# Synaptic plasticity associated with the transition to cocaine addiction

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# Neurobiology of transition to addiction

Transition to addiction (cocaine)

Animal model of transition to addiction

Synaptic plasticity & transition to addiction

# Cocaine abuse can lead to severe health problems

Cardiovascular

Respiratory

Gastrointestinal

Infectious diseases

Psychological

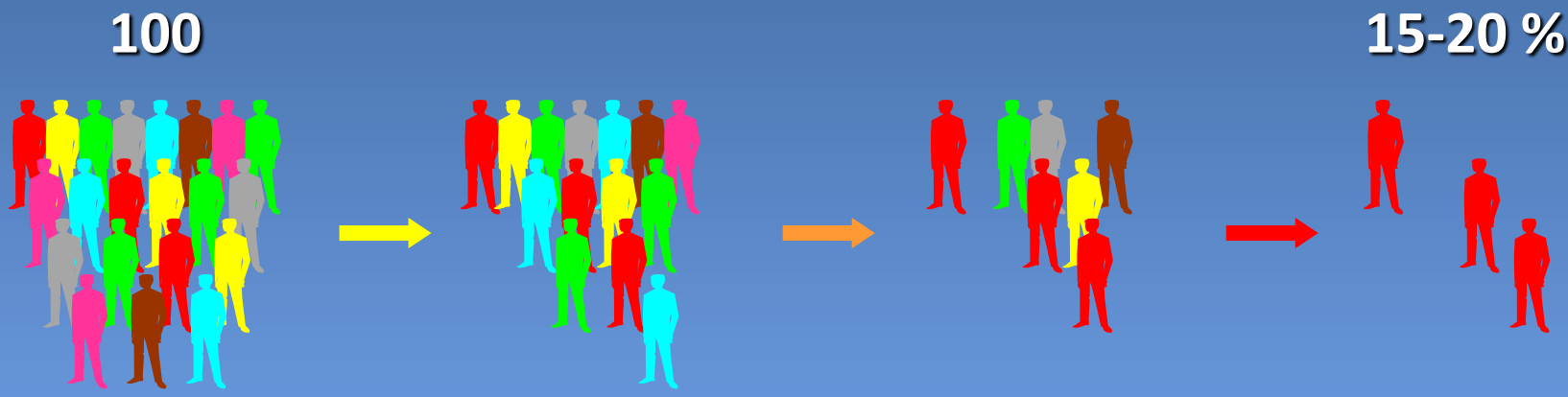
- Irritability
- Anxiety
- Paranoia
- **Addiction**

# Addiction

Dynamic, progressive and chronic disease

Compulsive drug use that is continue despite severe negative consequences

# Addiction is observed in a small proportion of drug users after prolonged periods of drug consumption



# Transition to Addiction

Shift from controlled drug use to compulsive drug taking


## Normal

## Addicted

Behavioral Repertoire

Lost of control

Consumatory

Reproductive

Drug use

Productive

Recreational

# Which are the neurobiological changes specifically associated with the transition to addiction?

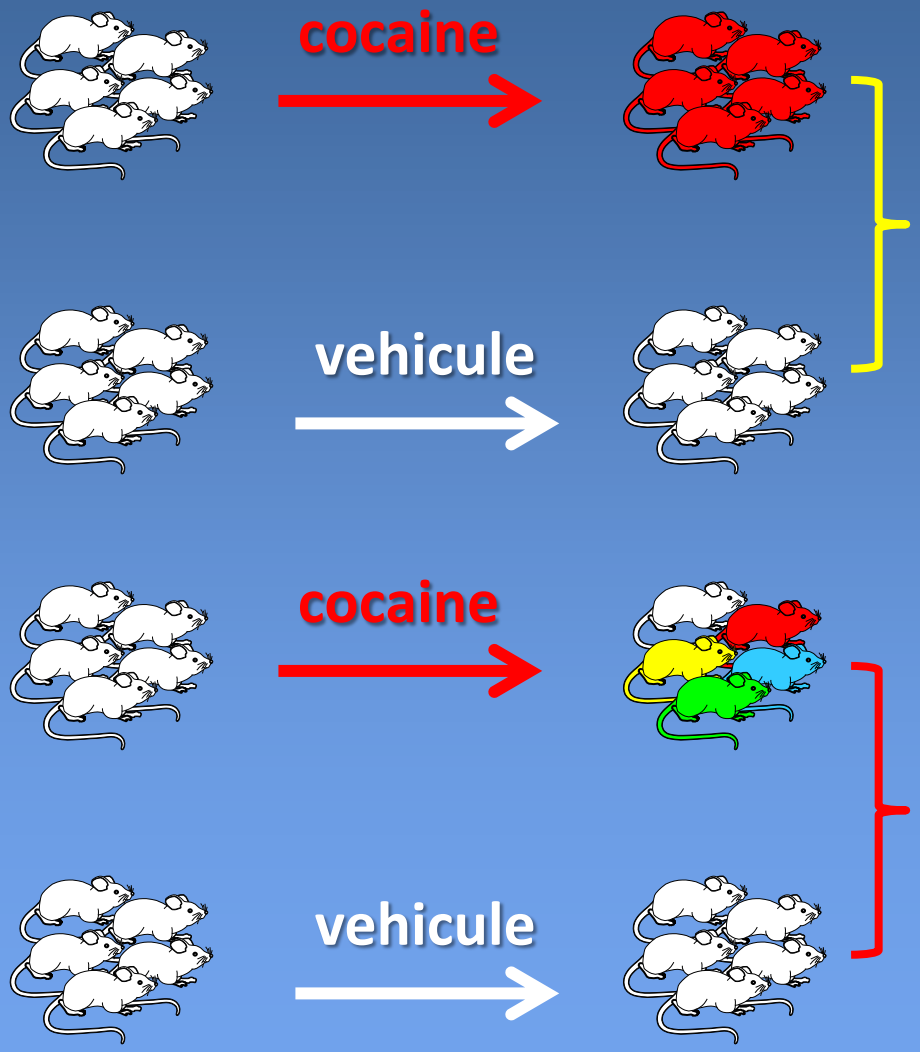
## ✓ Drug use

- Intracellular signaling cas*ca*des (Hyman et al. 2006; Girault et al. 2007)
- Gene expression (Nestler 2008; Shaham & Hope 2005)
- Neuronal excitability (White & Kalivas 1998; Huang et al. 2011)
- Synaptic plasticity (Kauer & Malenka 2007; Luscher & Malenka 2011; Kalivas 2009; Bowers et al. 2010)

## X Transition to addiction

**Lack of animal models differentiating between individuals with high and low vulnerability to develop addiction**

# Which are the neurobiological changes specifically associated with the transition to addiction?




**Modifications induced by drug experience**

↓

Reward, motivation, drug seeking, relapse

**Modifications associated with the behavioral manifestation of addiction**

# Addiction-like behaviors in rats

(Deroche-Gamonet et al. 2004)

## DSM IV

1. Tolerance

2. Withdrawal

**3-4.** Difficulty to stop or limit drug use

**5-6.** High motivation for the drug: activities focused on searching or consuming the drug

**7.** Drug use is maintained despite its negative consequences

## Rat world

**Persistence** in drug seeking although drug is signaled as unavailable

**Motivation** for the drug measured in a progressive ratio schedule

Persistence in responding for the drug when drug delivery is associated with a **punishment**

