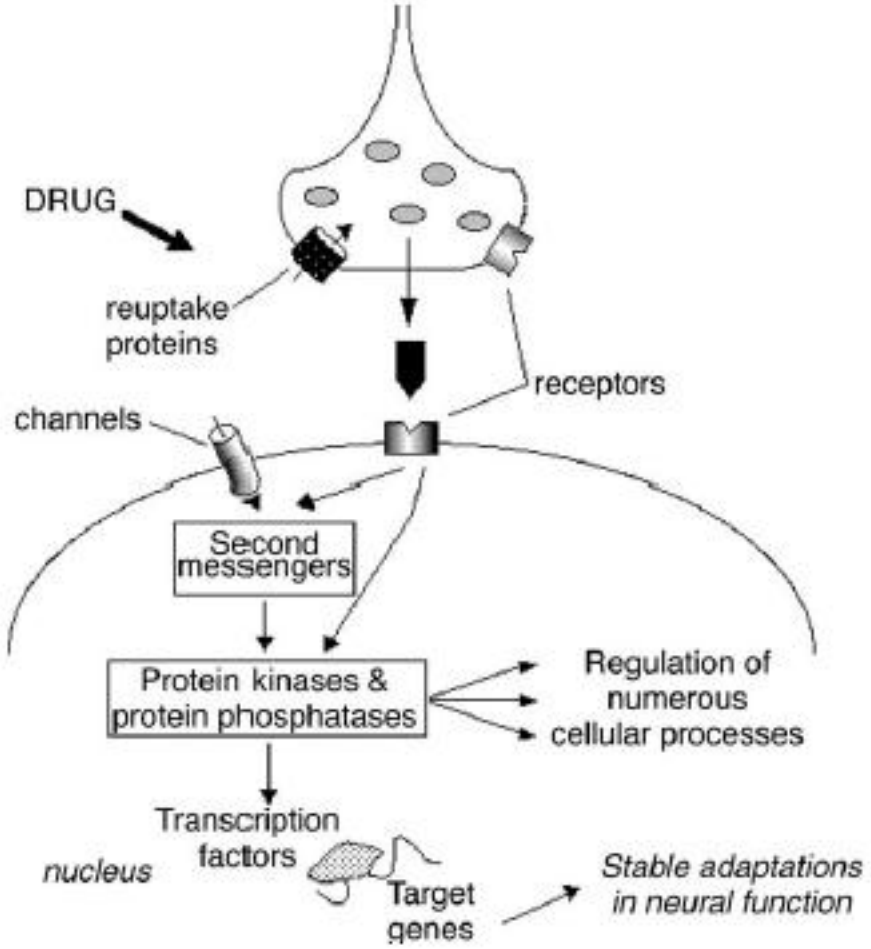






Valverde et al., Neuropsychopharmacology, 2004

Transcription factors



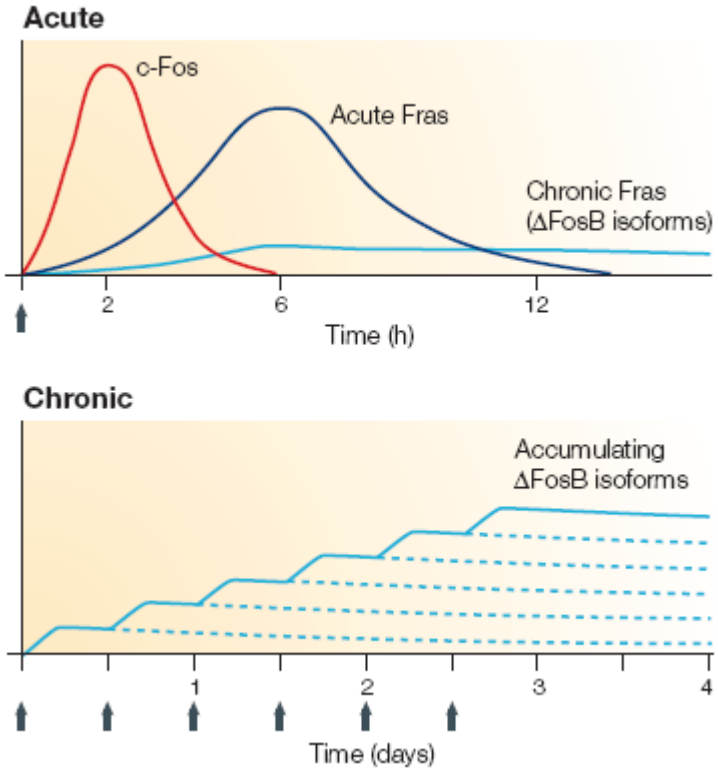
Short-term

Long-term

CREB → BDNF
ΔFosB → DYN
MEF2 → Glu
Epigenetic modifications

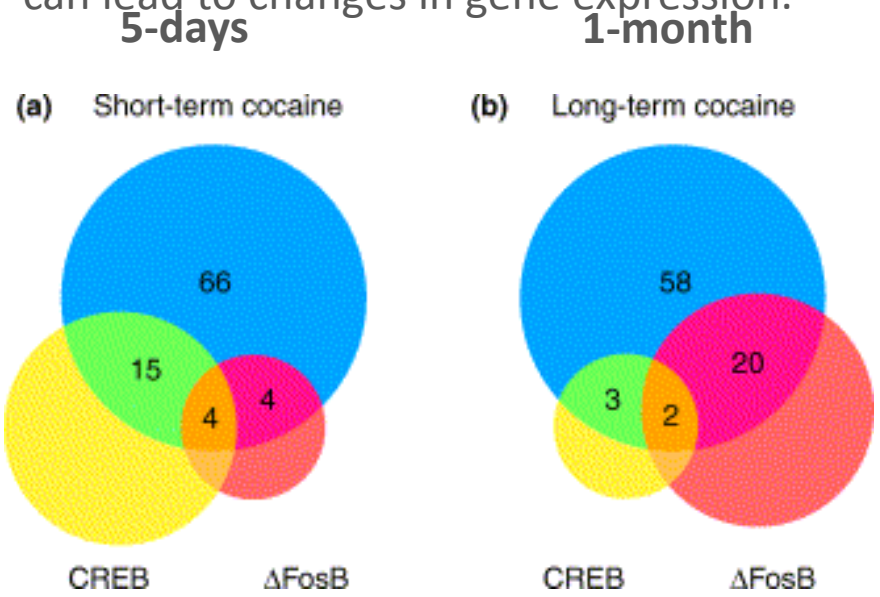
Nestler E. Neuropharmacology, 2004

Transcription factors: ΔFosB



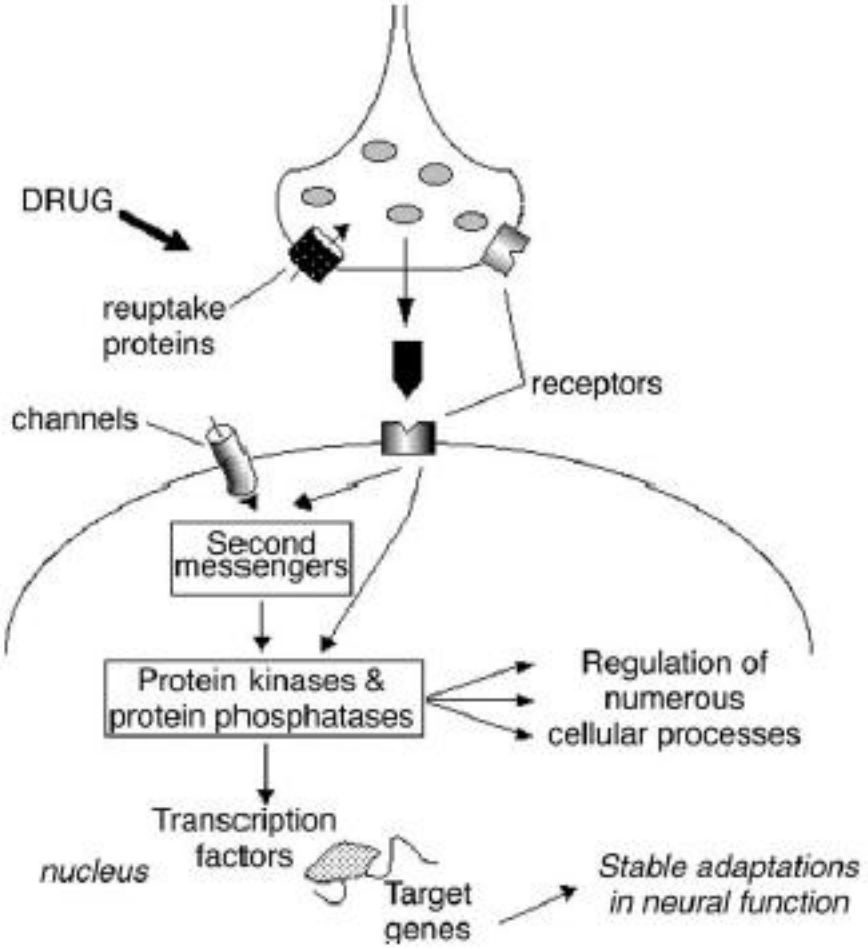
Nestler E. Neuropharmacology, 2004

- Acute drugs of abuse increase the expression of Fos and Jun proteins in the N. Acc
- Fos dimerize with a Jun family member to form activator protein-1 (AP-1)
- ΔFosB is produced in a small degree during acute administration. Accumulates after repeated exposure and results in a mechanism by which chronic drug exposure can lead to changes in gene expression.



McClung and Nestler, Nature Neurosci, 2003

Genes modulated



Short term

Long term

CREB → **BDNF**

ΔFosB — DYN

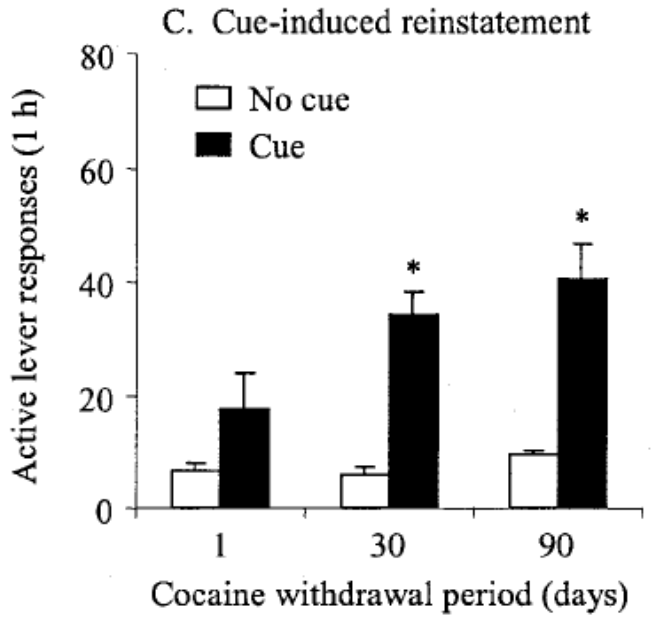
MEF2 — Glu

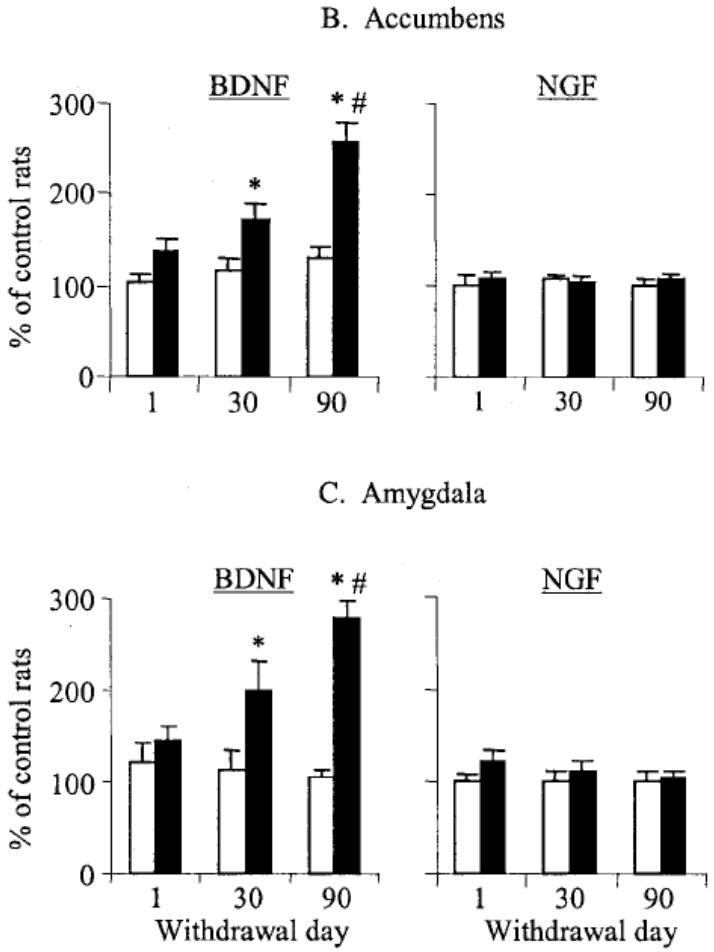
Epigenetic modifications

Nestler E. Neuropharmacology, 2004

BDNF: Brain Derived Neurotrophic factor

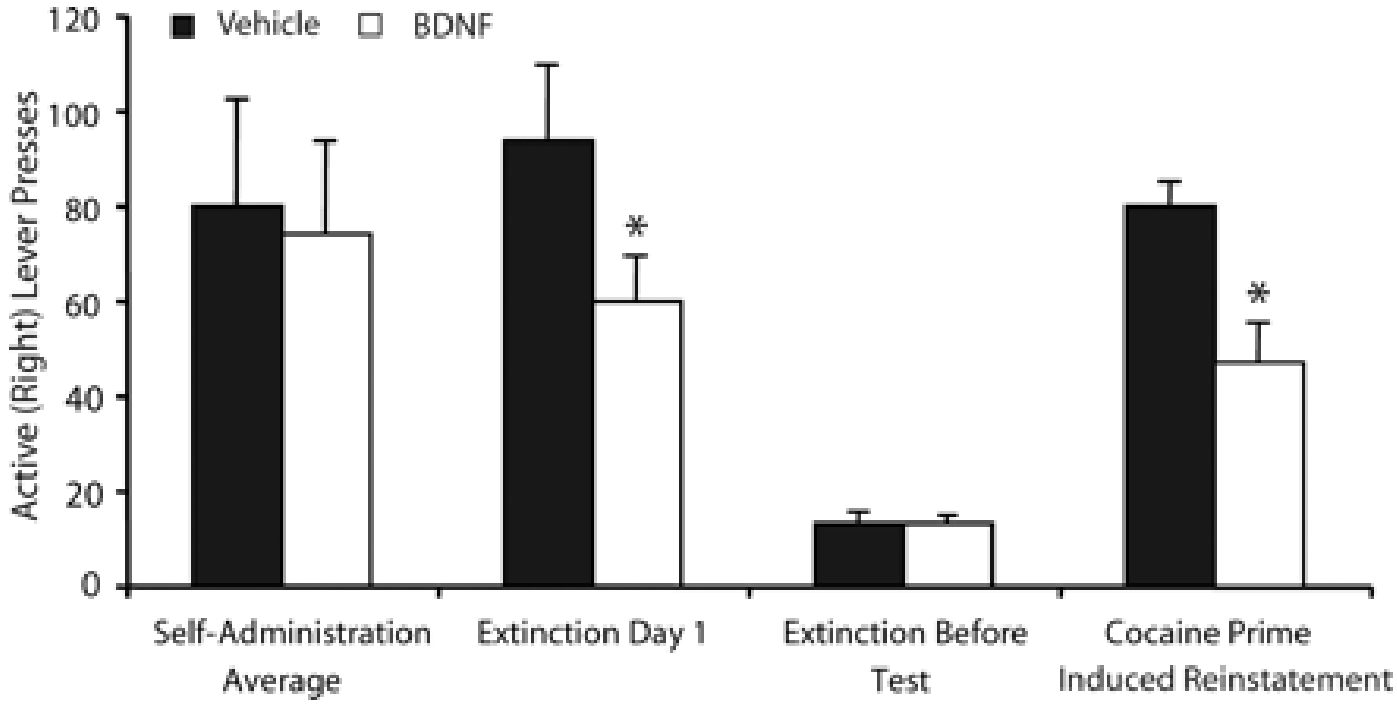
- Expression under the control of CREB
- Increased after cocaine withdrawal and maybe responsible for the enhanced responses to cocaine cues during craving





