

# In search of cellular memory and its link to substance abuse

Antonello Bonci, MD  
Scientific Director

NIDA/NIH

# NIH Biomedical Research Center

Facility overview



# BRC Facts

- Cost: \$252,000,000
- Total BRC Sq. Footage:
  - 563,000 gsf
    - NIA = 52%
    - NIDA = 46%
- 25 Year Lease Term:
  - Expiration: January 2027
- BRC Amenities:
  - Café
  - Fitness center
  - Multi-media Conference center



# NIDA Program Space

- Total NIDA Program 210,000 sf
  - Lab/Lab Office & lab support **45,000 sf**
  - Vivarium & Vivarium support **80,000 sf**
  - Clinical & Clinical support **34,000 sf**
  - Administrative Areas **46,000 sf**
  - Conference/Storage **5,000 sf**



# The three main areas of my program

Basic Science

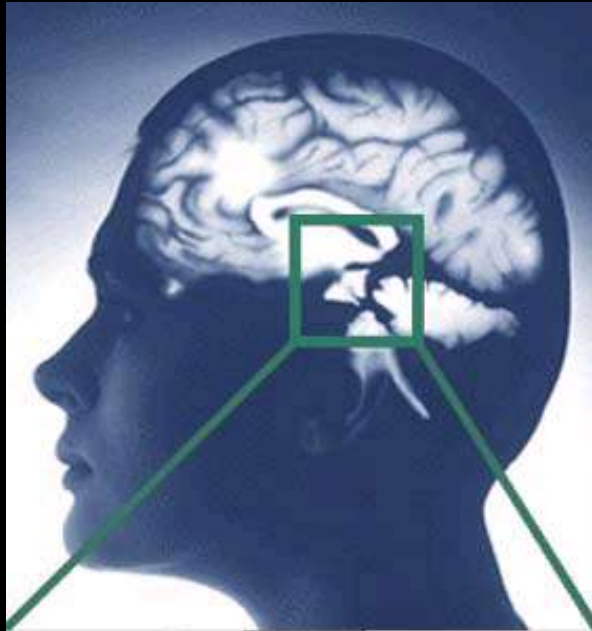
Medication Discovery

Clinical program

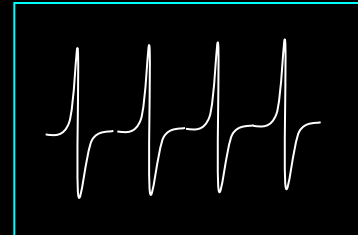
# For info:

- <http://irp.drugabuse.gov/>
- Antonello.bonci@nih.gov

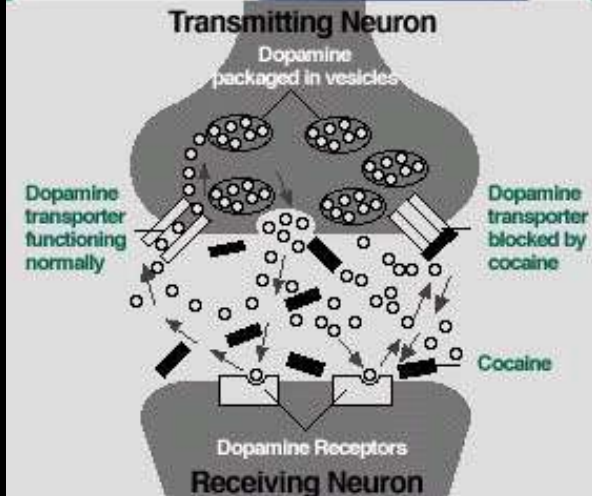
Any addictive behavior depends on changes in electrical activity of specific brain regions



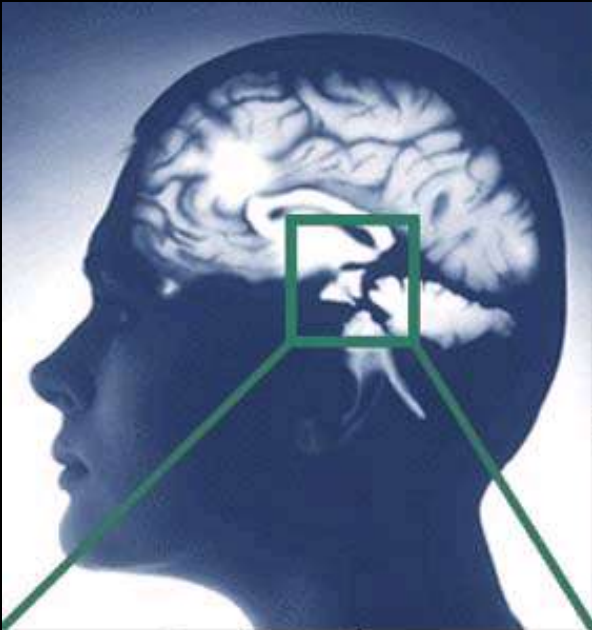
Genetic background



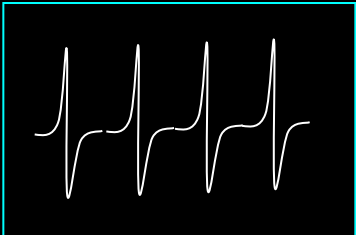
Environmental stimuli



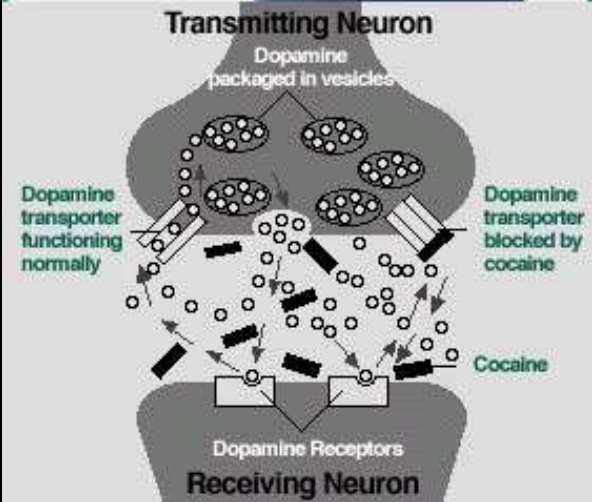
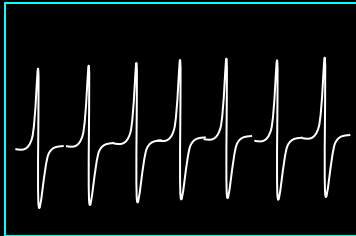
Any addictive behavior depends on changes in electrical activity of specific brain regions