# Addiction-like behaviors in rats: cocaine self-administration

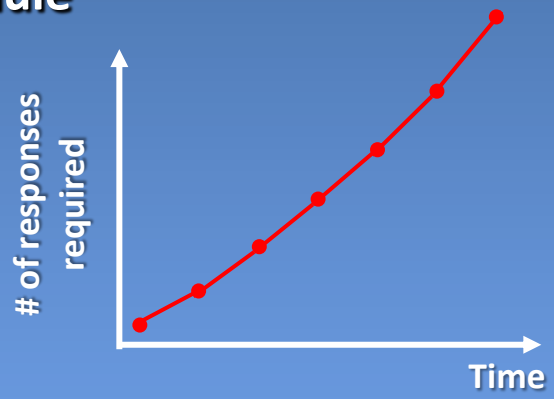
## •Persistence


Cue light + nose poke = Cocaine 0.8mg/Kg/40uL

Cue light = no drug available


## •Motivation: progressive ratio schedule

Cue light + X number of nose pokes = Cocaine 0.8mg/Kg/40uL





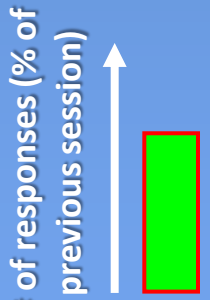
## •Punishment

Cue light + nose poke = Cocaine 0.8mg/Kg/40uL

Day 50

Cue light + nose poke = Cocaine 0.8mg/Kg/40uL + electric shock

Day 51



# Addiction-like behaviors in rats

## Daily sessions of cocaine SA

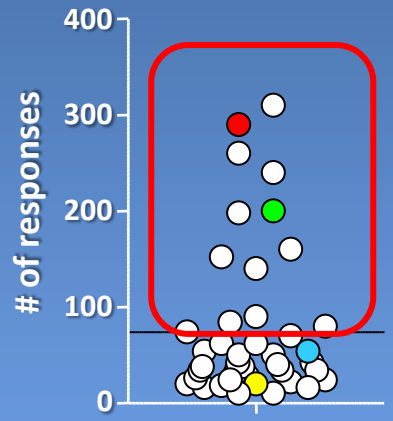

Cue light + nose poke = Cocaine 0.8mg/Kg/40uL

Cue light = no drug available

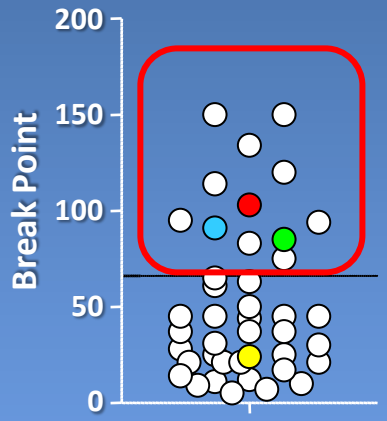
## Longitudinal study

# Addiction-like behaviors in rats: inter-individual differences

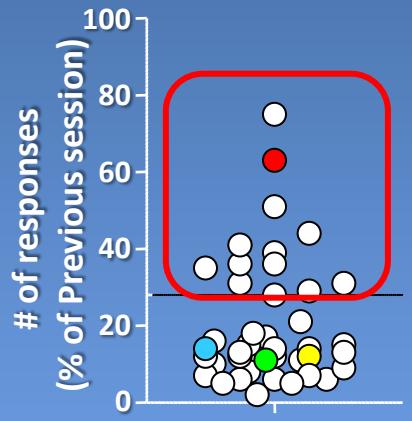
## Persistence

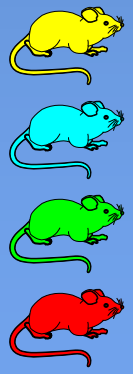



## Motivation




## Punishment



0 criteria

1 criterion

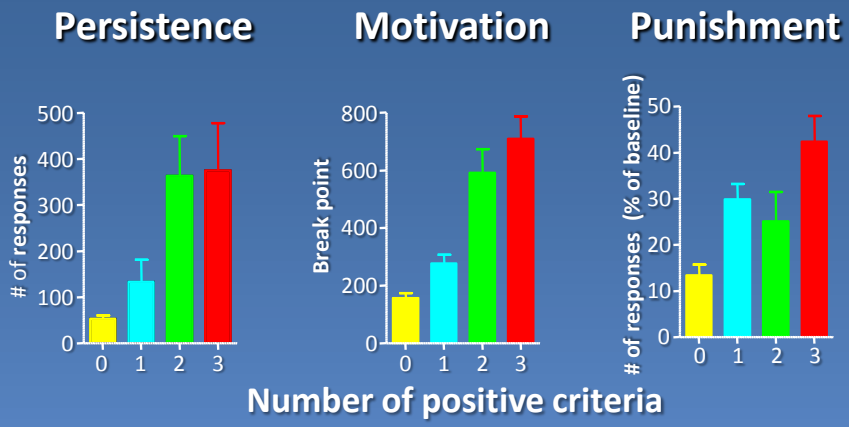
2 criteria

3 criteria

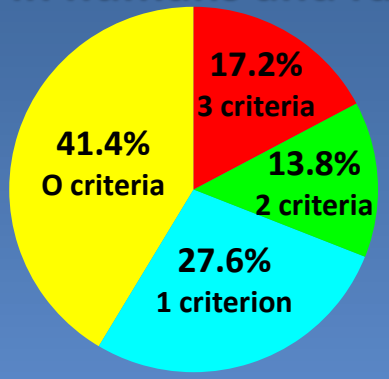
Non Addict

Addict

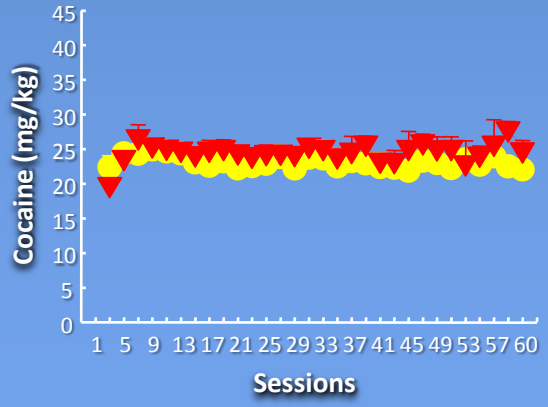
# Addiction-like behaviors in rats




## Similar prevalence of Addict individuals in humans and rats




## Identical amount of drug intake between Non Addicts and Addicts

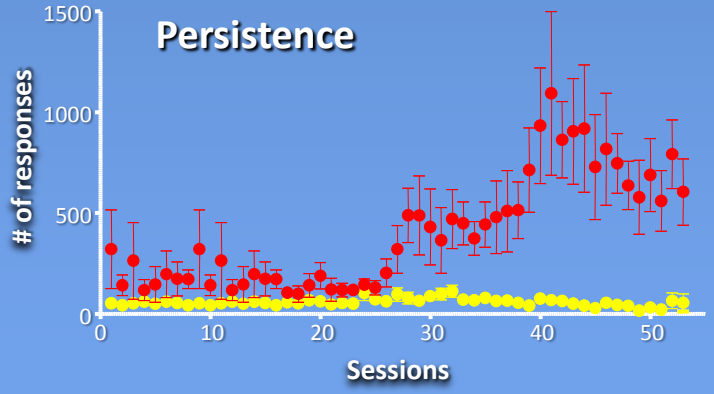




Non Addict


Addict

## Addiction-like behaviors appear only after prolonged drug experience



# Which are the neurobiological changes specifically associated with the transition to addiction?

✓ **Animal models differentiating between individuals with high and low vulnerability to develop addiction**

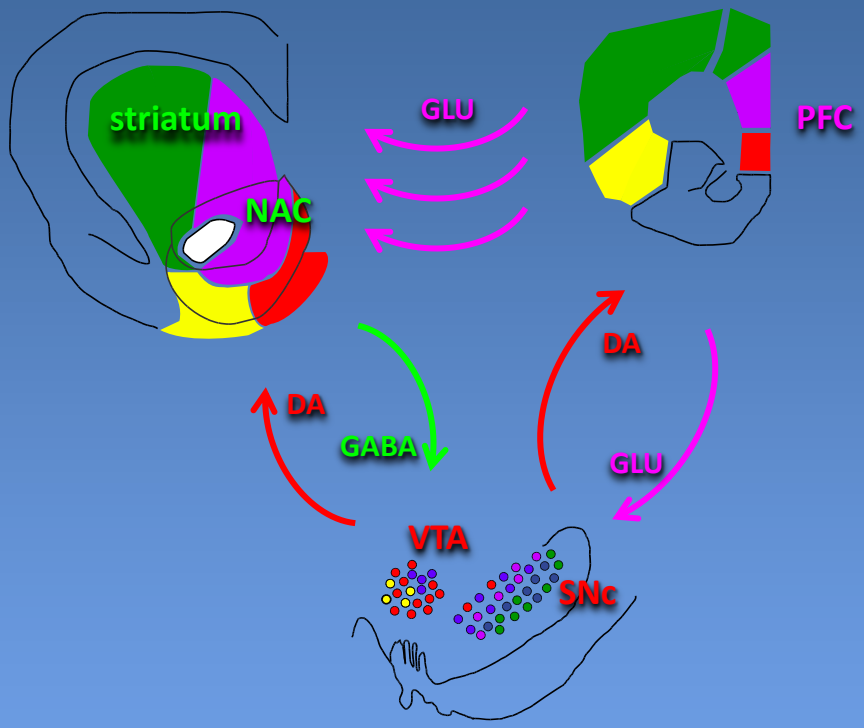
- **Intracellular signaling cas*ca*des** (Hyman et al. 2006; Girault et al. 2007)
- **Gene expression** (Nestler 2008; Shaham & Hope 2005)
- **Neuronal excitability** (White & Kalivas 1998; Huang et al. 2011)
- **Synaptic plasticity** (Kauer & Malenka 2007; Luscher & Malenka 2011; Kalivas 2009; Bowers et al. 2010)

# Synaptic plasticity
## activity dependent refinement of neuronal connectivity

- Synaptic plasticity is essential for the modulation of neural circuits by environmental contingencies.