Grimm et al., J Neurosci, 2003

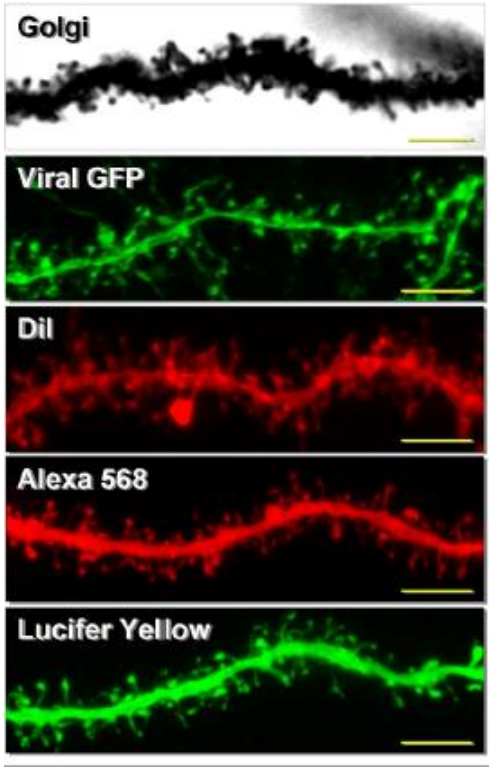
Intra-dmPFC BDNF suppressed cocaine-primed reinstatement



Berglind, W. J. et al. J. Neurosci. 2009.

BDNF signaling in the DL striatum keeps alcohol intake in moderation (Ron et al., J Neurosci, 2016).

Neuronal plasticity is associated to drug addiction



Russo et al., TINS, 2010

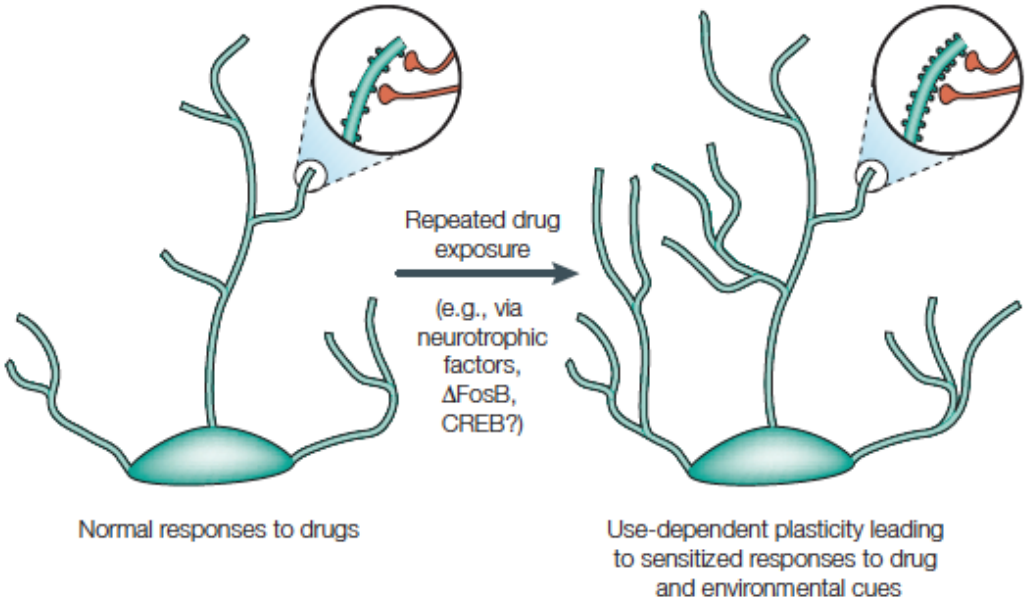


Figure 5 | **Regulation of dendritic structure by drugs of abuse.** The figure shows the expansion of a dendritic tree after chronic exposure to a drug of abuse, as has been observed in the nucleus accumbens and in the prefrontal cortex. The areas of magnification show an increase in dendritic spines, which is postulated to occur in conjunction with activated nerve terminals. Such alterations in dendritic structure, which are similar to those observed in other examples of synaptic plasticity such as long-term potentiation, could mediate long-lived sensitized responses to drugs of abuse or environmental cues.

Nestler, Nature Rev Neurosci., 2001

Drug-induced changes in neuronal morphology

Increase

Decrease

Stimulants	Drug regimen	Structural change	Molecular mediators
NAc medium spiny neuron	EA chronic cocaine (2-4 hr w.d.)	↑ Thin spines	NFκB, deltaFosB, G9A CDK5, MEF2
	EA or SA chronic cocaine (24 hr-months w.d.)	↑ Mushroom spines; dendrite complexity	
	EA chronic cocaine 3 week w.d. + challenge dose (24 hr w.d.)	↑ Thin spines	
VTA dopamine neuron	EA acute cocaine (2-4 hr w.d.)	↑ Spine density	NA
Hippocampus pyramidal neuron	NA	NA	NA
mPFC pyramidal neuron	EA or SA chronic cocaine (24 hr -months w.d.)	↑ Spine density; dendrite complexity	NA
oPFC pyramidal neuron	EA or SA chronic cocaine (24 hr -months w.d.)	↑ Spine density; dendrite complexity	NA

Opiates	Drug regimen	Structural change	Molecular mediators
NAc medium spiny neuron	SA and EA chronic morphine (1 month w.d.)	↓ Spine density; dendrite complexity	NA
VTA dopamine neuron	EA chronic morphine pellet (24 hr w.d.)	↓ Cell body size	BDNF, IRS2, Akt
Hippocampus pyramidal neuron & dentate gyrus granular cell	SA chronic morphine (1 month w.d.)	↓ Spine density	NA
mPFC pyramidal neuron	SA and EA chronic morphine (1 month w.d.)	↓ Spine density; dendrite complexity	NA
*oPFC pyramidal neuron	SA and EA chronic morphine (1 month w.d.)	↑ Spine density; dendrite complexity	NA

SA=self adminstered; EA=experimenter adminstered; w.d.=withdrawal; mPFC=medial prefrontal cortex; oPFC=orbital prefrontal cortex; NAc=nucleus accumbens; VTA=ventral tegmental area; BDNF=brain derived neurotrophic factor; IRS2=insulin receptor substrate 2; Akt=thymoma viral protooncogene; NFκB=nuclear factor kappa b; CDK5=cyclin dependent kinase 5; MEF2= myocyte enhancing factor 2; NA=not available.

* oPFC is the only brain region studied that morphine increases spine density and complexity.

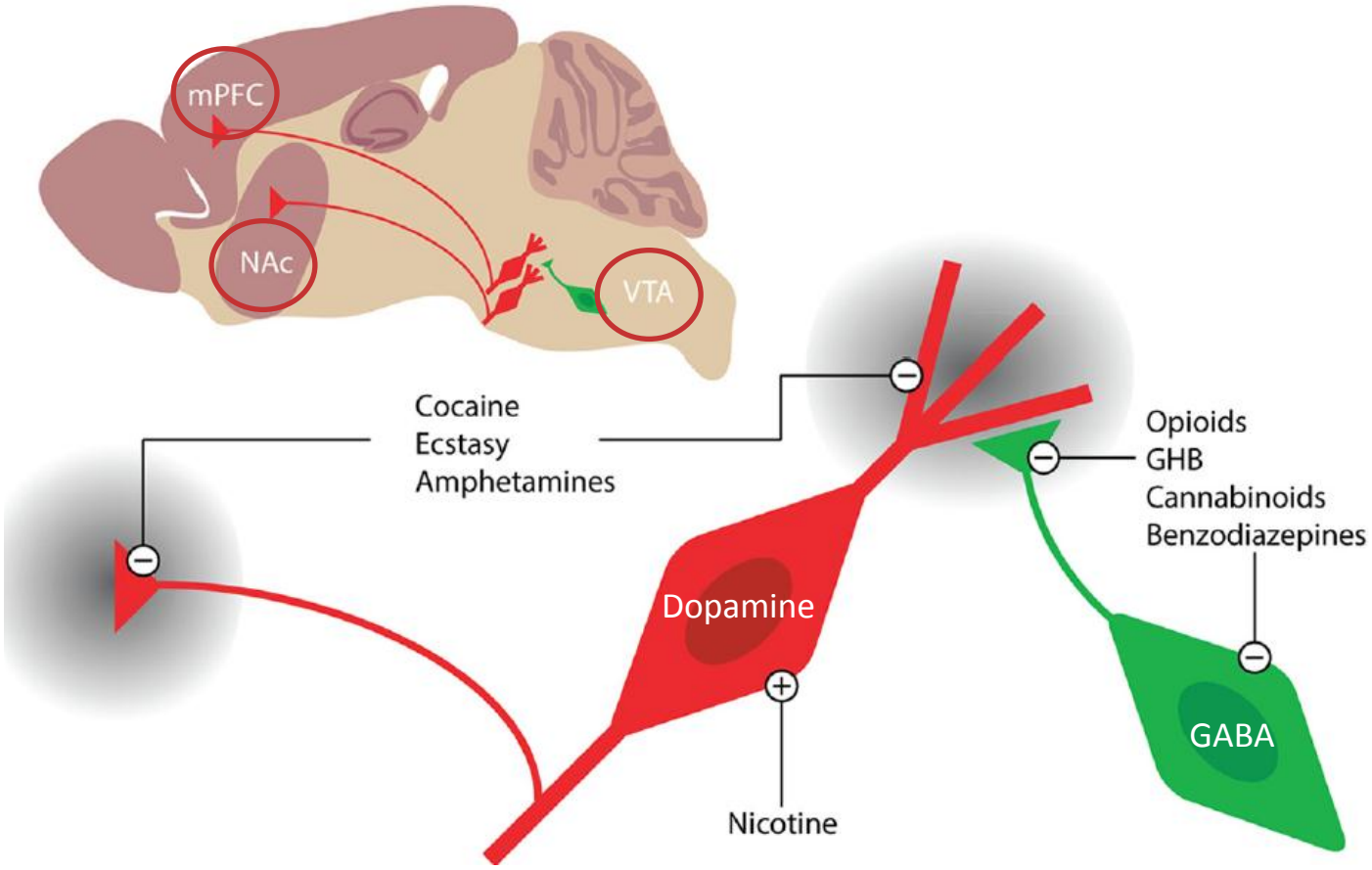
Russo et al., TINS, 2010

Structural plasticity

- ✓ Learning
- ✓ Environmental manipulations (isolated vs. complex environment)
- ✓ Recovery of function after brain damage
- ✓ Stress
- ✓Induce experience-dependent changes in behaviour and psychological function

Drugs of abuse may also induce long-lasting structural plasticity changes

The mesocorticolimbic dopamine system



Lüscher and Malenka, 2011

Brain regions forming the reward/addiction circuit

Prefrontal / Cingulate cortex

Dorsal striatum

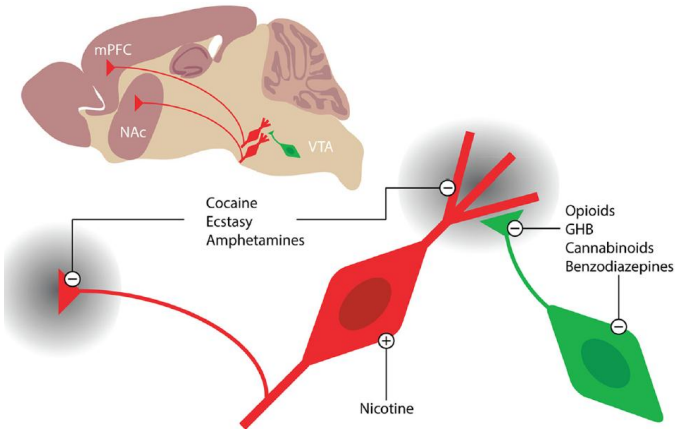
Hippocampus

Ventral striatum (N.accumbens)