Genetic background

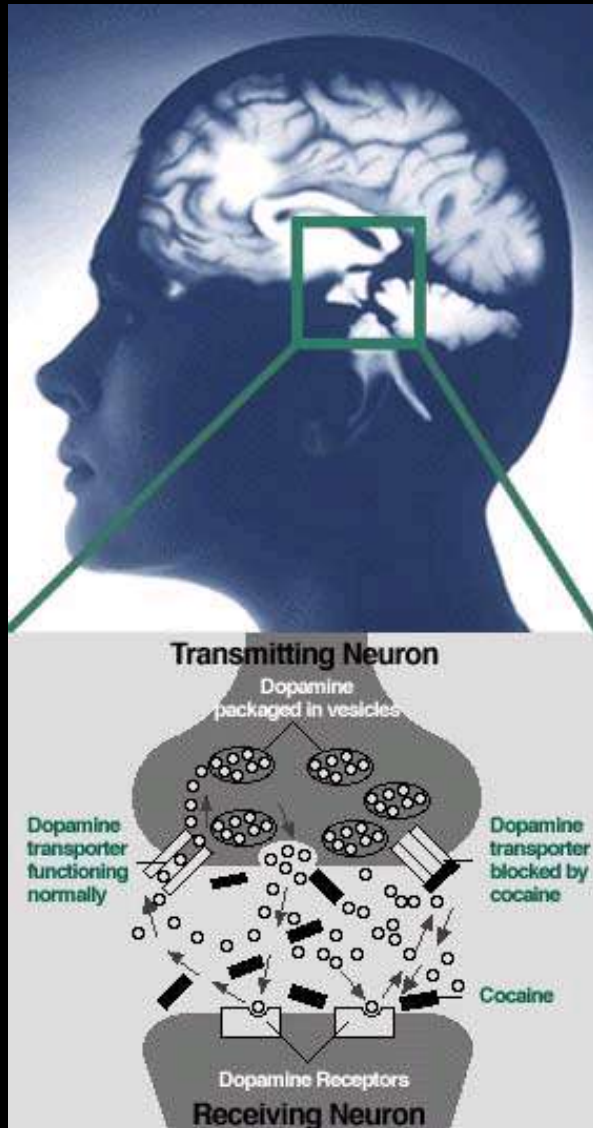


Environmental stimuli

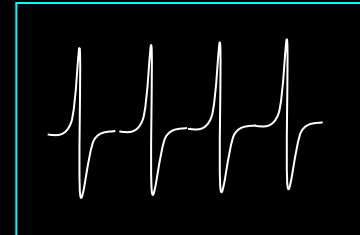




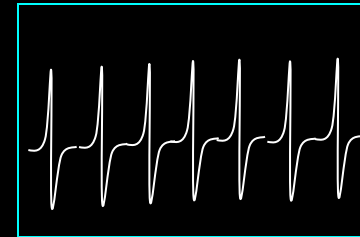
Any addictive behavior depends on changes in electrical activity of specific brain regions