- Drugs of abuse highjack the cellular mechanisms used to form normal memories (Hyman 1996; Berke & Hyman 2000)

# Drugs of abuse induce abnormal synaptic plasticity in the mesocorticolimbic system




Cocaine self-administration selectively abolishes LTD in the core of the nucleus accumbens

Miquel Martin[1,4], Billy T Chen[1,4], F Woodward Hopf[1], M Scott Bowers[1] & Antonello Bonci[1–3]

VOLUME 9 | NUMBER 7 | JULY 2006 NATURE NEUROSCIENCE

Long-term depression in the nucleus accumbens: a neural correlate of behavioral sensitization to cocaine

Mark J. Thomas[1], Corinne Beurrier[1], Antonello Bonci[2] and Robert C. Malenka[1]

nature neuroscience • volume 4 no 12 • december 2001

Nucleus Accumbens Long-Term Depression and the Expression of Behavioral Sensitization

Karen Brebner,[1,2*] Tak Pan Wong,[1,2*] Lidong Liu,[1,2] Yitao Liu,[1,2] Paul Campsall,[1,2] Sarah Gray,[1,2] Lindsay Phelps,[1,2] Anthony G. Phillips,[1,2†] Yu Tian Wang[1,2‡]

25 NOVEMBER 2005 VOL 310 SCIENCE

Neuron, Vol. 45, 647–650, March 3, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.neuron.2005.02.005

Unmanageable Motivation in Addiction: A Pathology in Prefrontal-Accumbens Glutamate Transmission

P.W. Kalivas,[1,*] N. Volkow,[2] and J. Seamans[3]

Neuron, Vol. 25, 515–532, March, 2000, Copyright ©2000 by Cell Press

Addiction, Dopamine, and the Molecular Mechanisms of Memory

2958 • The Journal of Neuroscience, March 14, 2007 • 27(11):2958–2968

Behavioral/Systems/Cognitive

Repeated Cocaine Administration Impairs Group II Metabotropic Glutamate Receptor-Mediated Long-Term Depression in Rat Medial Prefrontal Cortex

Chiung-Chun Huang,[1] Ping-Chun Yang,[1] Hsiao-Ju Lin,[1] and Kuei-Sen Hsu[1,2]

[1]Department of Pharmacology, College of Medicine, and [2]Center for Gene Regulation and Signal Transduction Research, National Cheng Kung University, Tainan 701, Taiwan

Single cocaine exposure *in vivo* induces long-term potentiation in dopamine neurons

Mark A. Ungless*, Jennifer L. Whistler*, Robert C. Malenka† & Antonello Bonci*

NATURE | VOL 411 | 31 MAY 2001 | www.nature.com

Neuron
Article

Cocaine but Not Natural Reward Self-Administration nor Passive Cocaine Infusion Produces Persistent LTP in the VTA

Billy T. Chen,[1,4] M. Scott Bowers,[1,4] Miquel Martin,[1,5] F. Woodward Hopf,[1] Anitra M. Guillory,[1] Regina M. Carelli,[2] Jonathan K. Chou,[1] and Antonello Bonci[1,2,*]

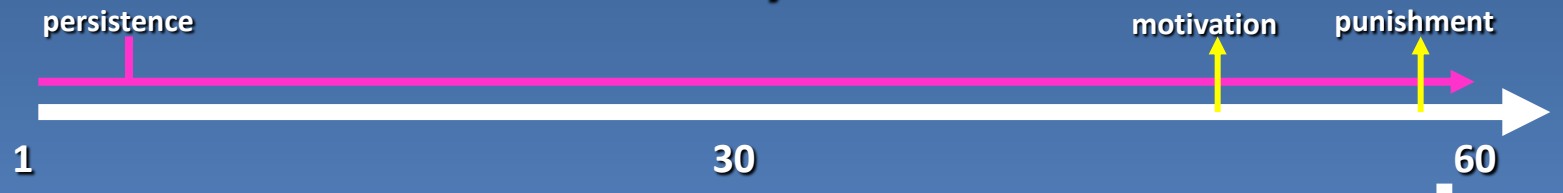
Repeated cocaine exposure *in vivo* facilitates LTP induction in midbrain dopamine neurons

Qing-song Liu[1], Lu Pu[1] & Mu-ming Poo[1]

Vol 437 | 13 October 2005 doi:10.1038/nature04050

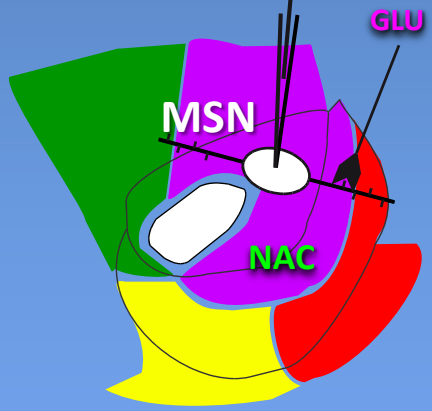
# Hypothesis

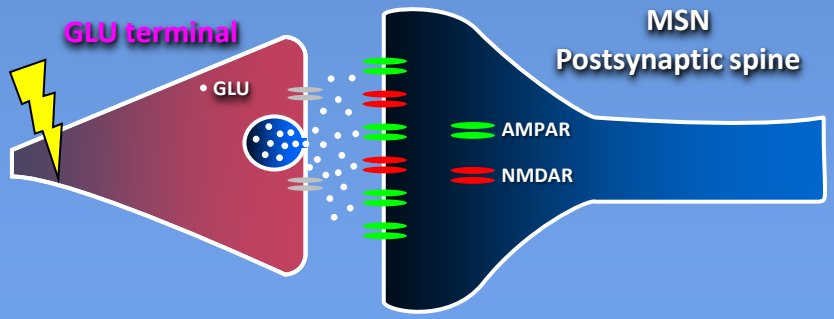
## The transition to addiction is associated with the development of specific synaptic (mal)adaptations in the mesocorticolimbic system




24 Hs after last SA

Brain slices for ex-vivo measurements of synaptic plasticity: whole cell patch clamp recording




Control (naïve)

Non Addict

Addict

# Long term synaptic plasticity: NMDA-dependent LTD

Cocaine self-administration selectively abolishes LTD in the core of the nucleus accumbens

Miquel Martin[1,4], Billy T Chen[1,4], F Woodward Hopf[1], M Scott Bowers[1] & Antonello Bonci[1–3]