Amygdala

Ventral tegmental area

Raphe Pontine Nuclei



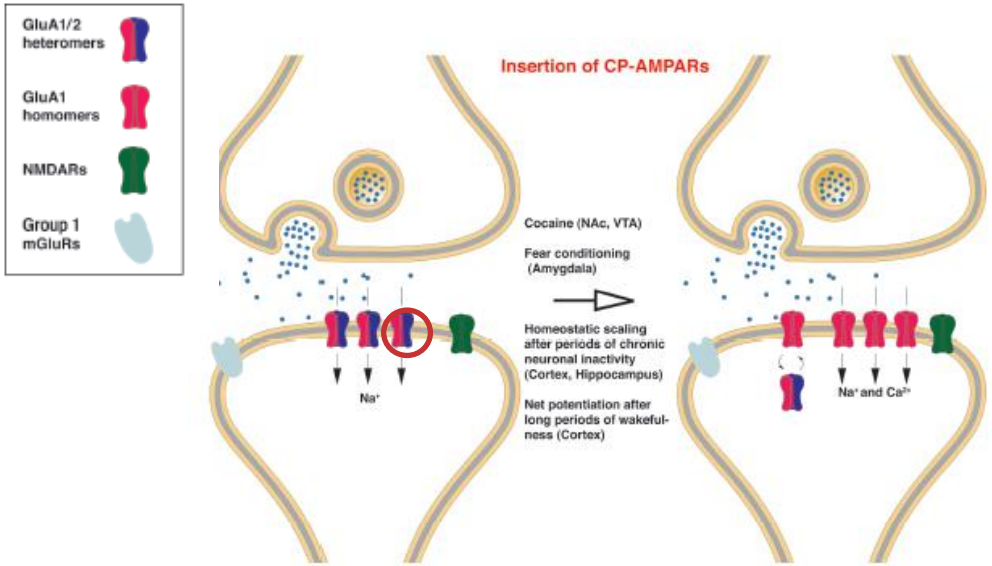
Lüscher and Malenka, 2011

Adapted from Jones and Bonci 2005

Structural plasticity involves redistribution of AMPARs and NMDARs

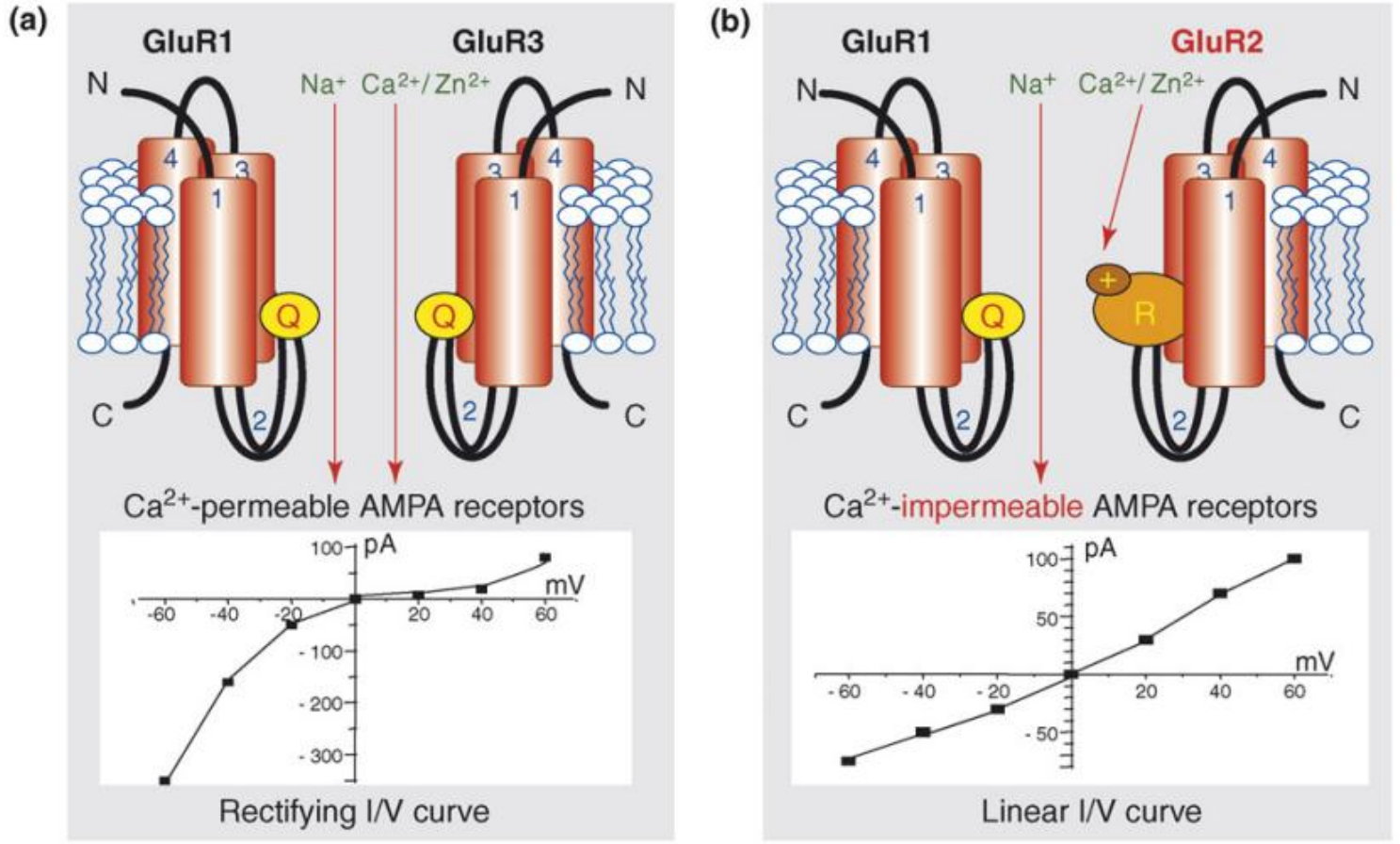
Absolute number of AMPARs and NMDA unchanged

- ✓ AMPA R. GluA1 -4 protein subunits. Mainly GluA1 and GluA2
- ✓ GluA2 not permeable to Ca++
- ✓ Majority of cells contains Ci-AMPA
- ✓ NMDA-heteromeric: GluN1, GluN2, GluN3
- ✓Developmental changes during development of AMPA and NMDA receptors



Bellone and Lüscher, 2012

Structural plasticity involves redistribution of AMPARs and NMDARs



Liu and Zukin, 2007

Structural plasticity involves redistribution of AMPARs and NMDARs

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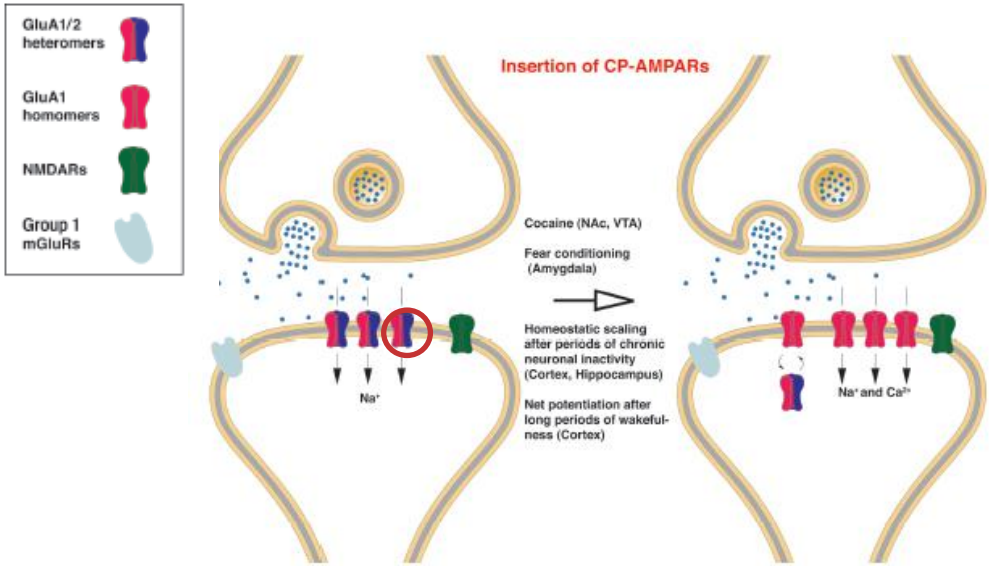


Bellone and Lüscher, 2012

Structural plasticity involves redistribution of AMPARs and NMDARs

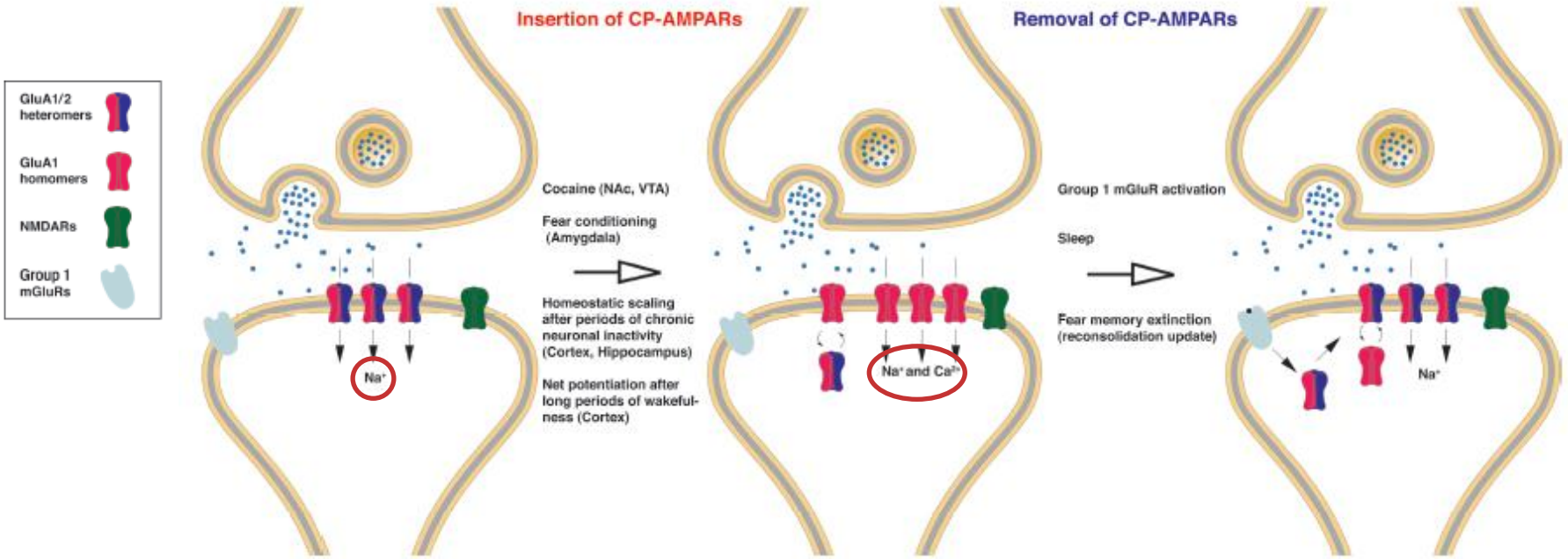
Absolute number of AMPARs and NMDA unchanged

✓ GluA1-containing receptors are exchanged for GluA2-lacking receptors (CP-AMPARs)

✓ GluN3A-containing NMDA appearance

Ratio A/N = EPSC AMPA

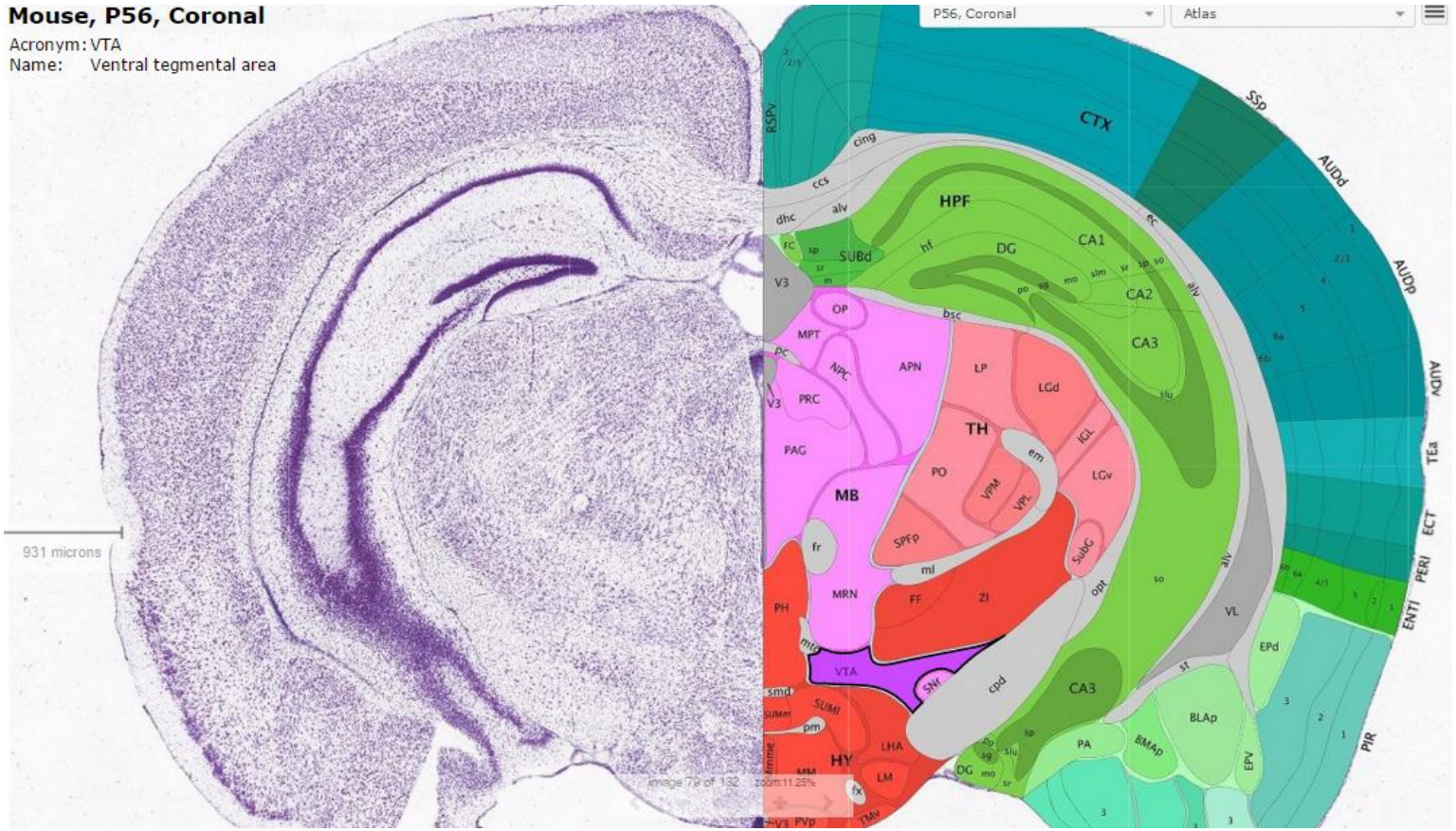
EPSC NMDA



Bellone and Lüscher, 2012

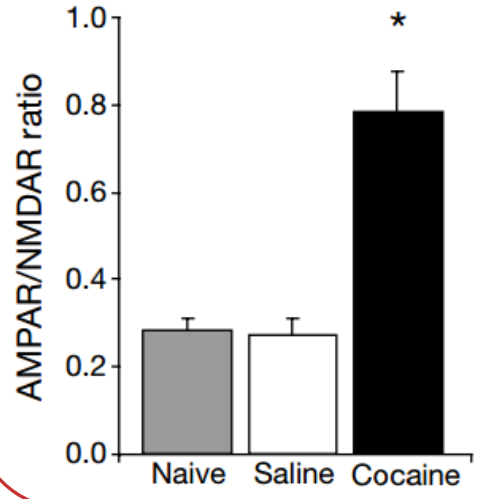
Ventral tegmental area (VTA)

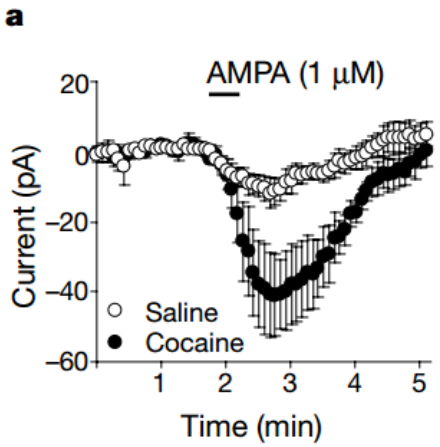
- 50-60% dopaminergic neurons
- Important population of GABAergic neurons
- Small percentage of excitatory glutamatergic neurons