Genetic background



Environmental stimuli



Substance abuse

# Why dopamine?

## Addiction

Apathy/motivation

Depression

Aggressive behaviors

Sexual, appetitive behaviors    Reward Deficiency Syndrome

Parkinson's disease

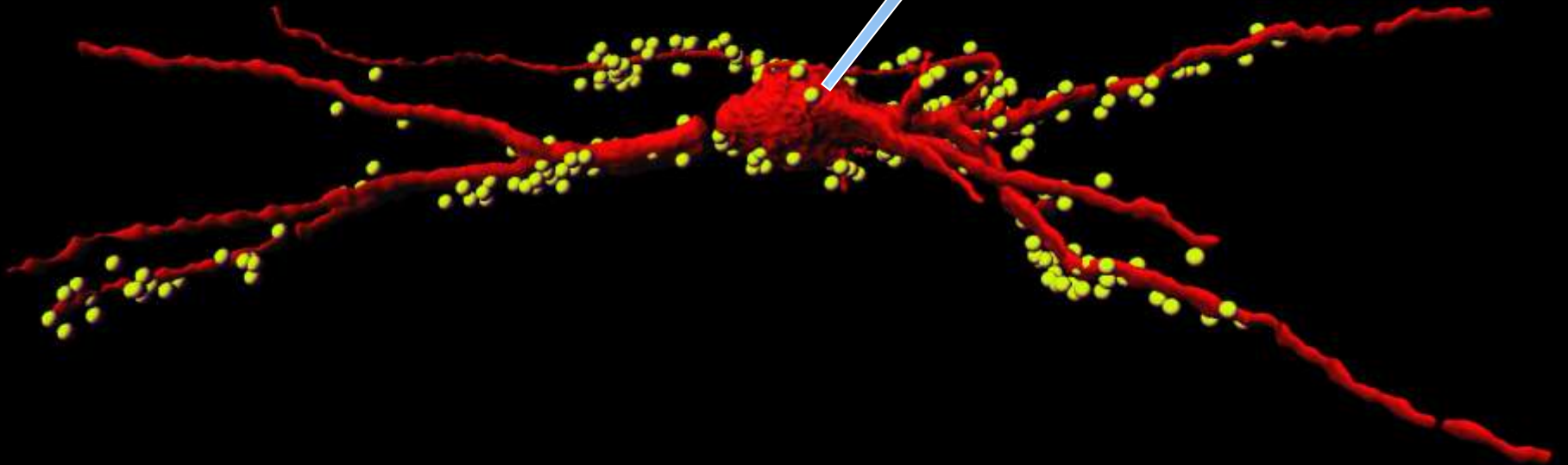
ADHD

Schizophrenia

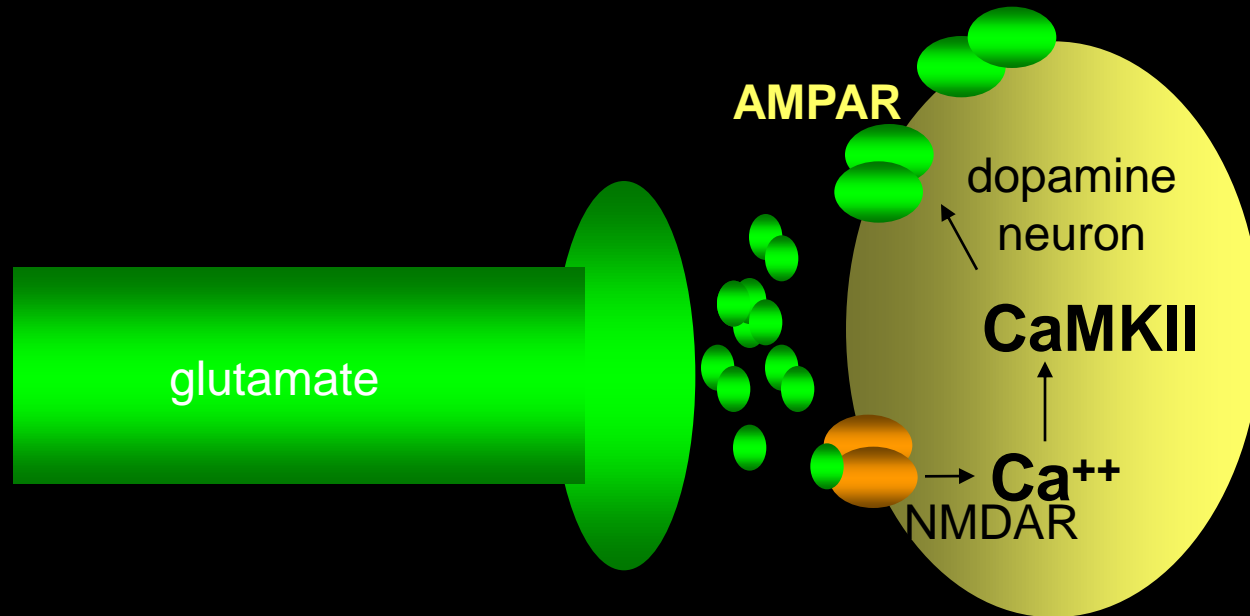
Dementias

Working memory

My second wife

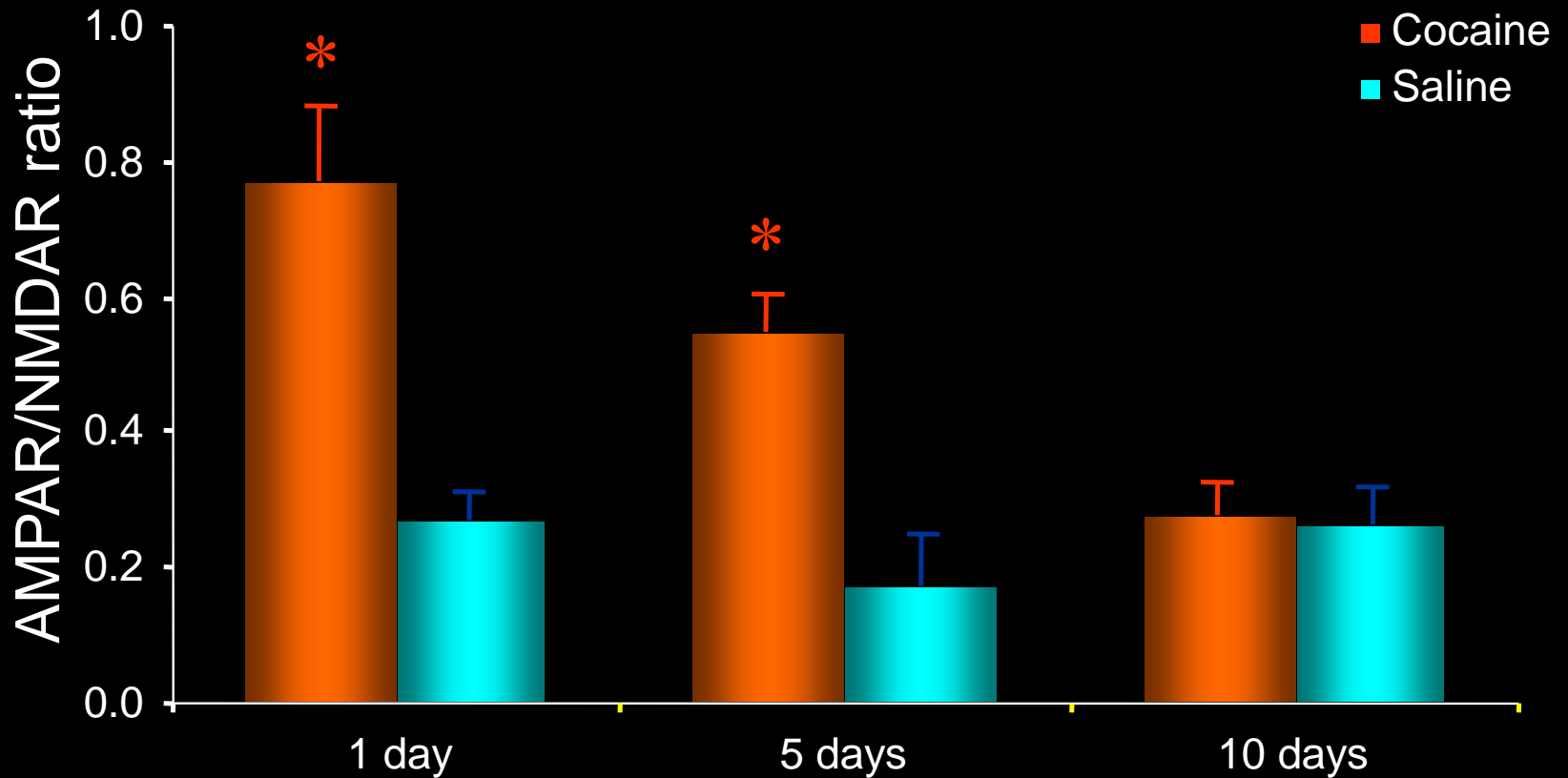


# A fundamental cellular model of learning and memory: long-term potentiation (LTP)



Are drugs of abuse capable of producing LTP?

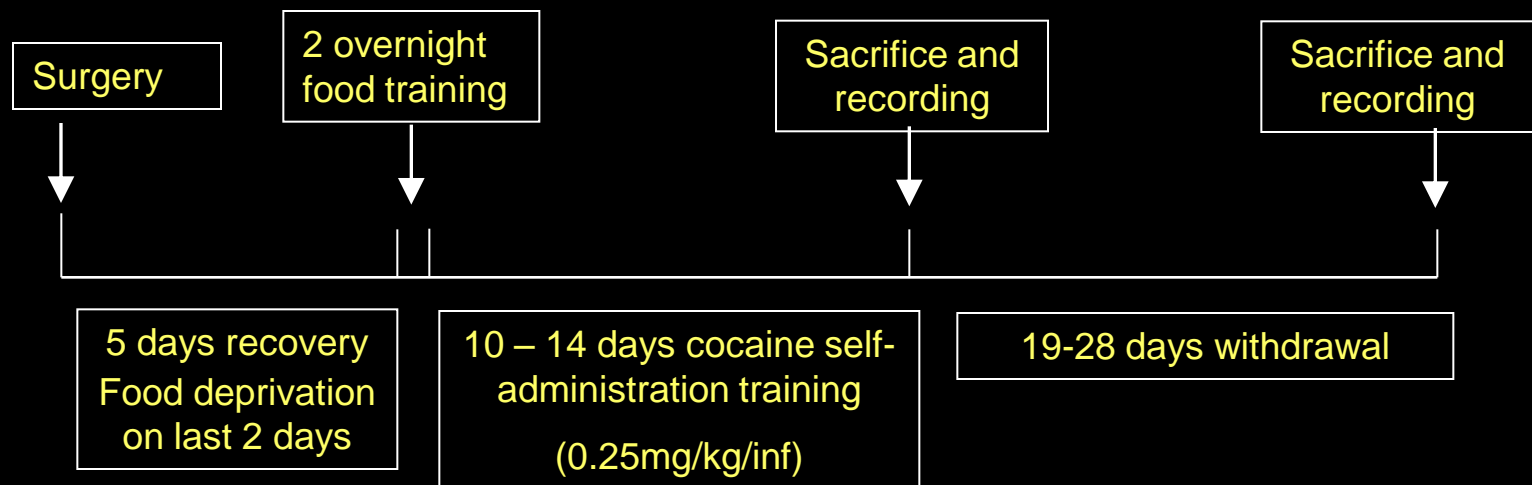
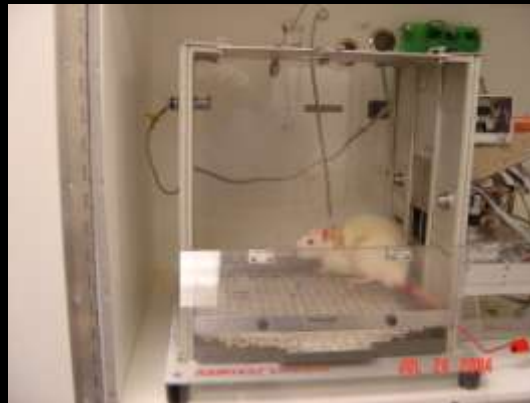
## The increase in the AMPAR/NMDAR ratio is long-lasting



# Passive versus active choice of taking cocaine

4) What about cocaine self-administration?

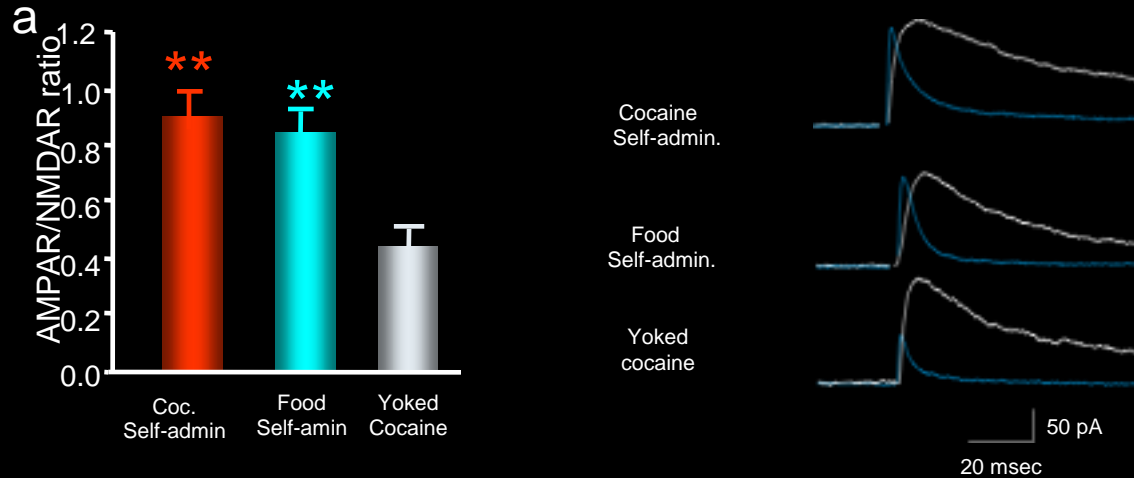
# Self-administration training and whole-cell recording schedule