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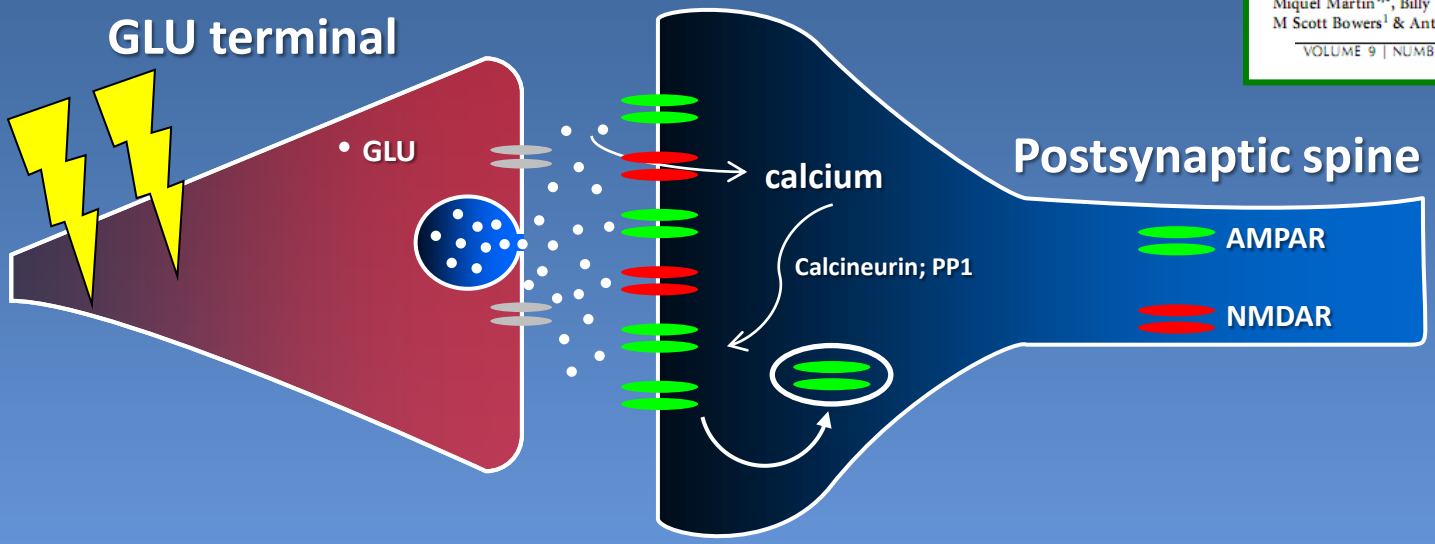
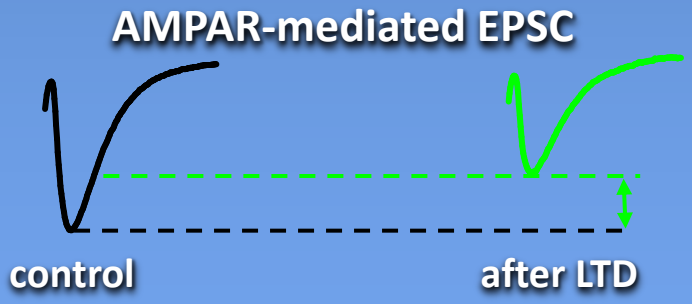
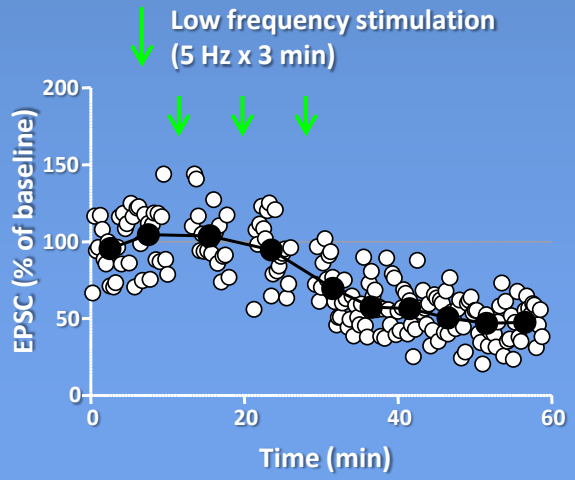
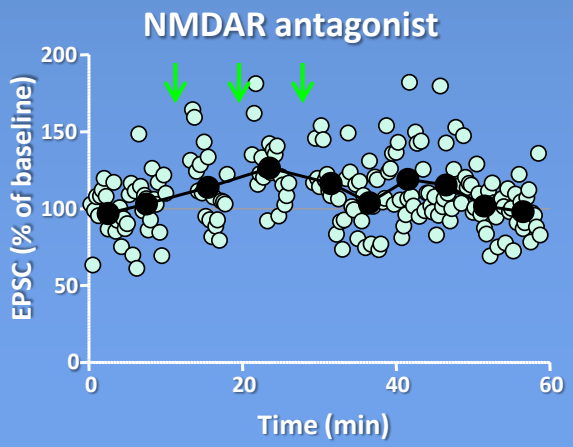
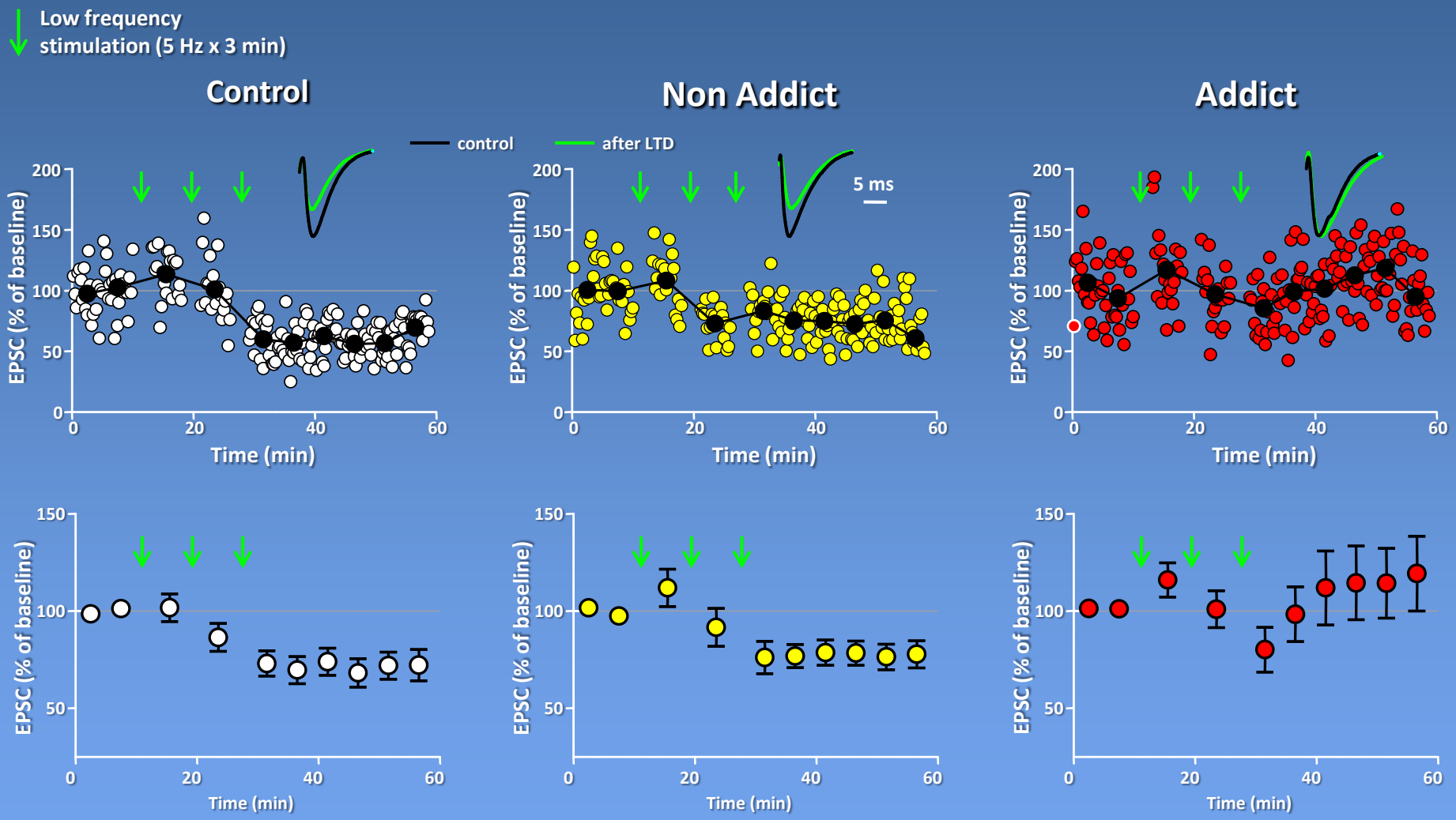


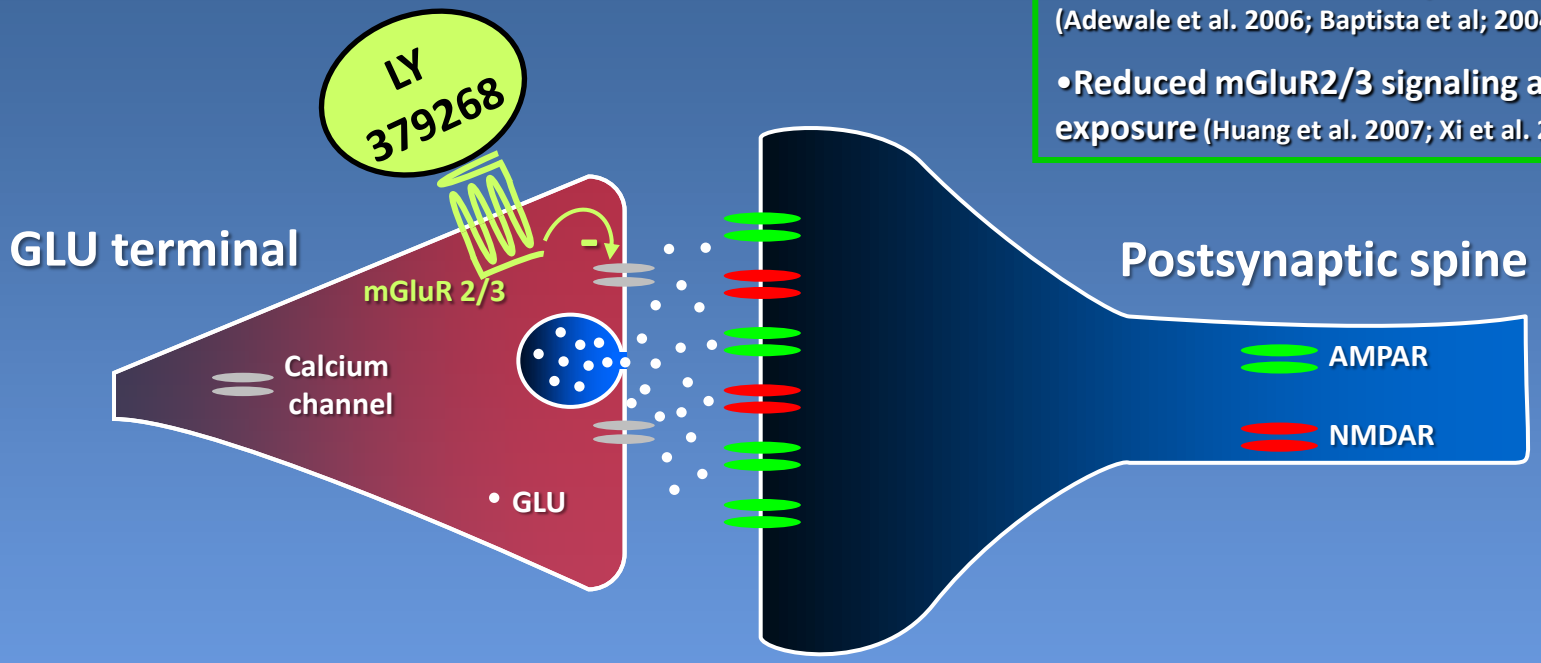
# NMDA-LTD is selectively disrupted in Addict animals