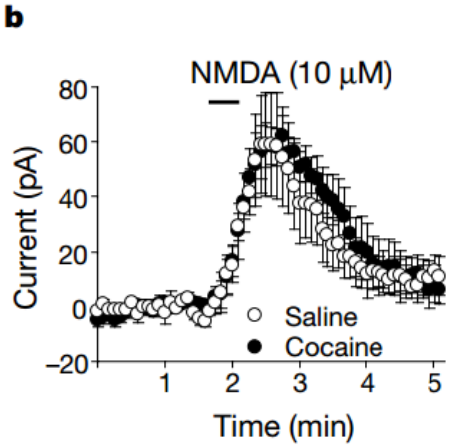


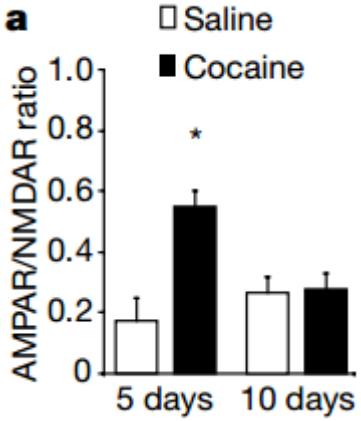
Drug-evoked synaptic plasticity in the VTA

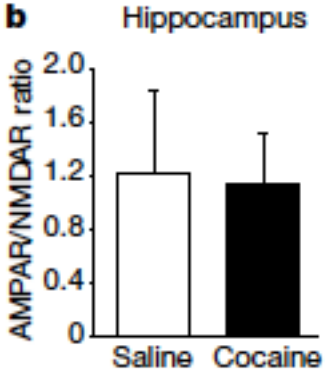
Ratio: AMPA/NMDA

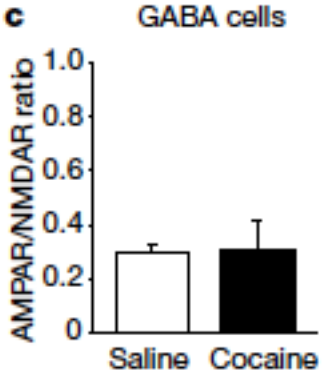


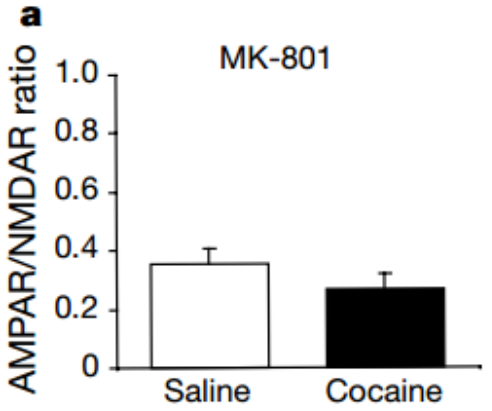






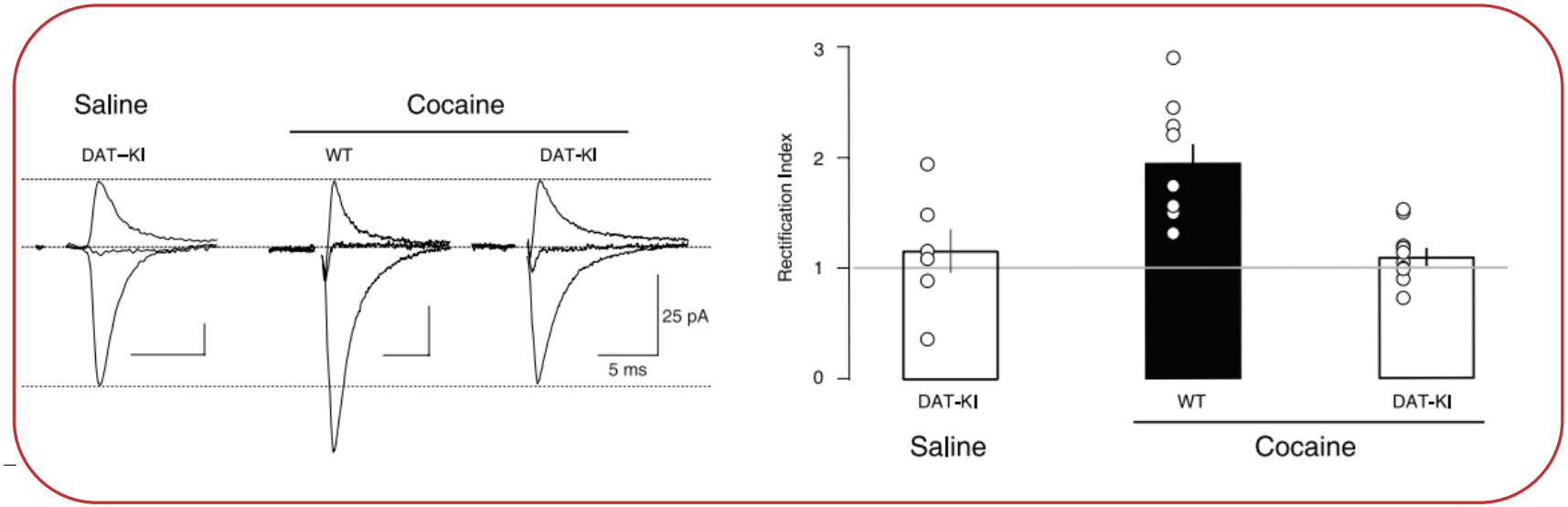


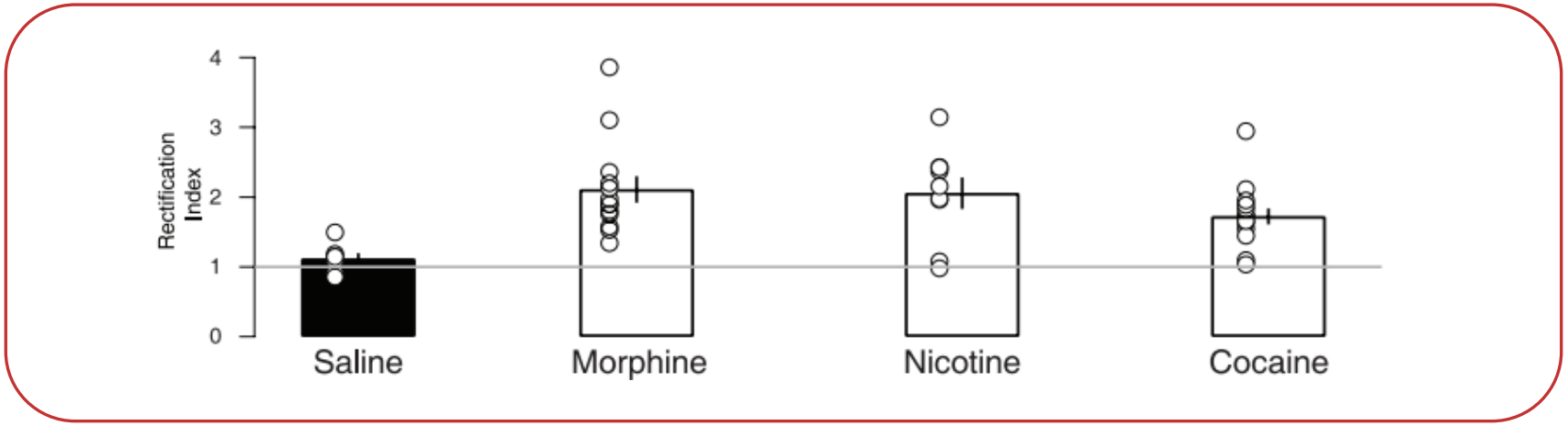




Ungless et al., 2001

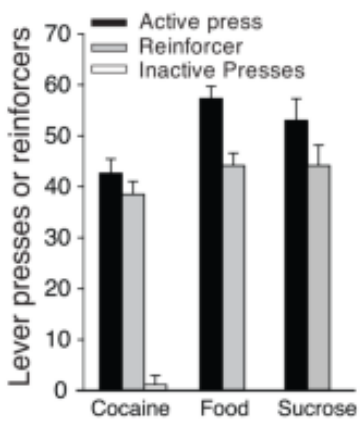
VTA dopamine is a critical trigger for synaptic plasticity

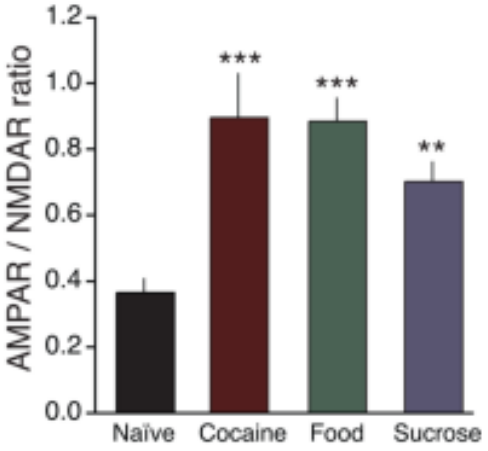


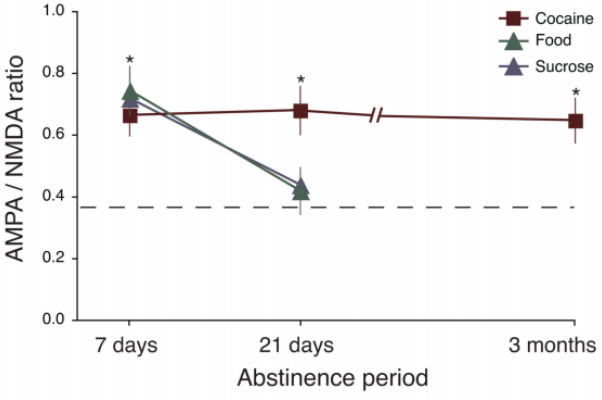


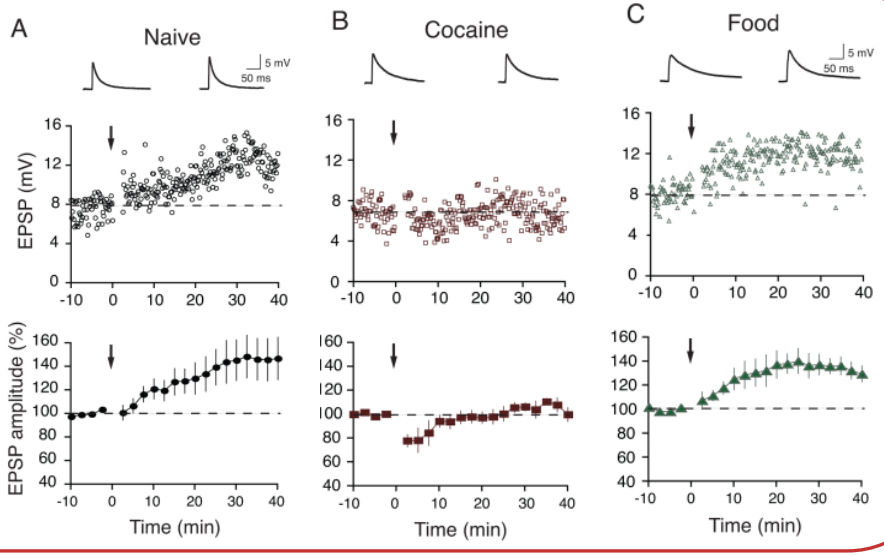
Brown et al., 2010

Natural rewards use similar cellular substrates



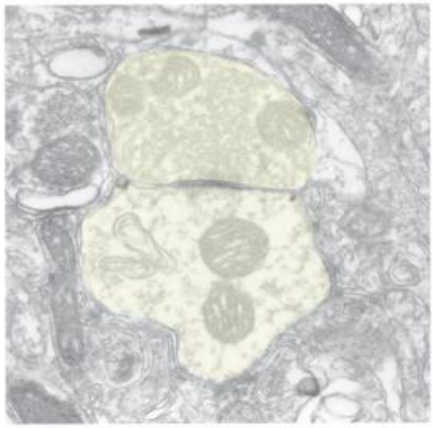


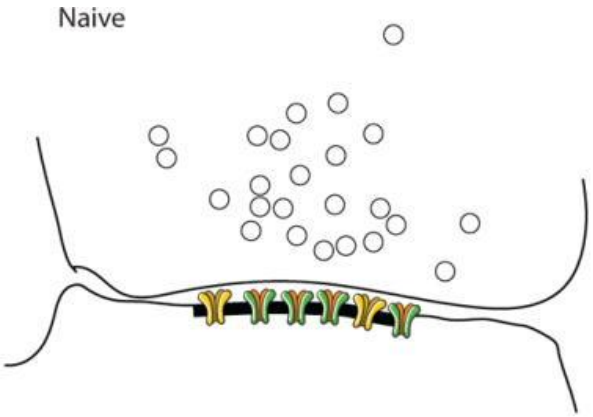


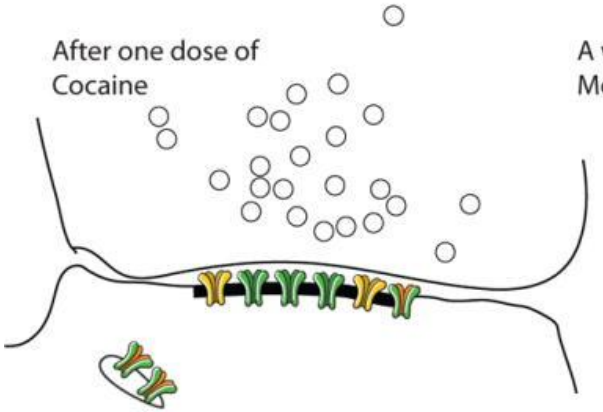


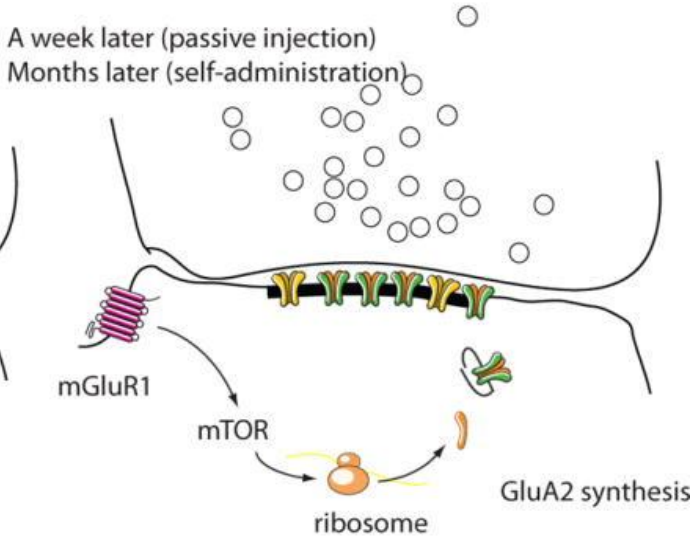
Chen et al., 2008

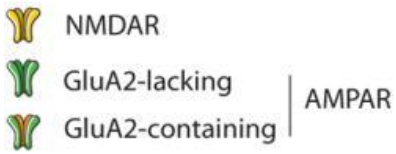
Structural plasticity involves redistribution of AMPARs and NMDARs in the VTA