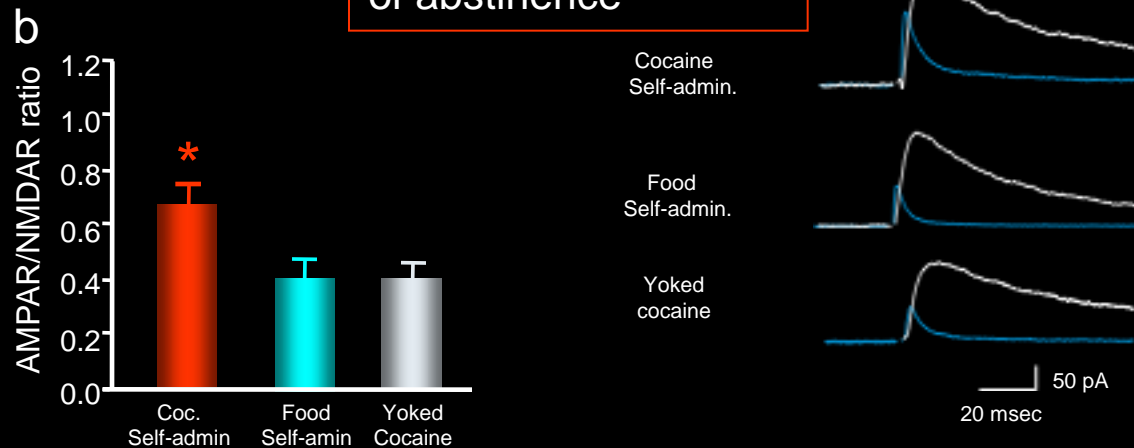


# Cocaine, but not food self-administration produces LTP in the VTA during abstinence

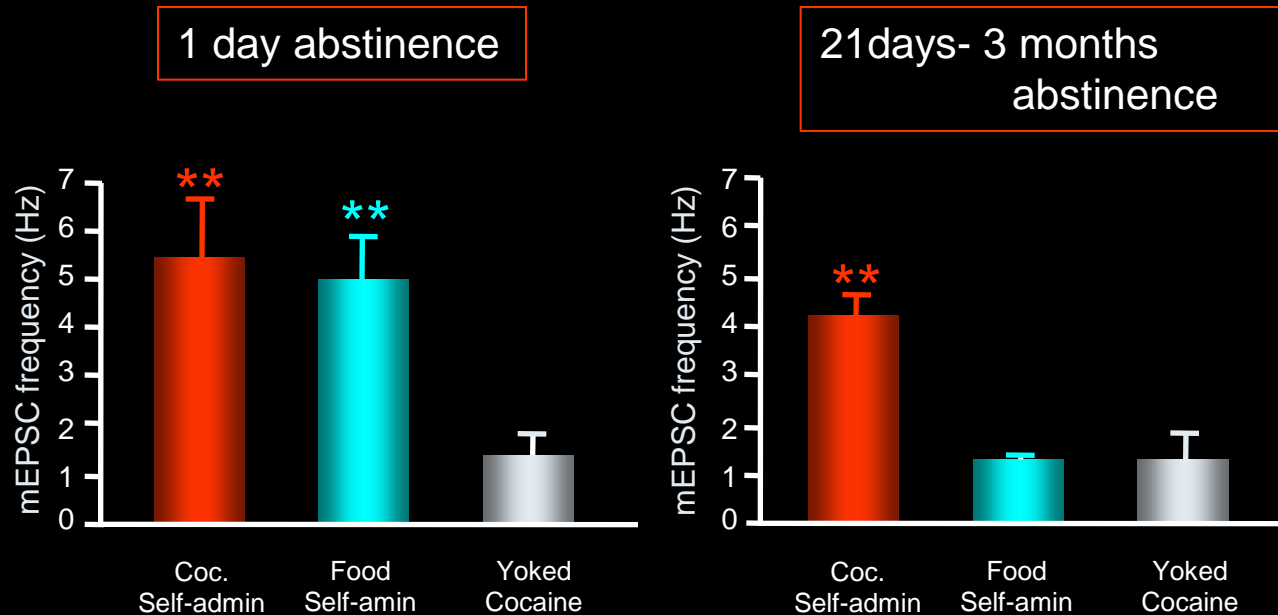
1 day abstinence



21 days-3 months of abstinence



# Cocaine, but not food self-administration increases glutamate release in the VTA during abstinence



Can we reduce cocaine self-administration and thus synaptic plasticity?

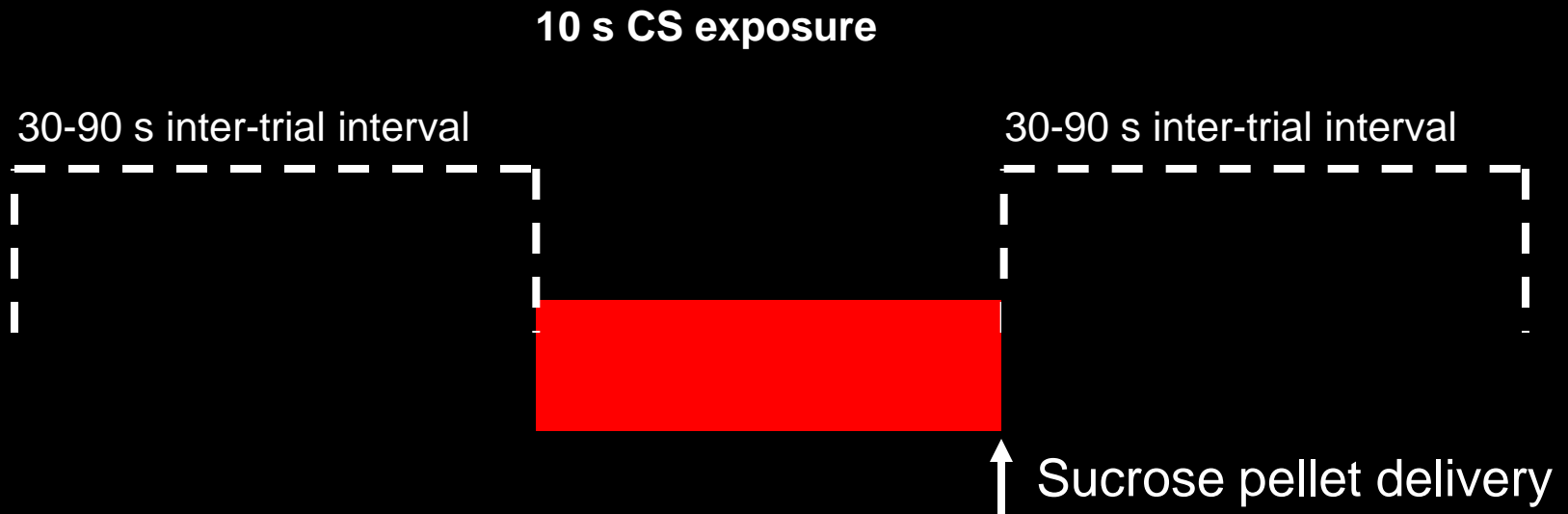
# AMPA antagonists are used in clinical trials