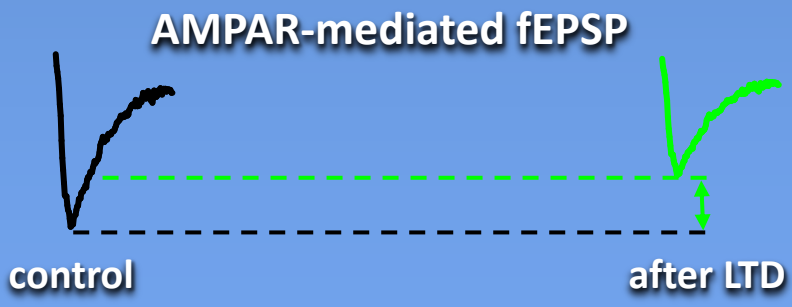



Kasanetz et al. 2010

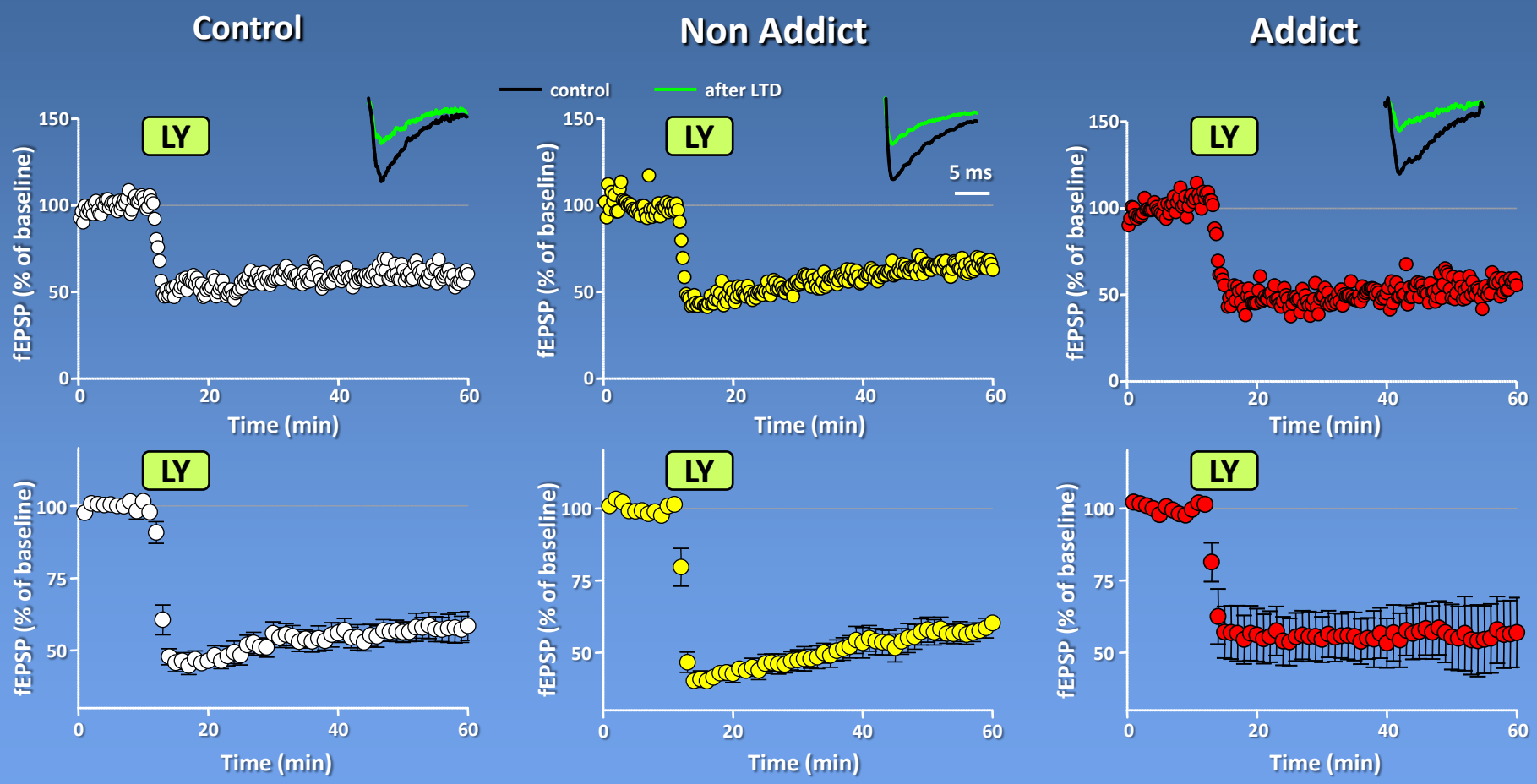
# Long term synaptic plasticity: mGluR 2/3-dependent LTD

- Stimulation of mGluR2/3 reduces drug seeking (Adewale et al. 2006; Baptista et al; 2004; Peters et al. 2006)
- Reduced mGluR2/3 signaling after cocaine exposure (Huang et al. 2007; Xi et al. 2002; Kalivas 2009)



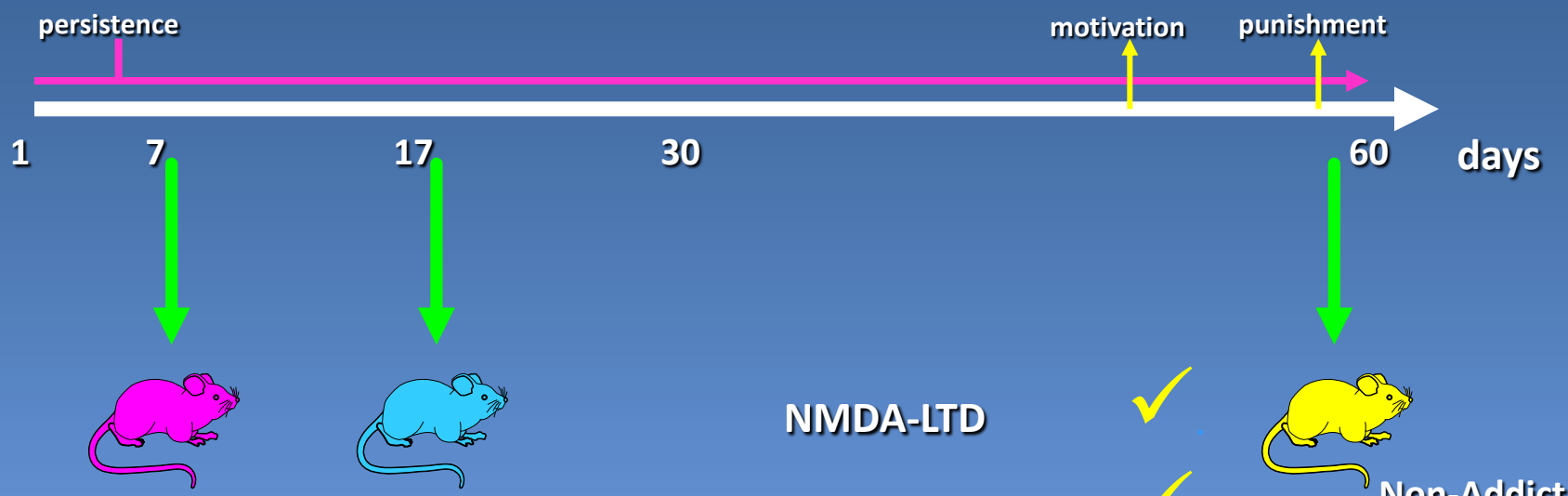



# mGluR 2/3 LTD is conserved after extended cocaine experience




Kasanetz et al. 2010

# Summary: specific abnormal synaptic plasticity associated with cocaine addiction-like behaviors




Cocaine self-administration selectively abolishes LTD in the core of the nucleus accumbens