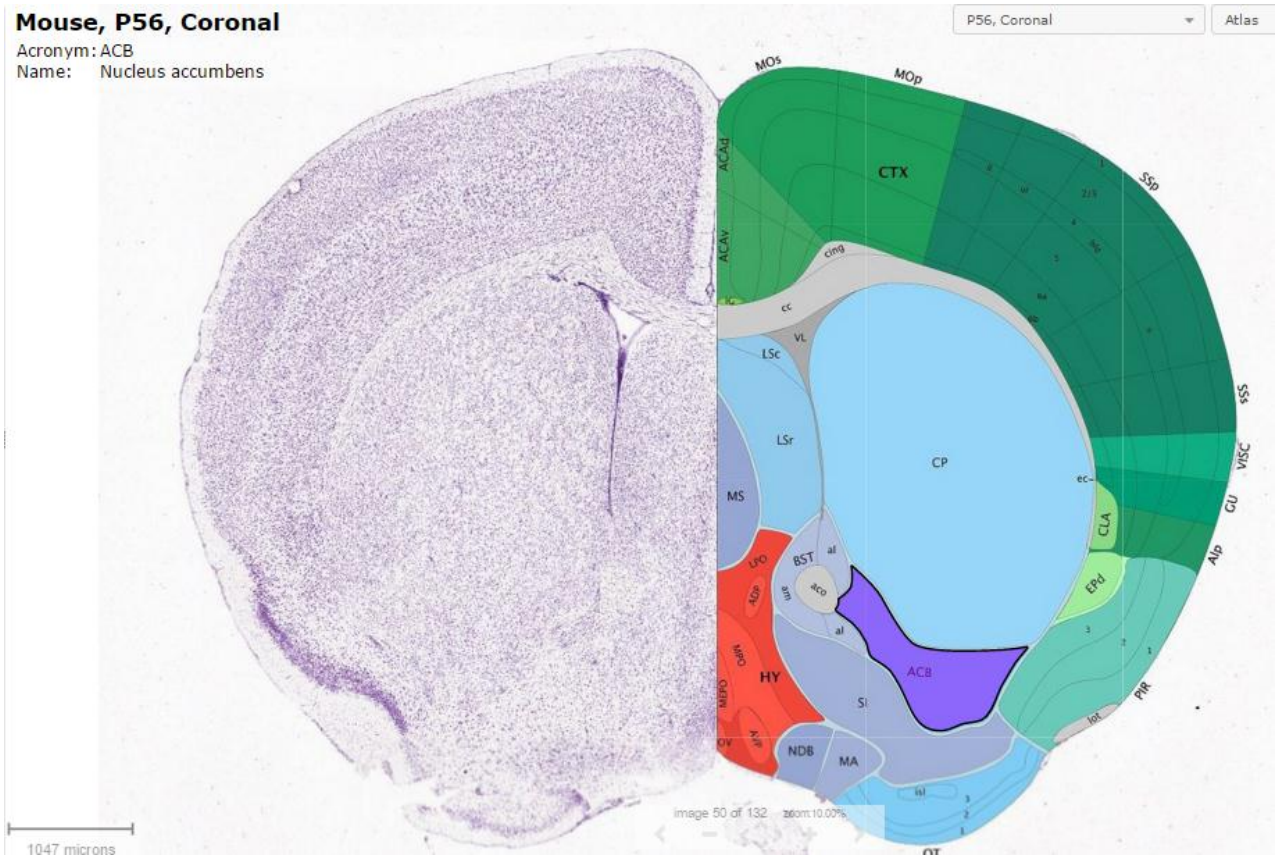




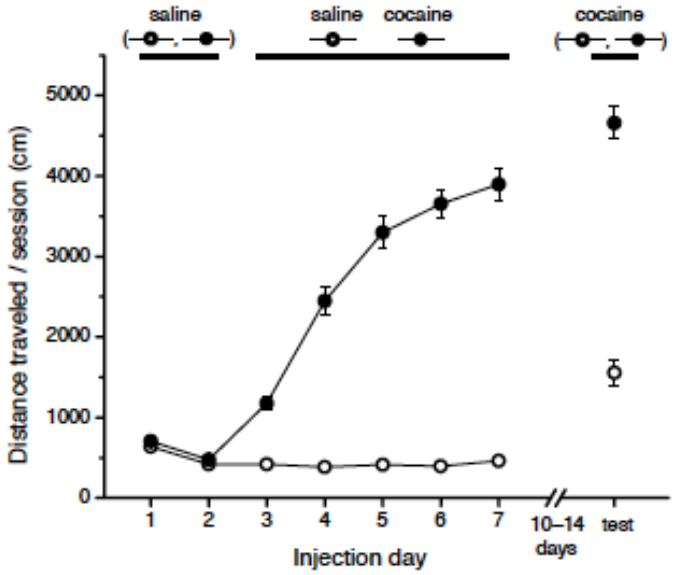
Lüscher and Malenka, 2011

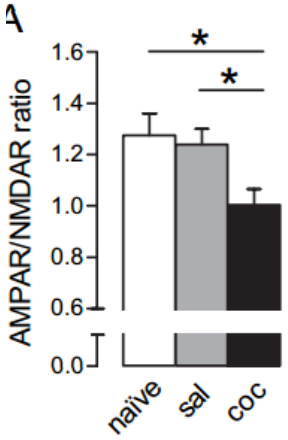
Nucleus Accumbens (NAc)

- 95% medium-sized spiny neurons (MSNs) (GABA)
- 5% GABAergic and cholinergic interneurons
- Core and shell regions

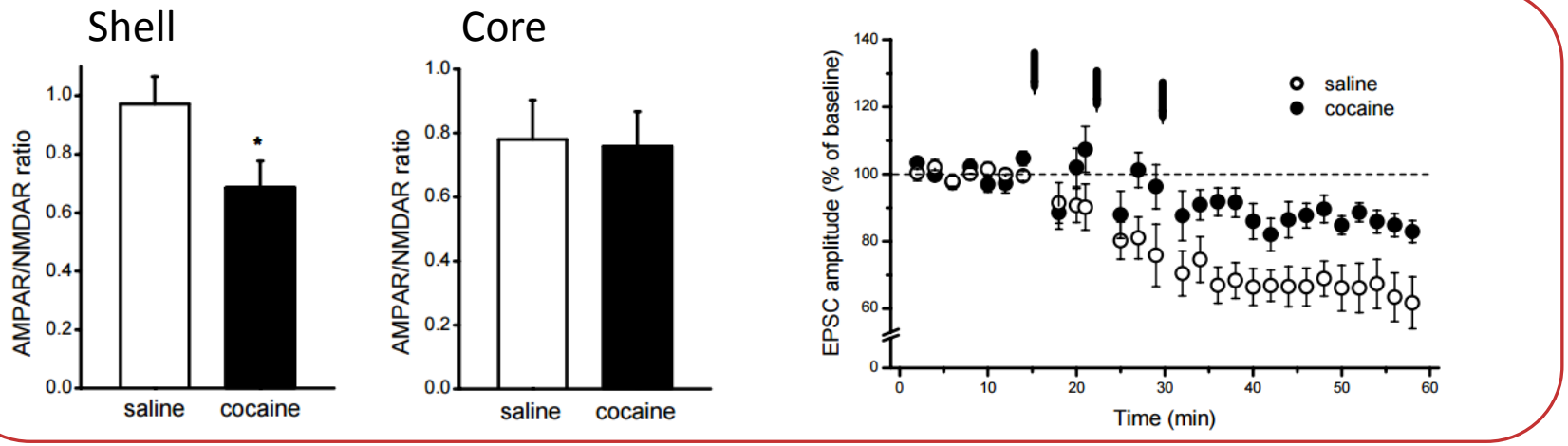


Drug-evoked synaptic plasticity in the NAc



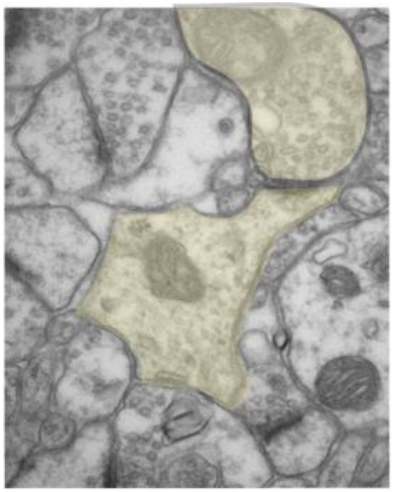


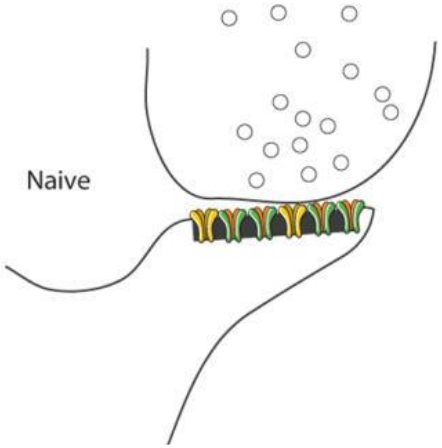
Kourrich et al., 2007

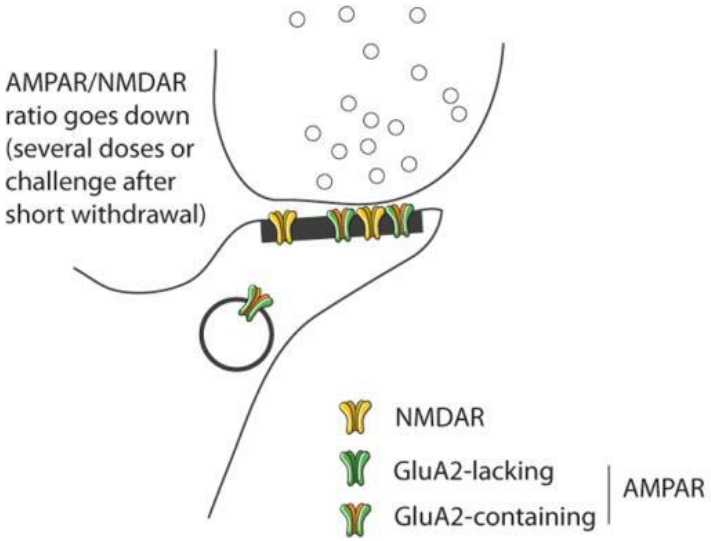


Thomas et al., 2001

Structural plasticity involves redistribution of AMPARs and NMDARs in the NAc



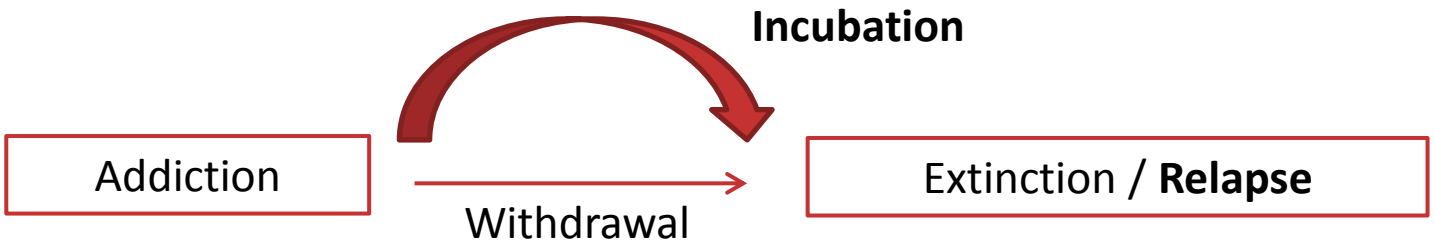


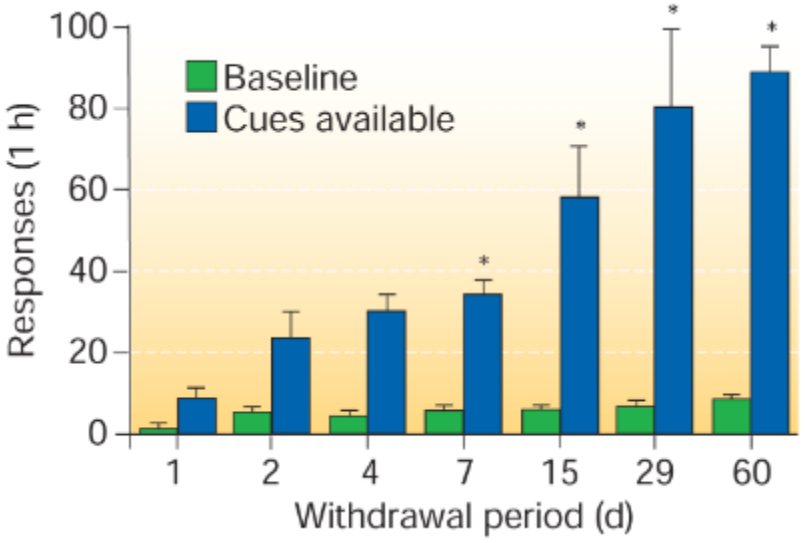


Lüscher and Malenka, 2011

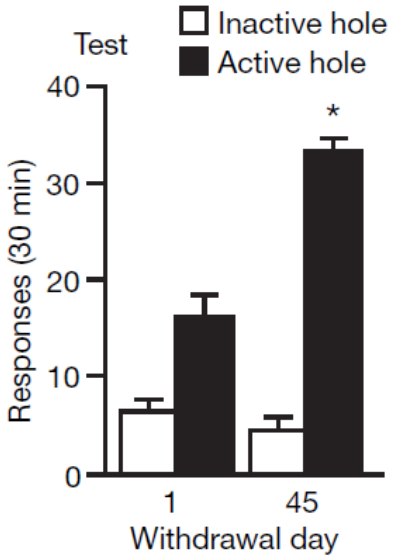
INCUBATION OF CRAVING

- ✓ Relapse after prolonged abstinence
- ✓ Induced by exposure to cues associated with the drug use