Table 2. Past and ongoing clinical trials with selective AMPAR antagonists			
Talampanel			
Status	Study	Condition	Intervention
Terminated	A Study to Investigate the Absorption, Metabolism and Excretion of Talampanel	Healthy	Drug: Talampanel (non-radiolabeled), [14C] Talampanel
Not yet recruiting	A Phase 1 Study to Investigate the Effects of Talampanel on the Heart Rhythm	Healthy	Drug: Talampanel; Drug: Moxifloxacin; Drug: Placebo
Active, not recruiting	Talampanel for Amyotrophic Lateral Sclerosis (ALS)	ALS	Drug: Talampanel; Drug: placebo
Completed	Multicenter Trial for Adults With Partial Seizures	Epilepsy	Drug: Talampanel; Drug: Placebo
Active, not recruiting	Talampanel in Treating Patients With Recurrent High-Grade Glioma	Brain and Central Nervous System Tumors	Drug: talampanel
Active, not recruiting	Safety and Efficacy of Talampanel in Glioblastoma Multiforme	Glioblastoma Multiforme	Drug: Talampanel
Completed	Effects of Talampanel on Patients With Advanced Parkinson's Disease	Dyskinesias; Parkinson's Disease; Movement Disorders	Drug: talampanel
Terminated	Phase 2 Trial Using Talampanel in Patients With Recurrent High Grade Gliomas	Glioblastoma Multiforme; Anaplastic Astrocytoma; Anaplastic Oligodendroglioma; Anaplastic Mixed Oligoastrocytoma	Drug: Talampanel
Completed	Talampanel to Treat Parkinson's Disease	Parkinson's Disease	Drug: IV Levodopa; Drug: Talampanel

**Time course of natural reward versus cocaine**

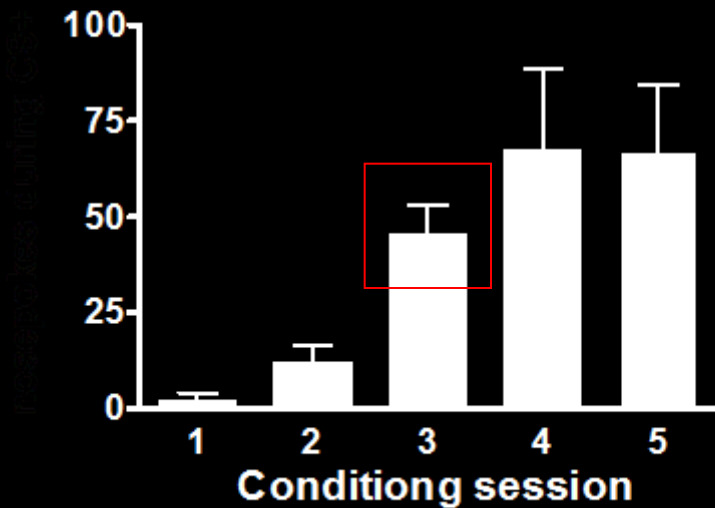
# Behavioral Paradigm

Rats are randomly assigned to CS+ or CS- group and trained for 1 - 5 sessions.

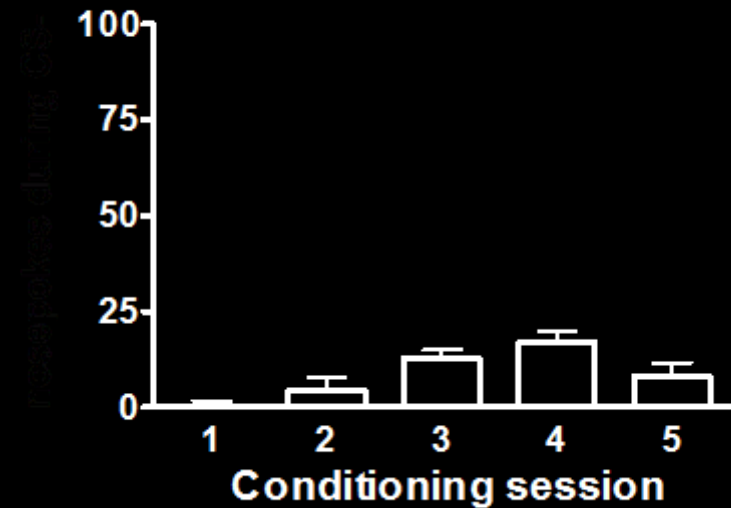


- All rats receive 32 trials per behavioral session
- CS- rats receive the exact same exposure to stimuli and sucrose pellets except pellet delivery is not contingent upon CS presentation.