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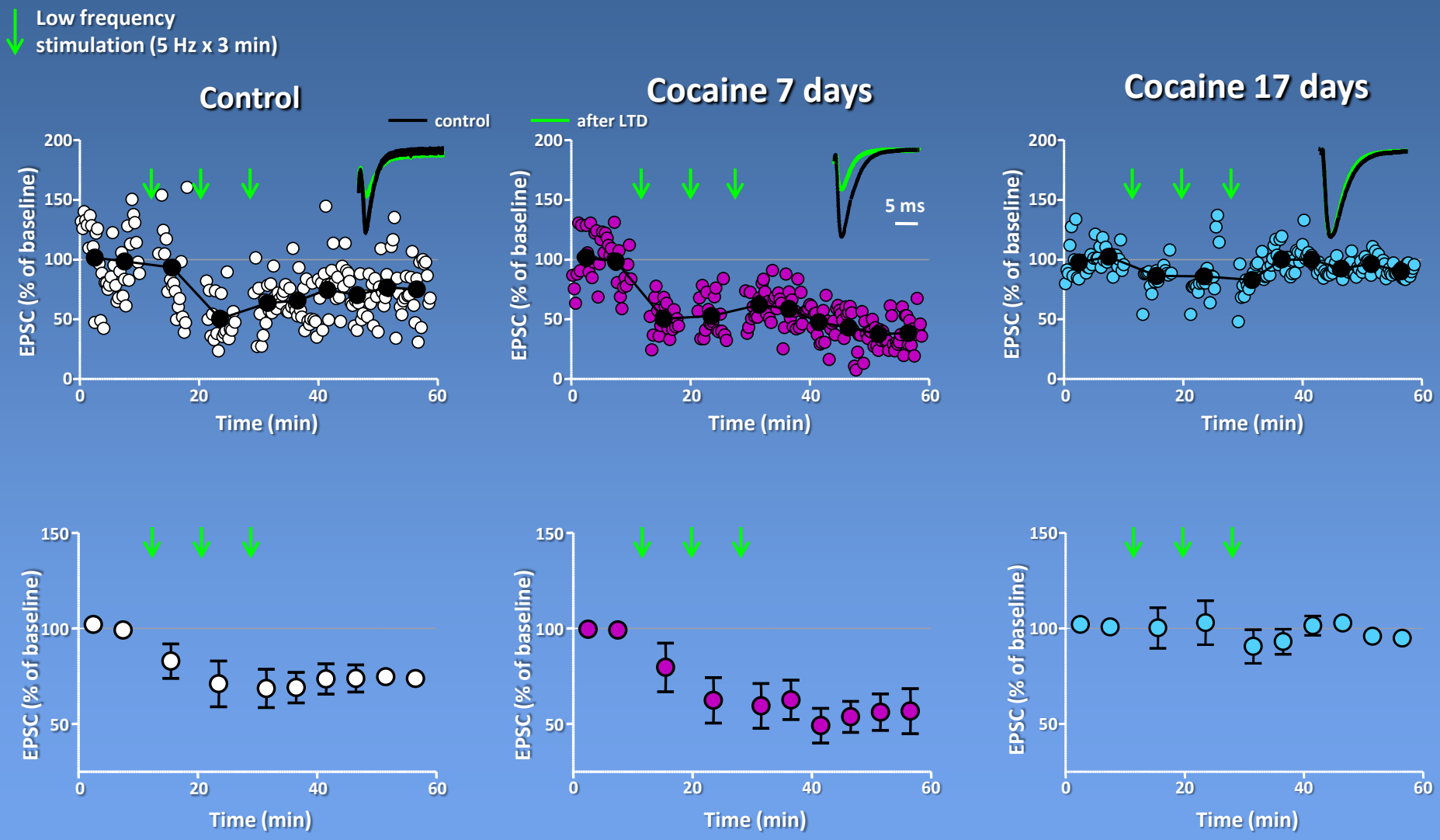
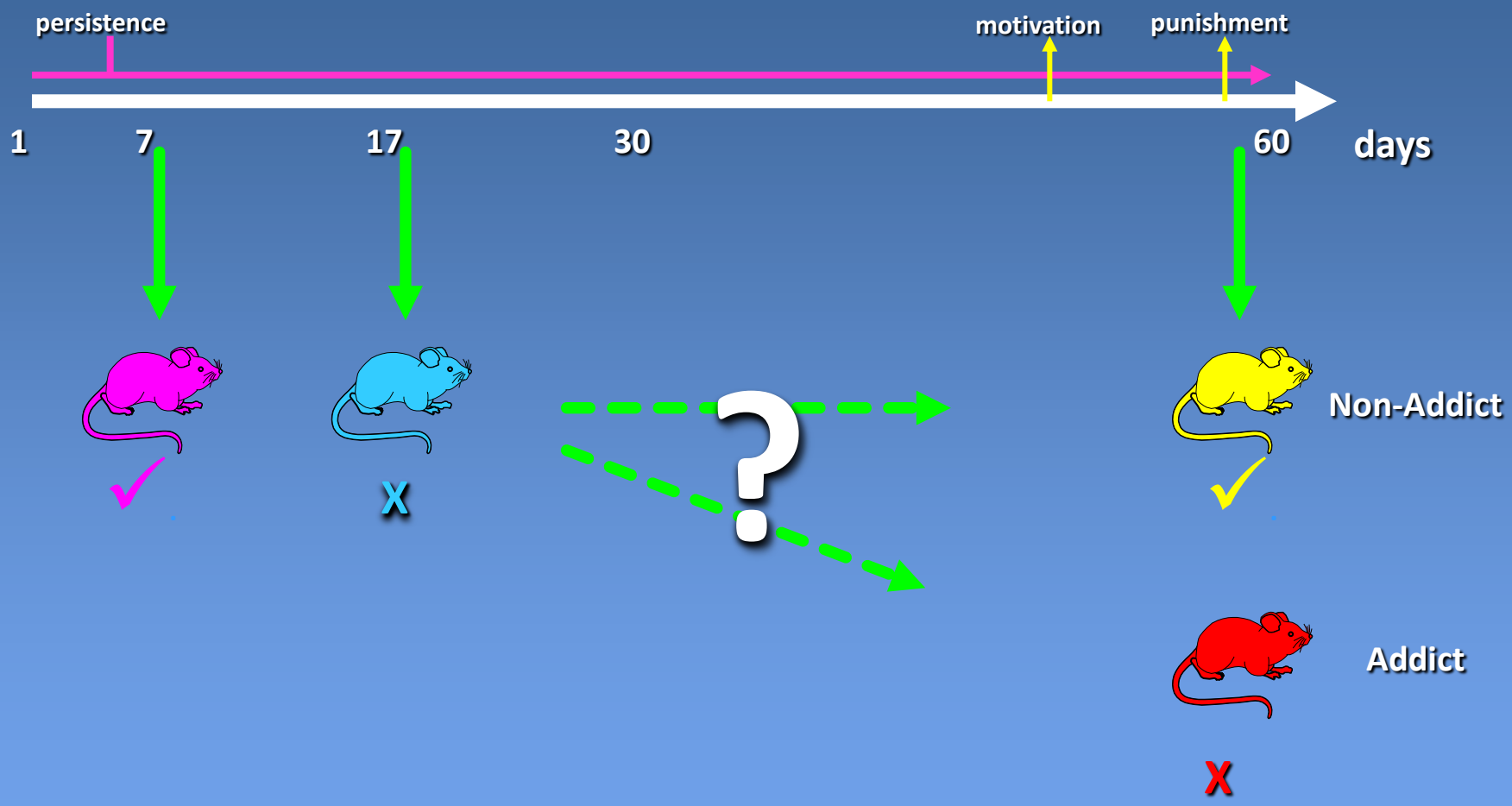
# NMDA-LTD is impaired during early stages of cocaine self-administration.