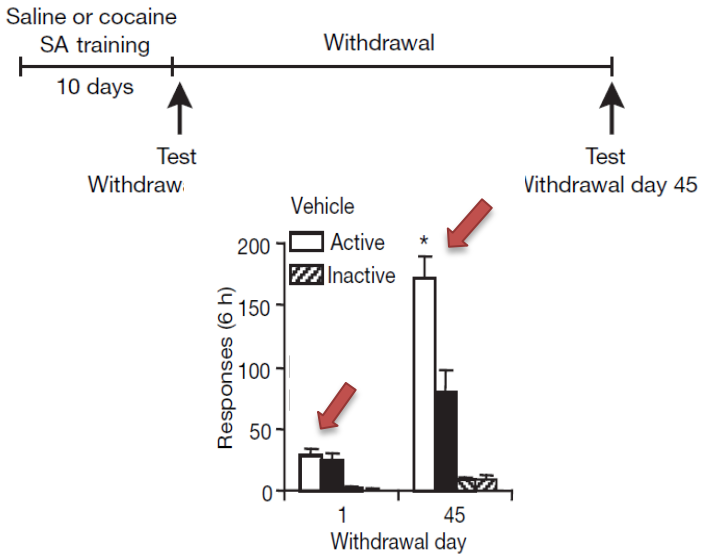


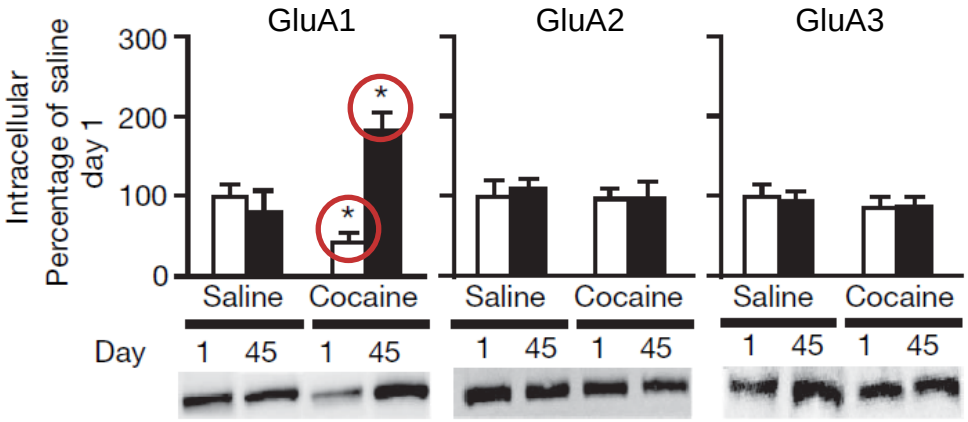
Grimm et al., 2001



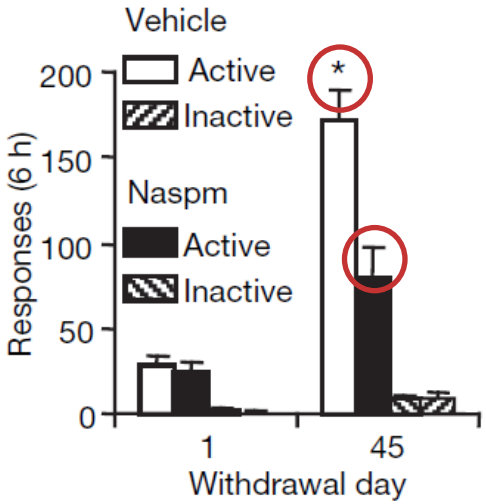
Conrad et al., 2008

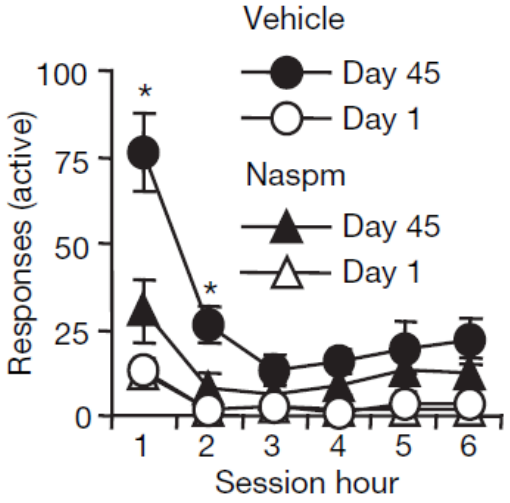
GluA2-lacking AMPA mediate incubation of cocaine craving in Nac …





… that is reversed by NASPM

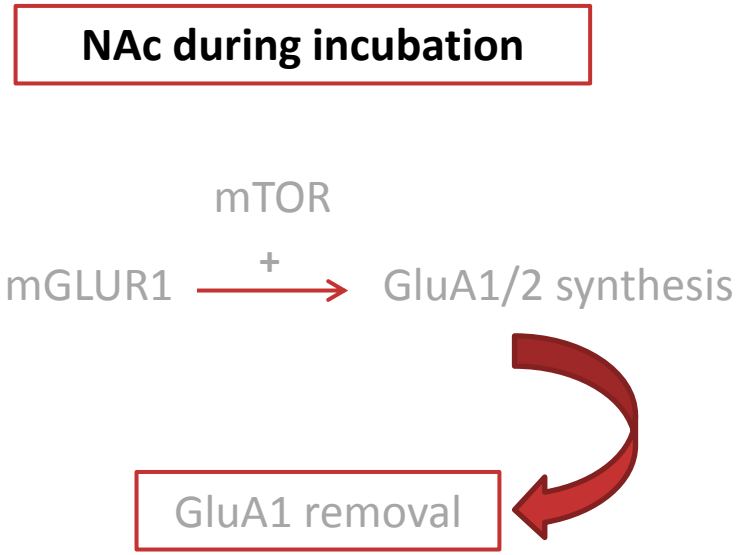




Conrad et al., 2008

mGluR1 negatively regulate AMPA transmission in NAc during incubation

- ✓ “Anti-addictive” effects after mGluR1 transmission
- ✓ Negatively regulates GluA2 lacking receptors



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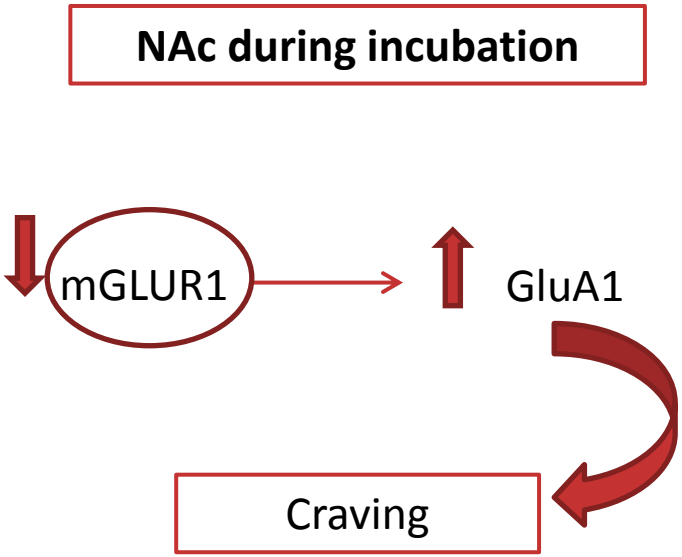
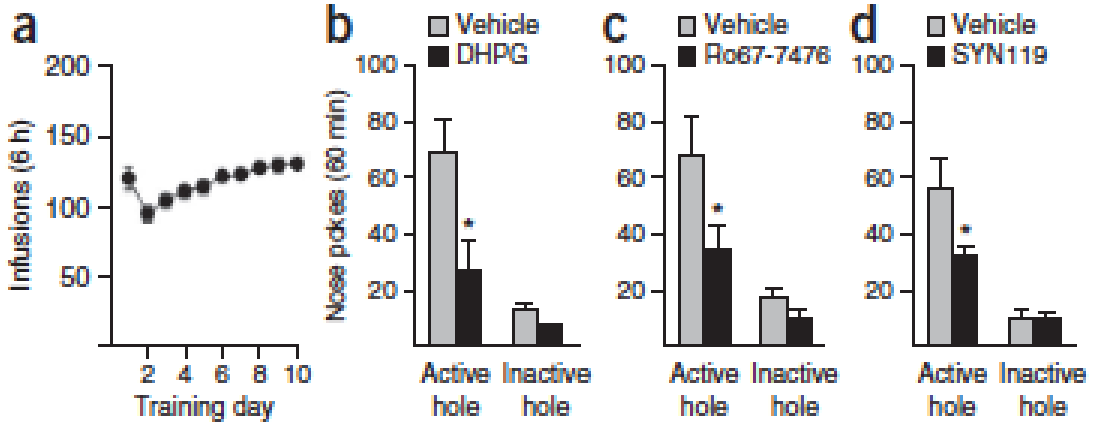
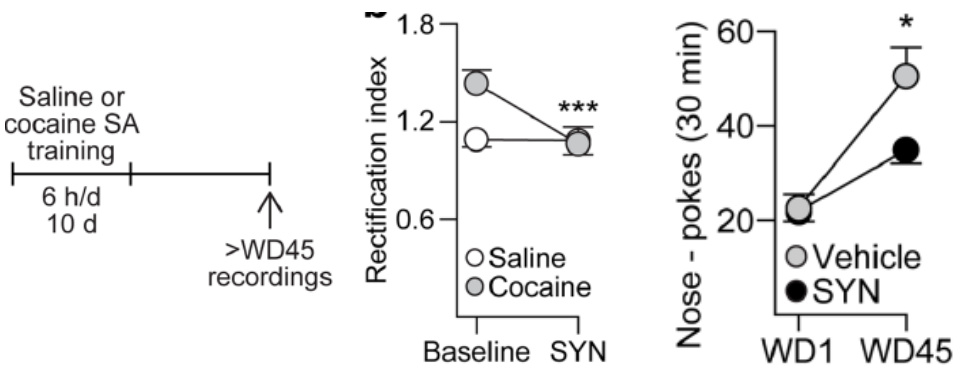


Synaptic depression via mGluR1 suppresses cue-induced cocaine craving



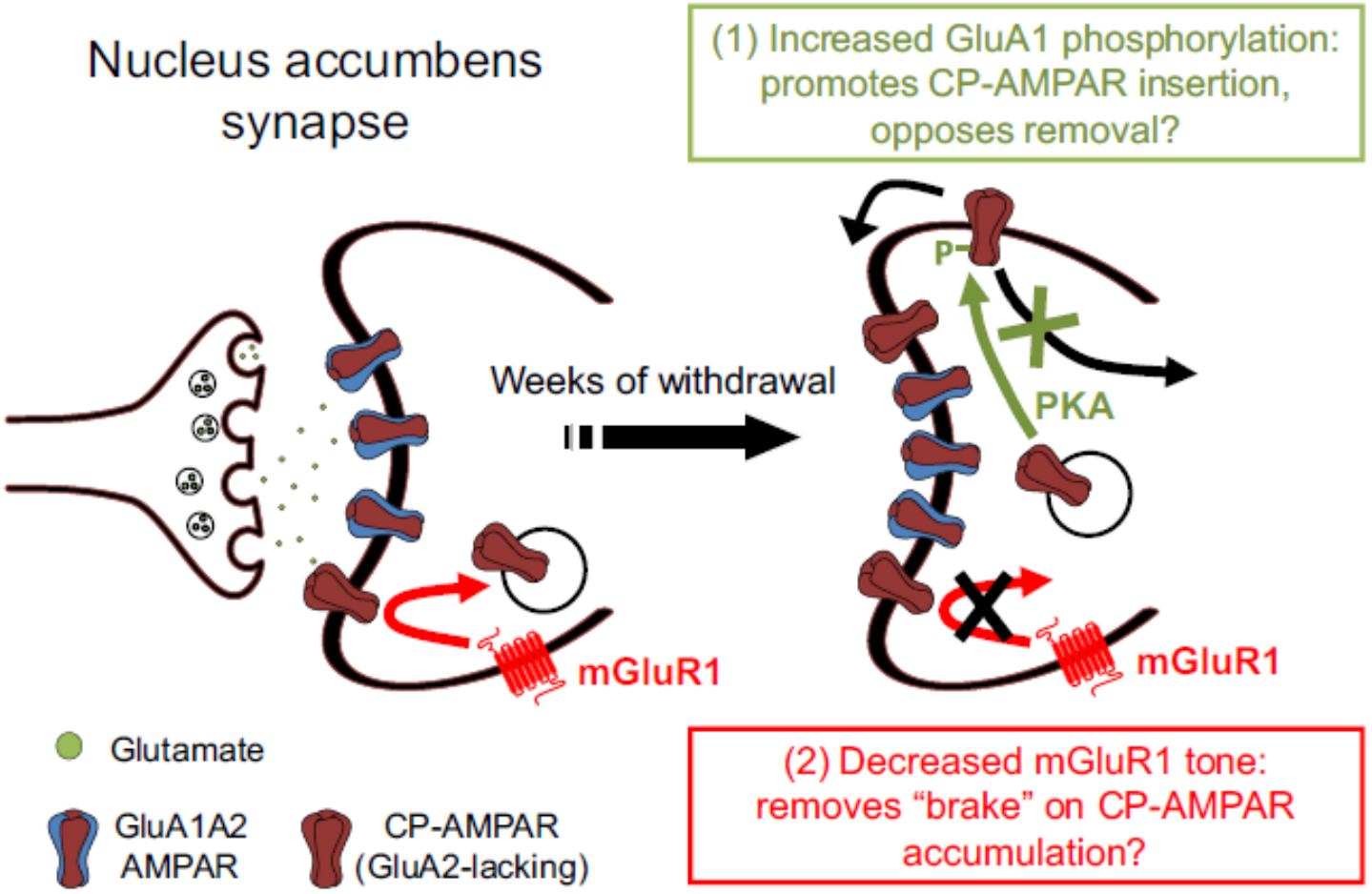
NAc direct administration



Systemic administration

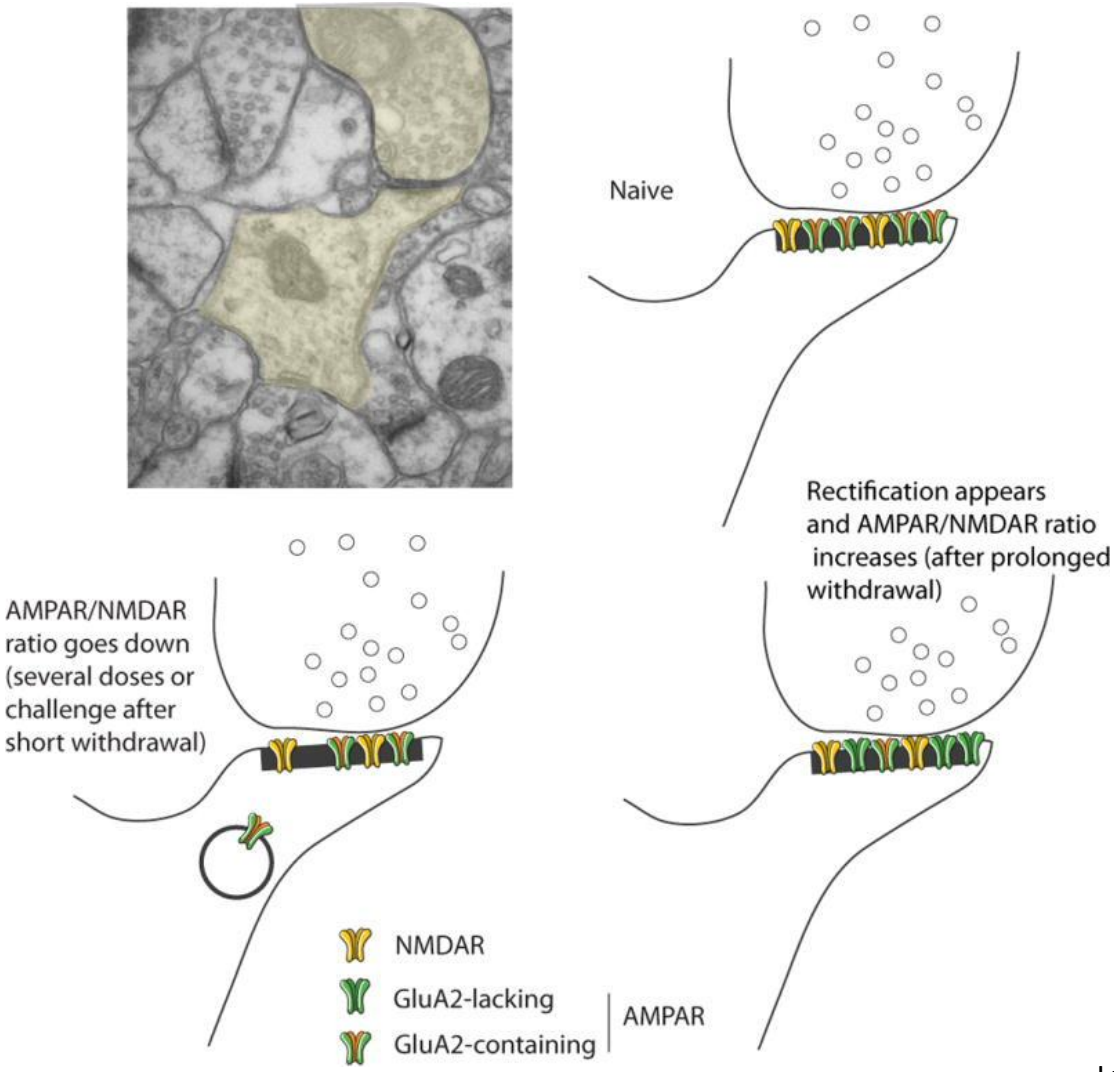
Loweth et al., 2014

GLOBAL PERSPECTIVE



Loweth et al., 2014

Structural plasticity involves redistribution of AMPARs and NMDARs in the NAc



Lüscher and Malenka, 2011

Drug-evoked synaptic plasticity in other brain areas

PFC

✓ Glutamate receptor redistribution related to drug consumption

✓ GluA1 endocytosis → decreased AMPA/NMDA ratio

✓ Increased expression of BDNF during acute withdrawal: ↑ cue-induced drug craving and drug-seeking behavior