# Cue-reward associations develop gradually over multiple conditioning sessions

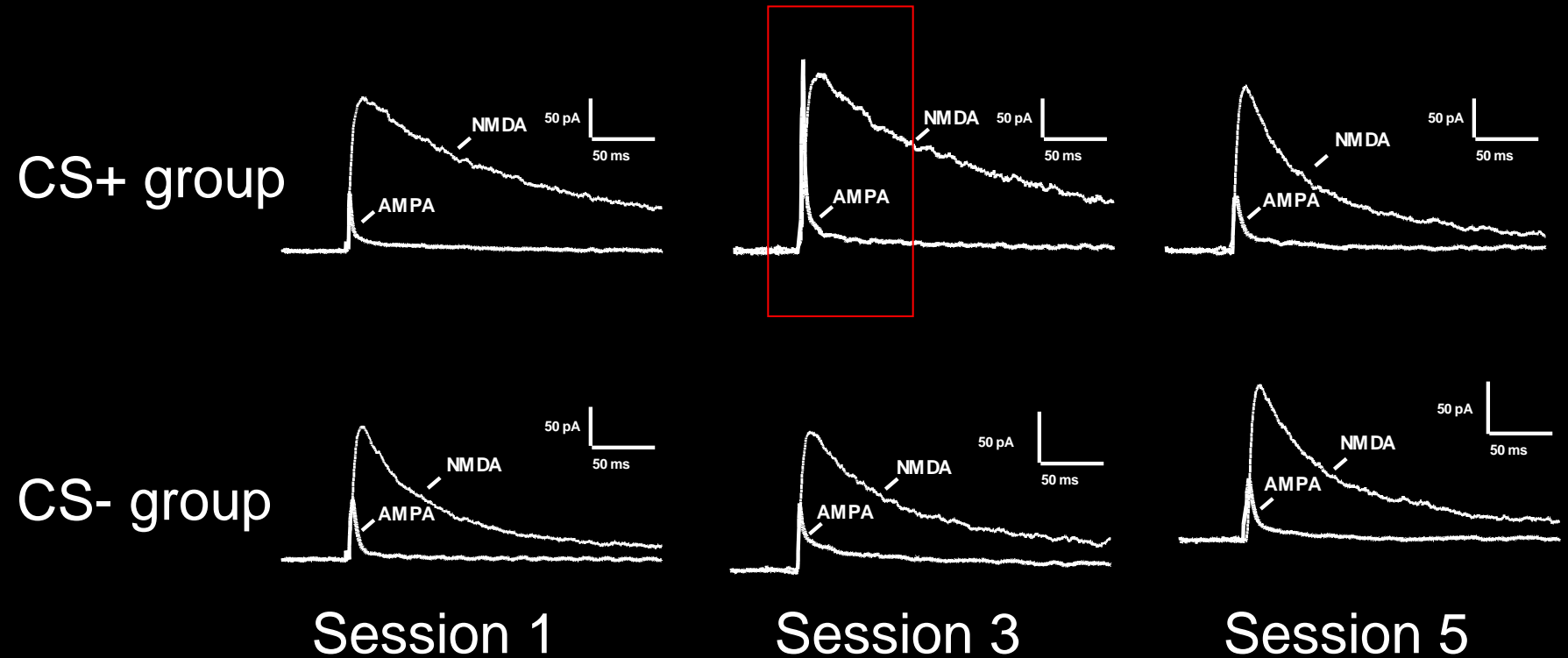


CS+ group



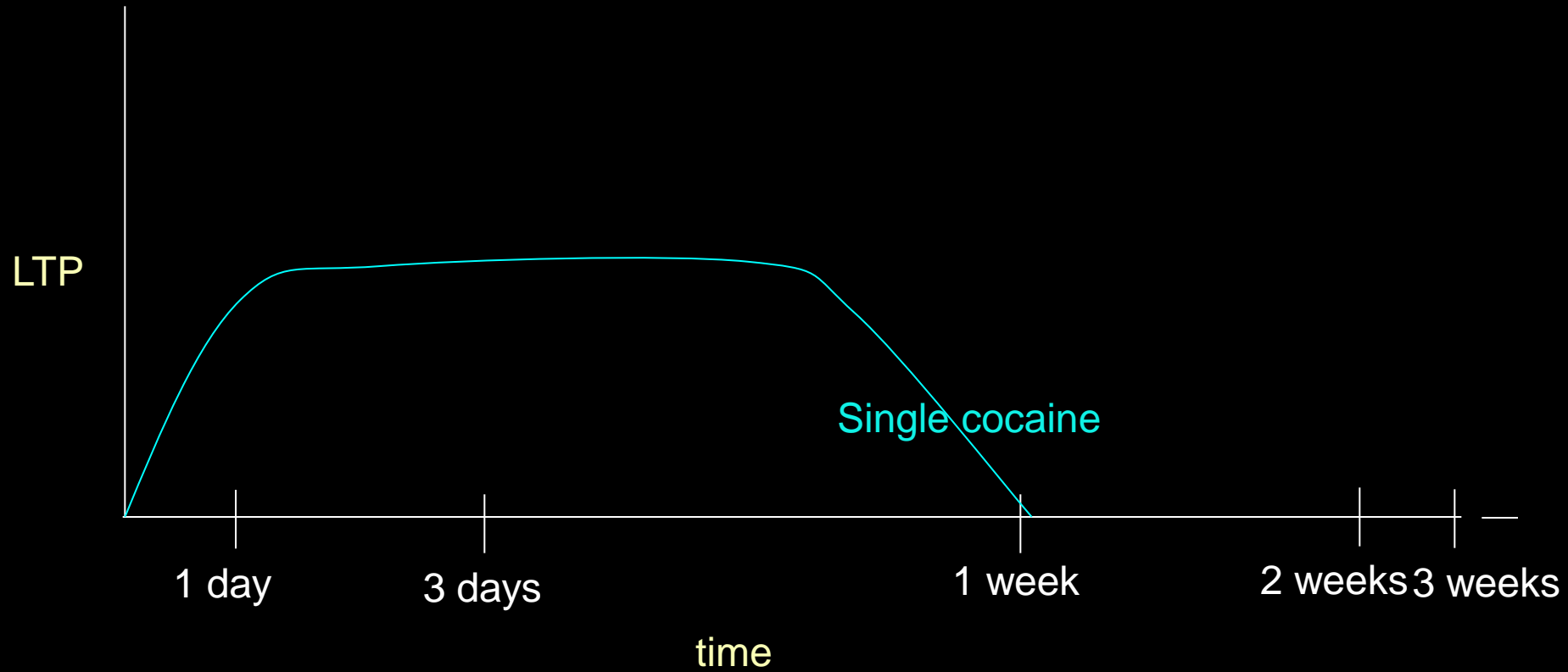
CS- group

# AMPA/NMDA ratio is transiently elevated during reward learning

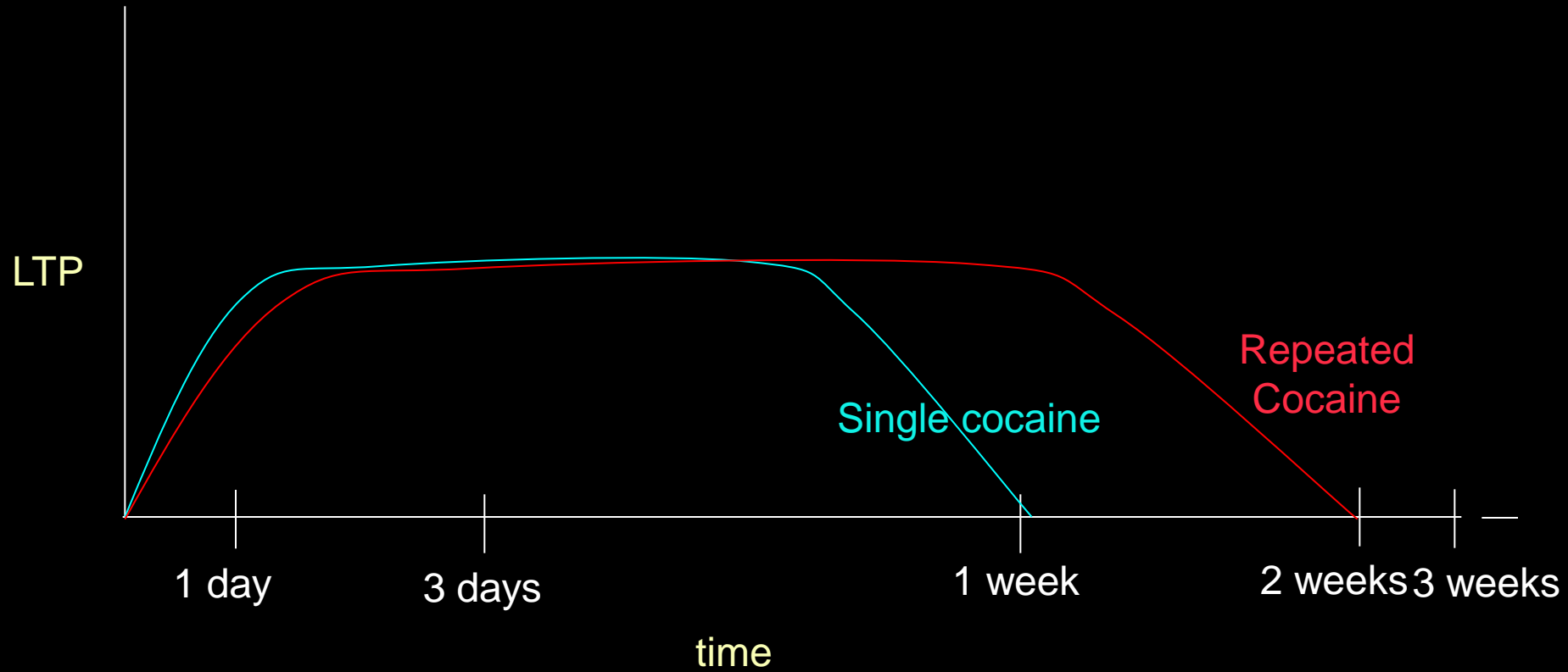




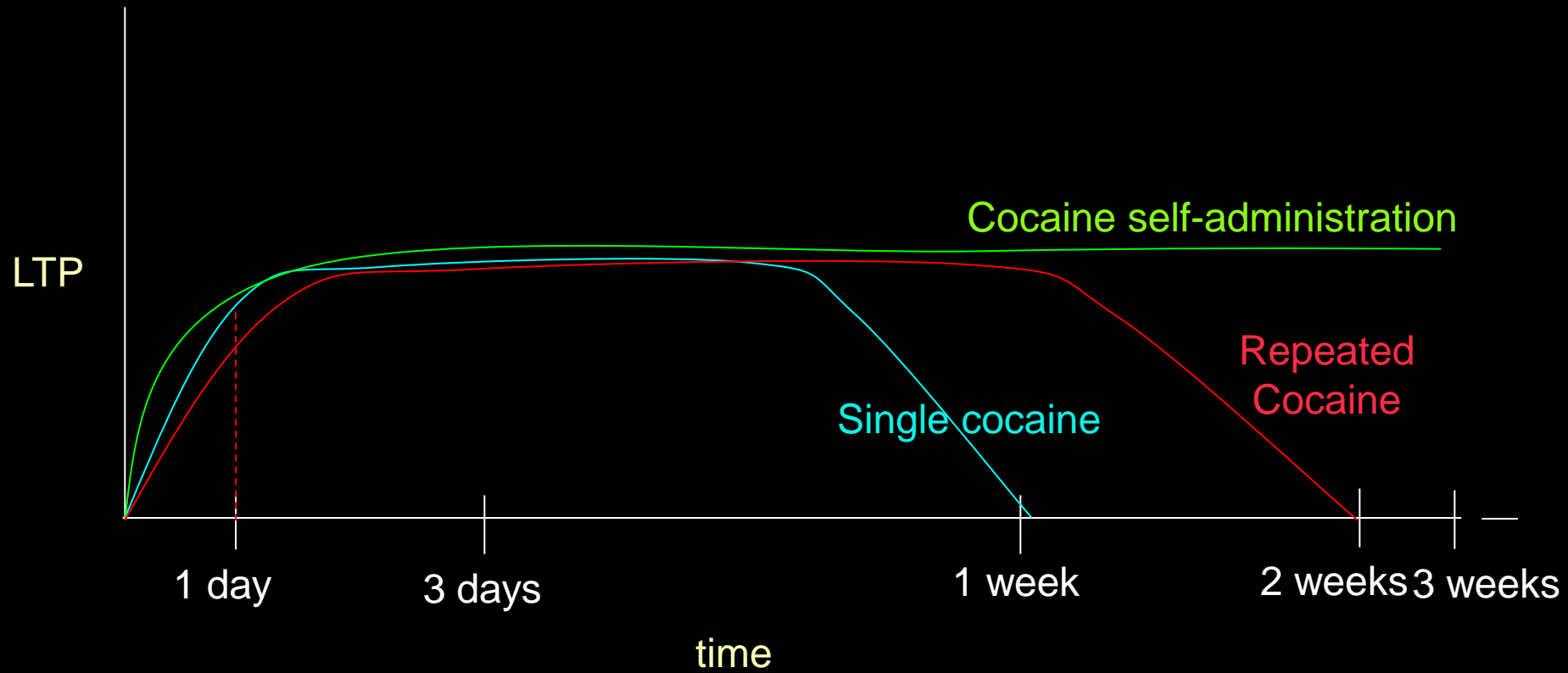
## The time course of LTP



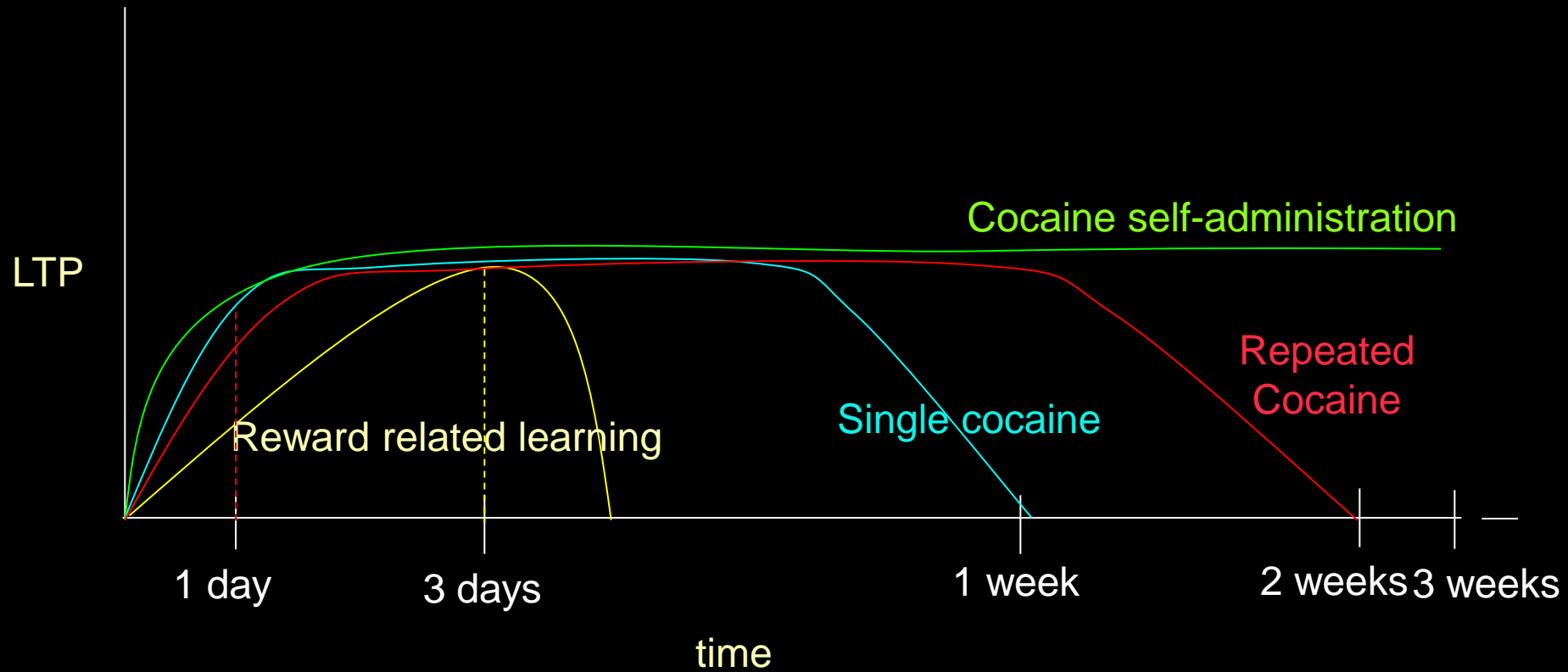
## The time course of LTP



## The time course of LTP



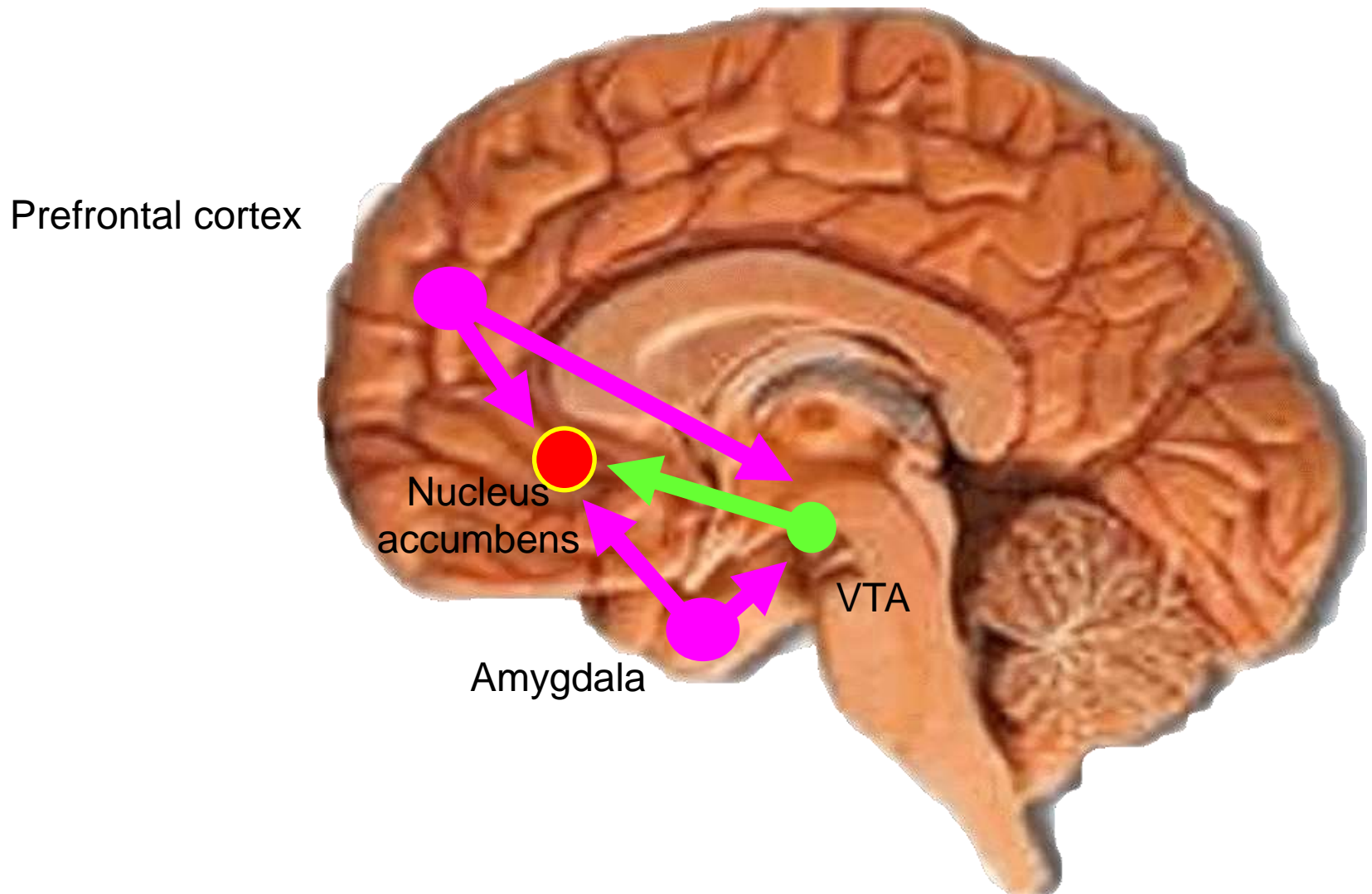