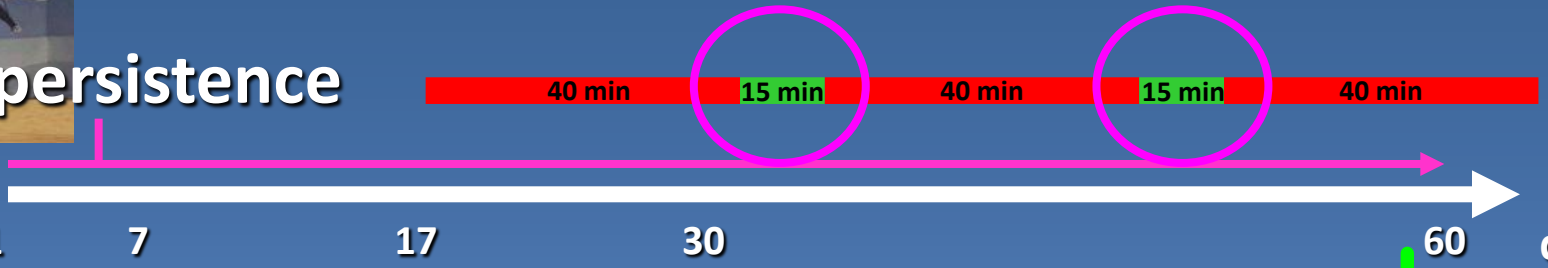

Kasanetz et al. 2010

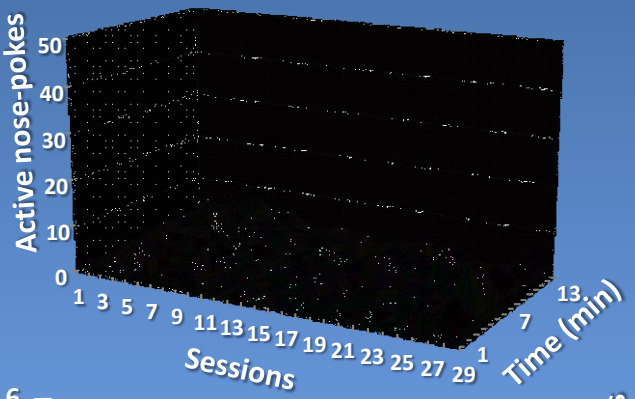
# Summary: NMDA-LTD during the transition to cocaine addiction



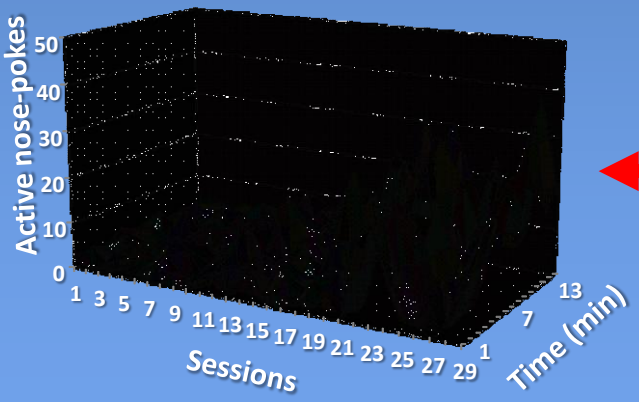
# Early identification of individuals at risk to develop addiction-like behaviors