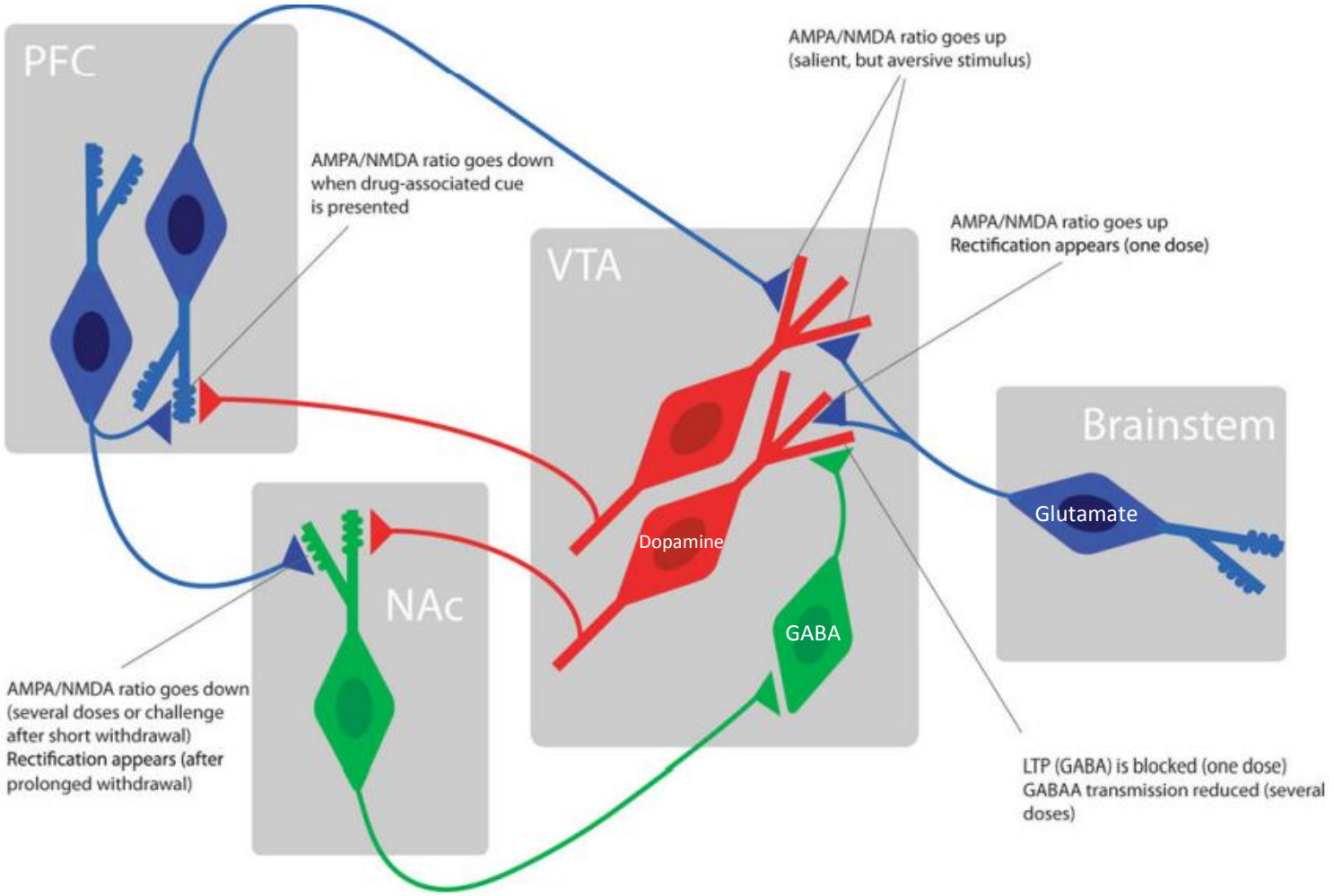
Amygdala

✓ Cocaine-associated cues inducing craving alter neuronal activity in the amygdala

✓ LTP increases associated with time of withdrawal

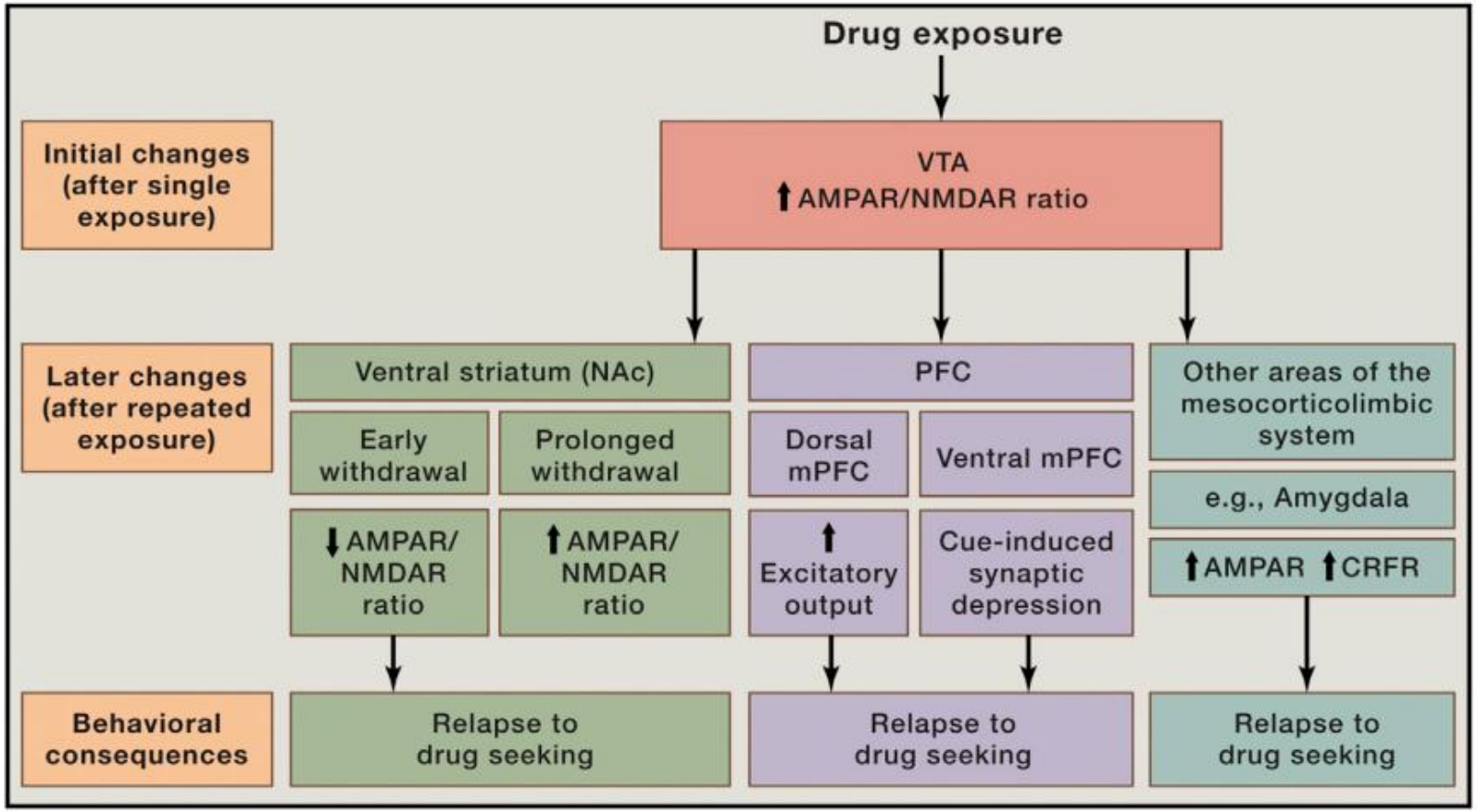
✓ Correlation with the aversiveness of withdrawal symptoms

GLOBAL PERSPECTIVE



Lüscher and Malenka, 2011

GLOBAL PERSPECTIVE



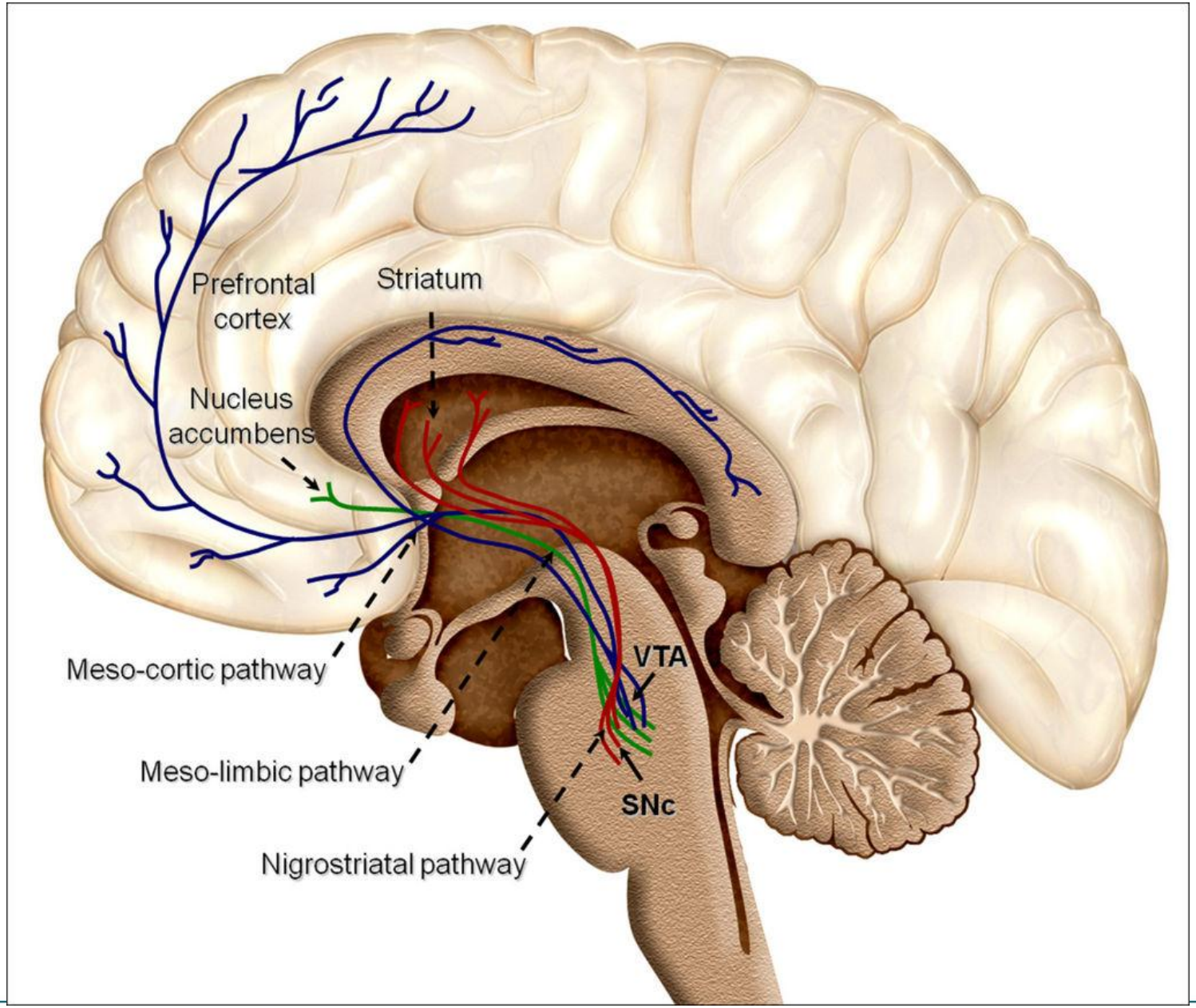
Volkow and Morales, 2015

Must take home message:

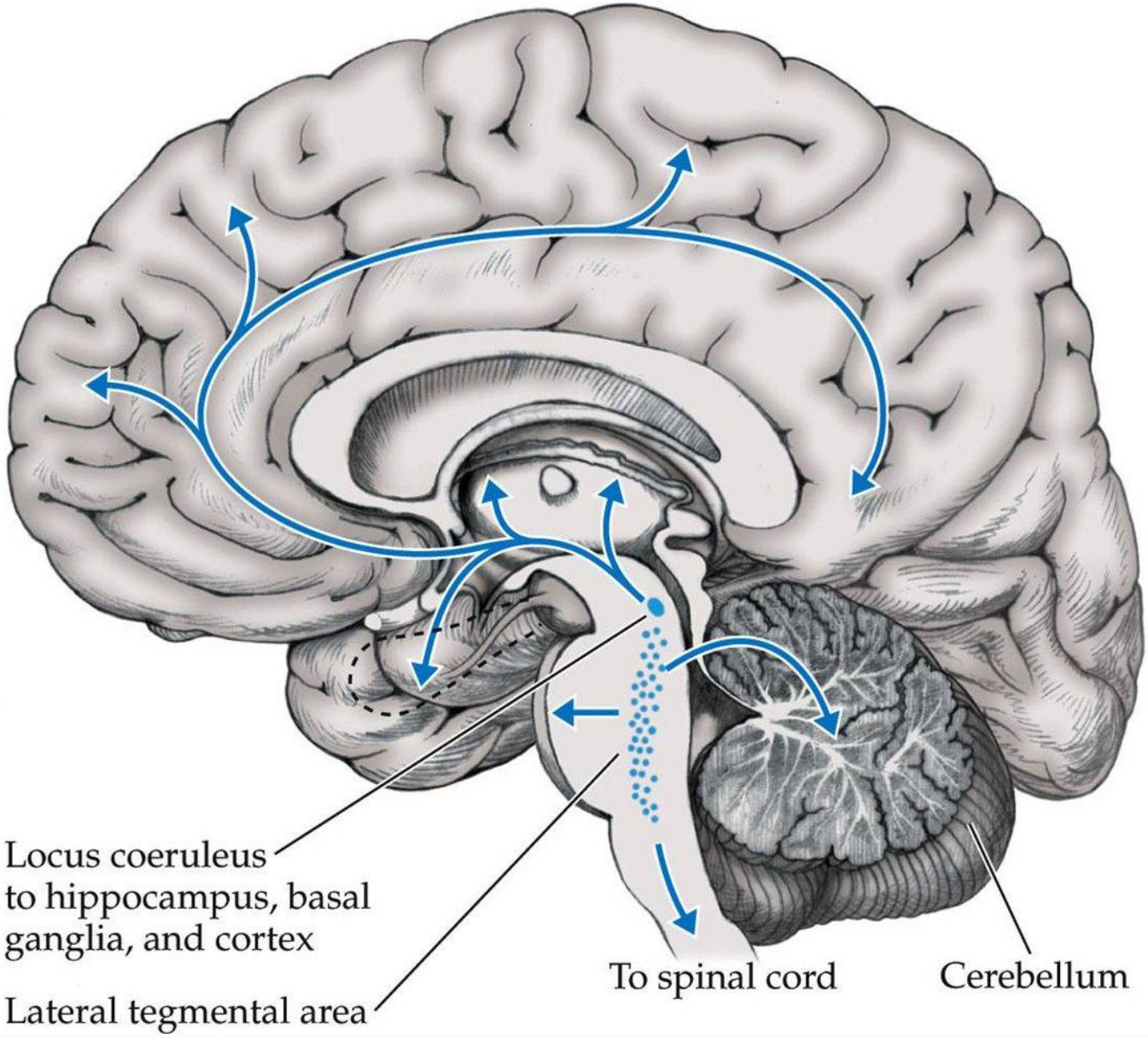
- Drug addiction is a chronic and relapsing disorders. Aberrant plasticity is developed in discrete brain areas.
- Drugs produce long-term modulation in molecular players, transcriptional factors, gene expression and also epigenetic modifications.
- Synaptic plasticity due to drugs of abuse induces redistribution of NMDA and AMPA receptors
- The redistribution involves the inclusion of GluA2-lacking receptors and changes in AMPA/NMDA ratio.
- GluA2-lacking receptors activity is increased during incubation of craving
- mGluR1 may be useful targets to diminish craving after long withdrawal periods
- Synaptic plasticity changes also involve changes in dendritic branching

WHY ADDICTION IS COMORBID WITH MENTAL DISORDERS?