## The time course of LTP



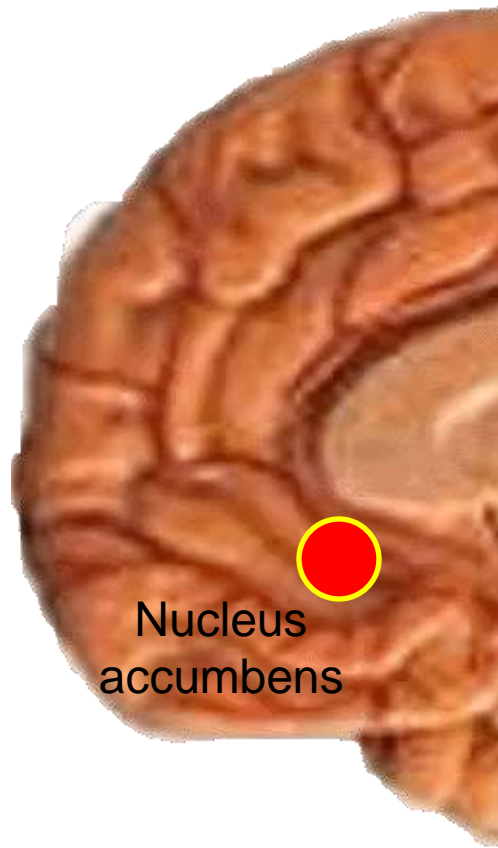
## Part II

A novel therapeutic target to reduce ethanol consumption

## Reward/Reinforcement Pathway



# The NAcb is critical for control of many motivated and addiction-related behaviors



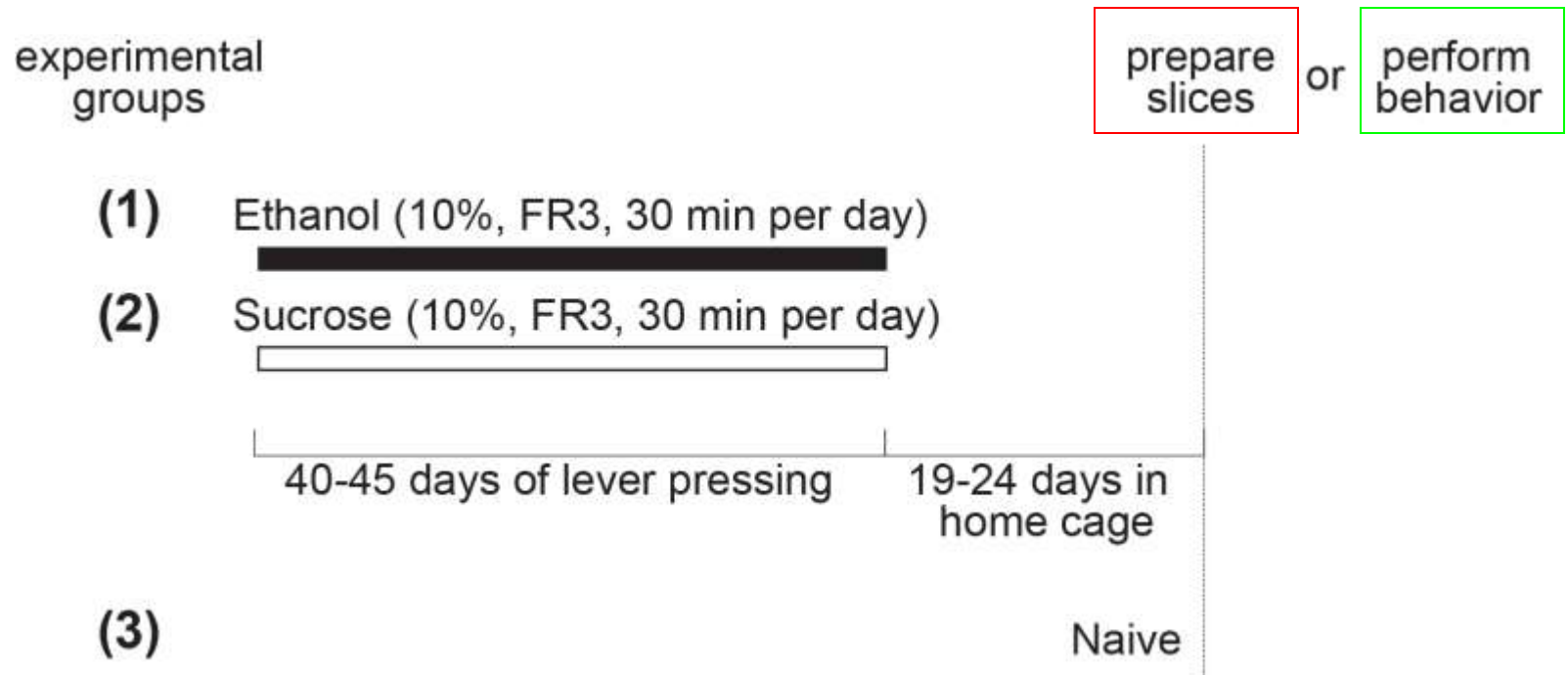
- NAcb neurons show action potential firing to conditioned cues that control behavior