persistence

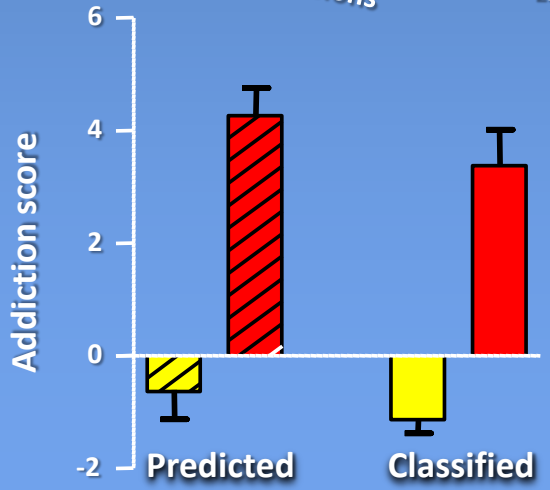



Non-Addict




Addict

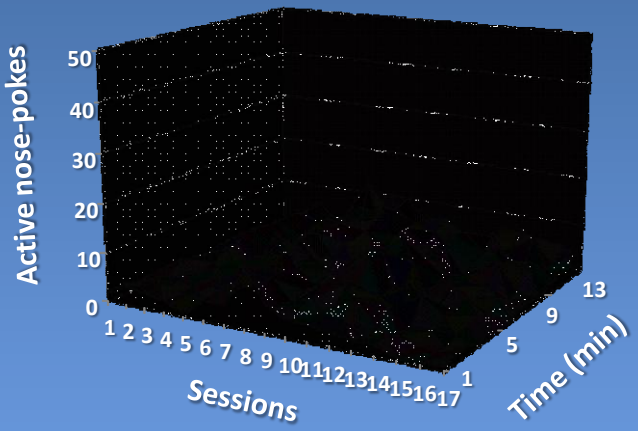



Kasanetz et al. 2010
Kasanetz et al. 2012

# Early identification of individuals at risk to develop addiction-like behaviors

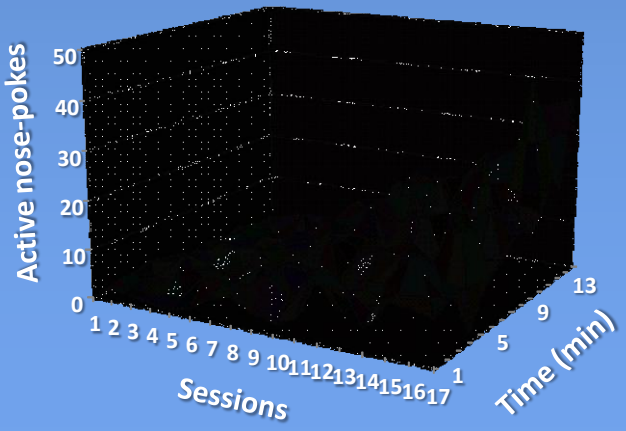
persistence


Addiction Resistant

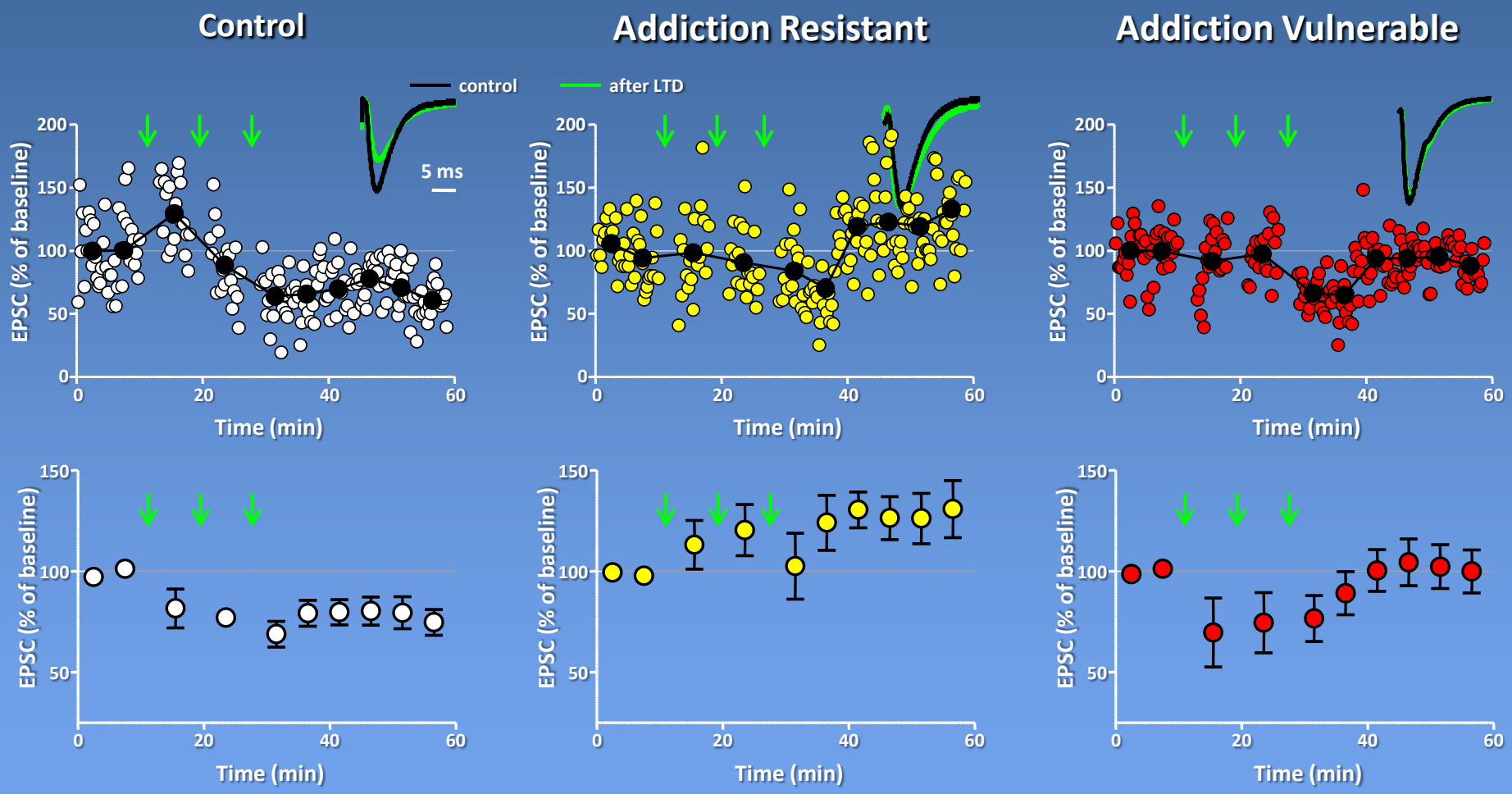



NMDA-LTD

Addiction Vulnerable

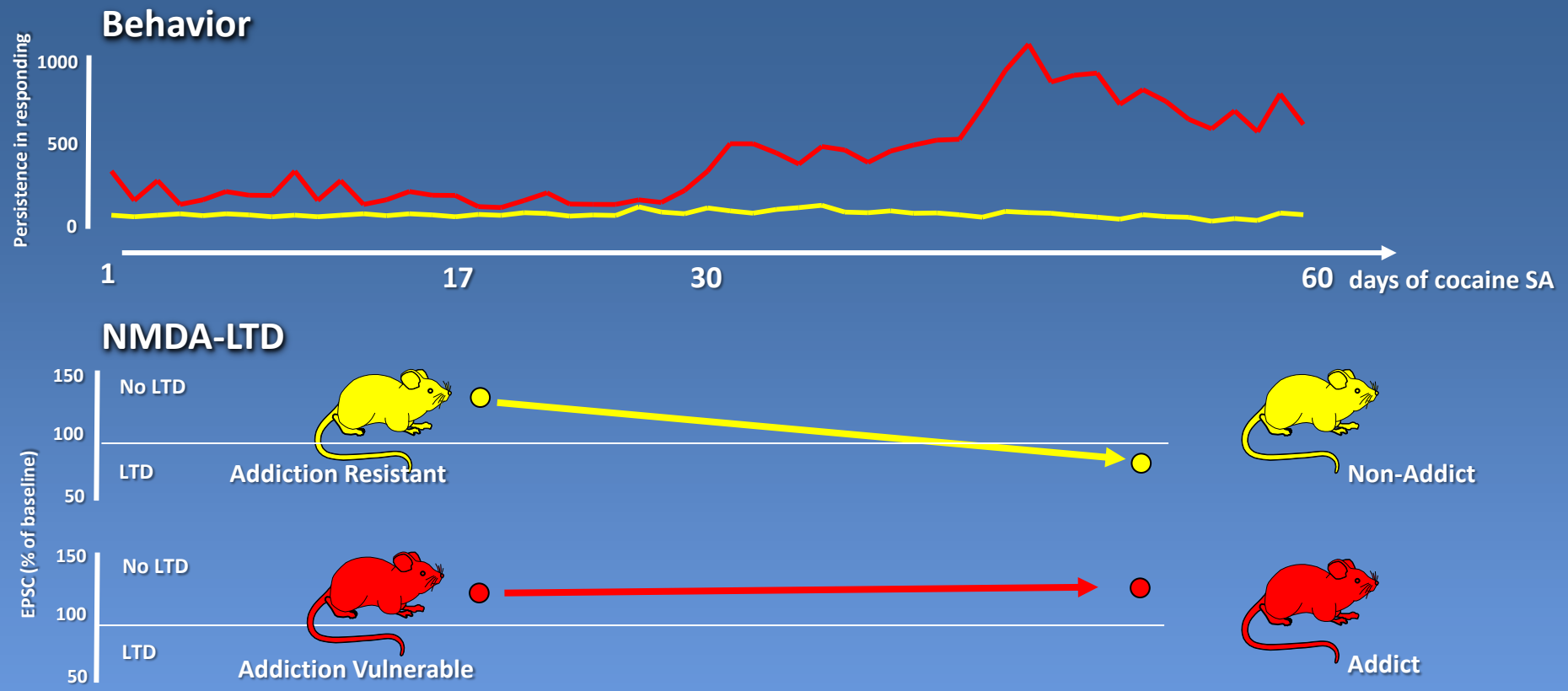


# Cocaine-induced impairment of NMDA-LTD was not correlated with the risk to develop addiction




Kasanetz et al. 2010

# Conclusion




**In the NAC, transition to addiction is associated with a form of *Anaplasticity,* the inability to reverse the impairments in synaptic plasticity that initially occurs in all drug-exposed individuals**

# Summary

- Uncovered a specific and persistent impairment of NMDA-LTD in the NAC core as the first neurobiological correlate of the transition to cocaine addiction in animal models

- Transition to addiction may be characterizes not only by the development of specific adaptations in addicts (as expected) but by the inability to recruits active compensatory mechanisms to reverse the drug-induced neuronal changes (ANAPLASTICITY)

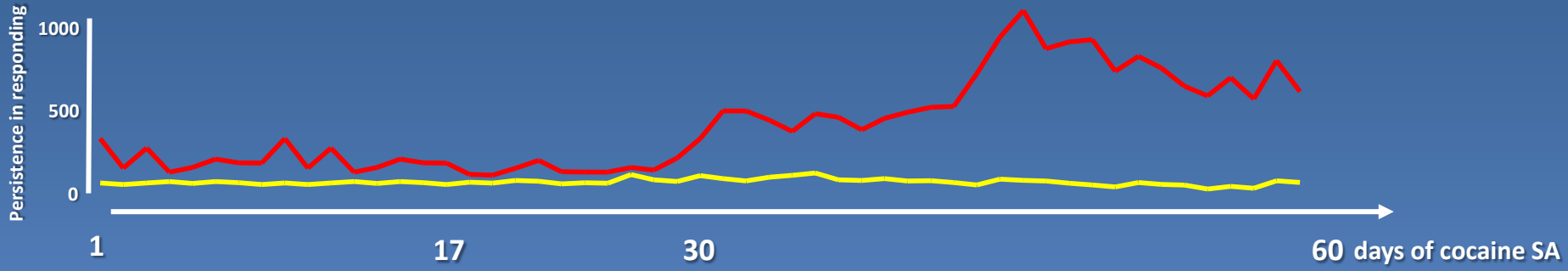
- Supports the notion that abnormal synaptic plasticity is a core marker of addiction.

The large loss in synaptic plasticity in Addicts could explain their loss of control on drug intake by making its neural circuits resistant to modulation by environmental contingencies.

- Provided a method to identify individuals at high risk to develop addiction-like behaviors as early as 17-20 days of cocaine SA allowing longitudinal studies.

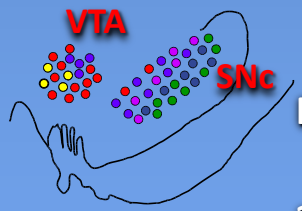
- Remains to be clarified the specific role of the abnormal synaptic plasticity during the transition to addiction and its underlying molecular mechanism.

# *Transition to cocaine addiction: hierarchical shift of aberrant synaptic plasticity from* reward-related to executive-related structures?




**Reward** → **Compulsive drug seeking** → **Loss of control**

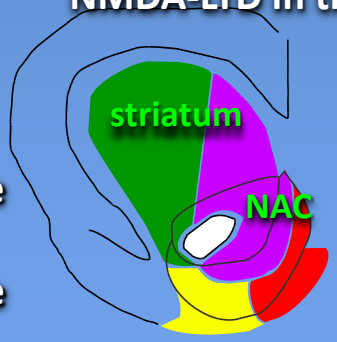
**Rapid drug-induced synaptic plasticity in DA cells**




Ungless et al. 2001; Bellone et al. 2005; Chen et al. 2008

**Persistence in the VTA triggers adaptations in the NAC** (Mameli et al. 2009)

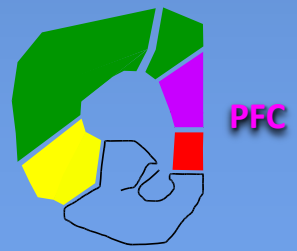
**…from an early & persistent impairment of NMDA-LTD in the NAC**




Martin et al. 2006; Kasanetz et al. 2010

***The inability to reverse NMDA-LTD in the NAC of Addicts may facilitates the adaptations in the PFC***

**…to a late impairment of mGluR2/3-LTD in the PFC**




Kasanetz et al. *Molecular Psychiatry* 2012

# Acknowledgments

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