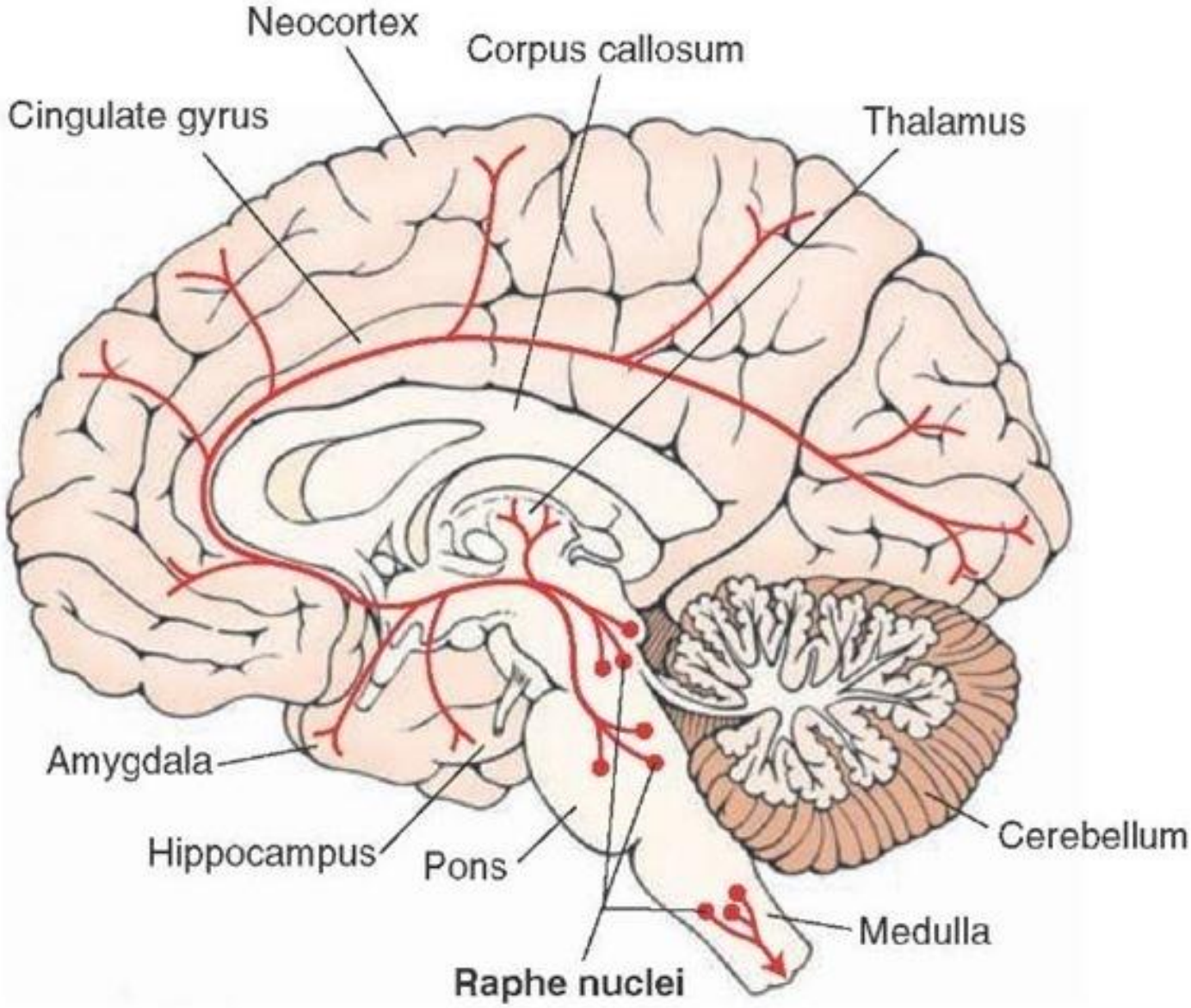
- **ADDICTION PACIENTS SHOW A HIGH PREVALENCE OF MENTAL DISORDERS**
- **SEVERAL THEORIES IDENTIFY ADDICTION AS AN EPIPHENOMENON OF THE UNDERLYING MENTAL DISEASE: PATIENTS SEF-MEDICATE TO ALLEVIATE SYMPTMATOLOGY**
- **THERE IS EVIDENCE THAT SOME MENTAL DISORDERS ARE INDUCED BY REPEATED ADMINISTRATION OF DRUGS OF ABUSE**
- **AN IMPORTANT EXPLANATION ARISES FROM FUNCTIONAL NEUROANATOMY AND FROM NEUROPSYCHOPHARMACOLOGY:**
  - **THE ASCENDING MONOAMINERGIC TRANSMISSION SYSTEM ARE INVOLVED IN BOTH, ADDICTION AND MENTAL DISORDERS**
  - **DRUGS OF ABUSE USE THE SAME TARGETS AS THOSE USED BY MOST EFFICIENT PSYCHOPHARMS**



DOPAMINE CIRCUITS IN THE BRAIN



NORADRENALINE CIRCUITS IN THE BRAIN



SEROTONINE CIRCUITS IN THE BRAIN

MOST FREQUENT TYPES OF PSYCHOPHARMS….DRUGS?

- INHIBITION OF MONOAMINE TRANSPORTERS
- INHIBITION OF MONOAMINE DEGRADATION
- ANTAGONISM OF MONOAMINE RECEPTORS
- AGONISM OF MONOAMINE RECEPTORS
- AGONISM /ALLOSTERIC POTENTIATION GABA-A RECEPTORS
- MODULATORS OF ENDOCANNABINOID SIGNALING / RECEPTORS
- MODULATORS OF GLUTAMATE RECEPTORS

NEUROBIOLOGY OF ADDICTION

- **Addiction = Transition = Plasticity**

Drugabuse.com

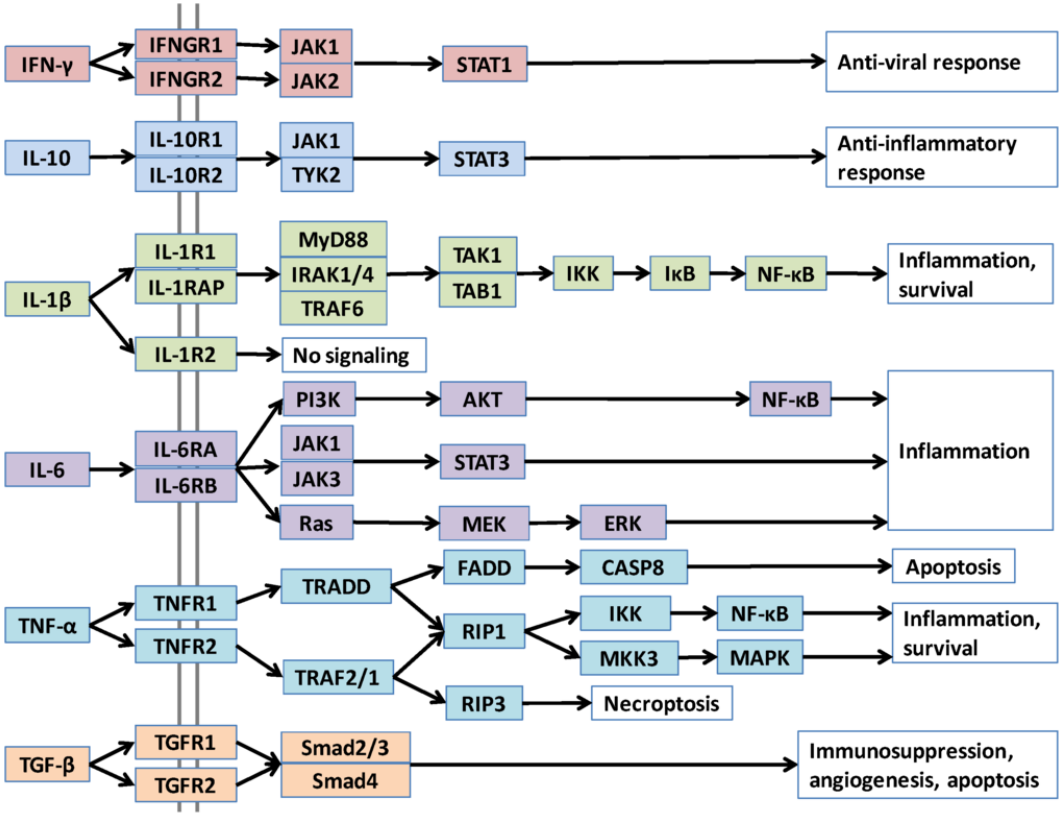
- Dopamine
- Serotonin and other monoamines
- Opioid peptides
- GABA and Glutamate
- CRF and NPY
- Growth factors (BDNF, IGF-1…)
- More and more

- Cytokines
- Fatty acid derivatives

PRO/ANTI-INFLAMMATORY SIGNALS

CYTOKINES

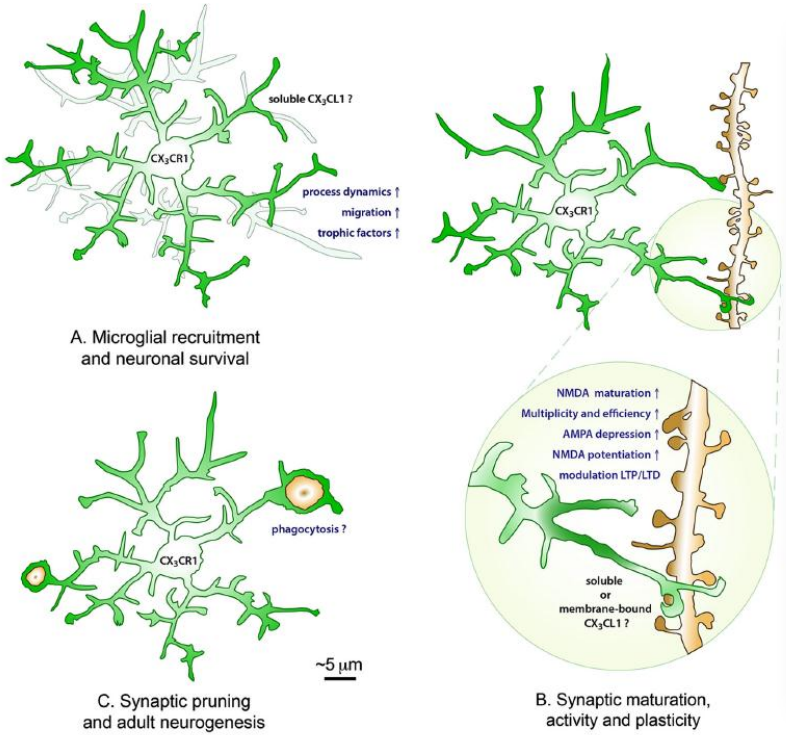
Cytokines: **Interleukins, lymphokines, monokines, interferons, chemokines…**



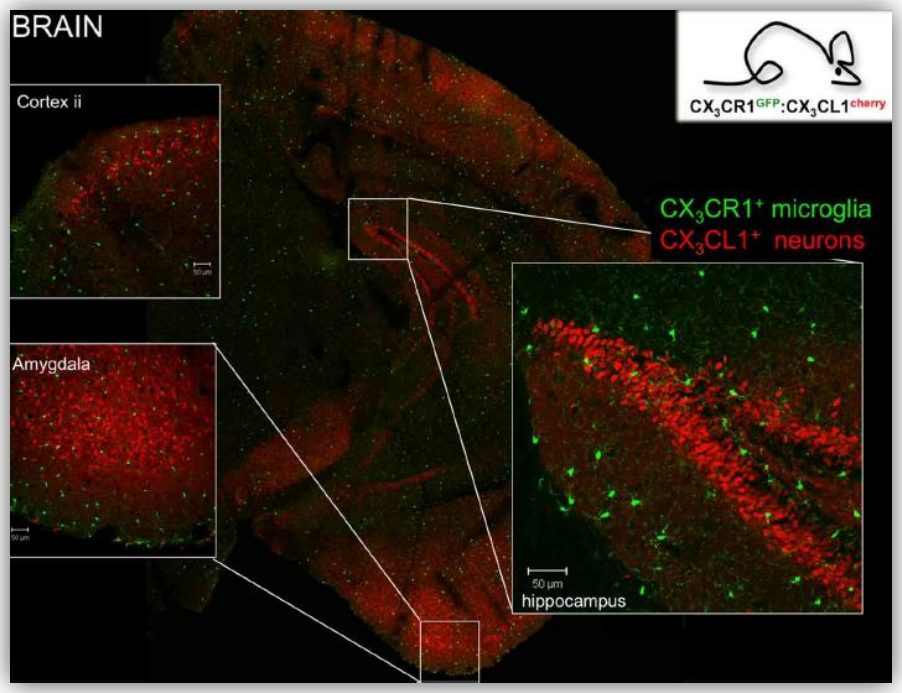
Guven-Maiorov et al., 2014

CYTOKINES

CX3CL1: Fractalkine is a neuronal chemokine



Paolicelli et al, 2014



Wolf et al, 2013

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ACKNOWLEDGEMENTS

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pnsd
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Thank you!

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