  - Cue, stress, and drug-primed reinstatement of drug seeking require the NAcb
- Ethanol odor cues activate the NAcb in human alcoholics, and induce cravings.

## **Hypothesis:**

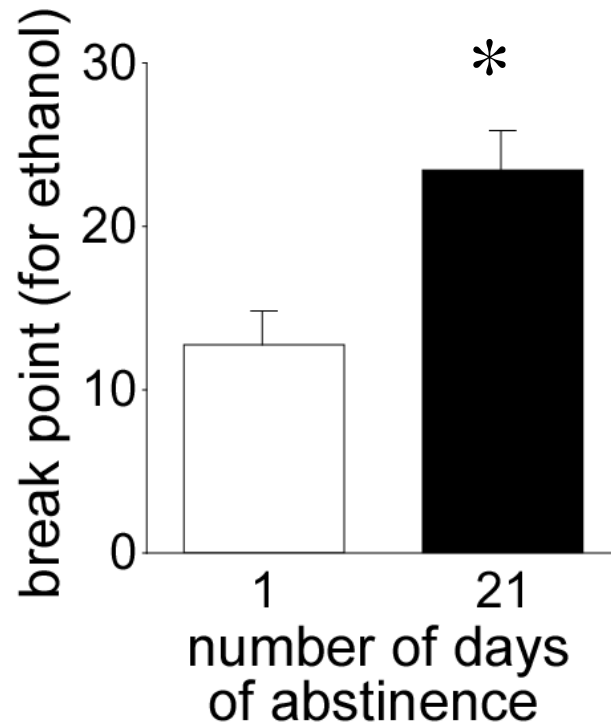
- Relapse in alcoholics is driven by maladaptive, long lasting changes within the NAcc that persist even after months or years of abstinence from alcohol.
- Action potential firing is the primary mechanism through which brain cells transmit information and control behaviors.



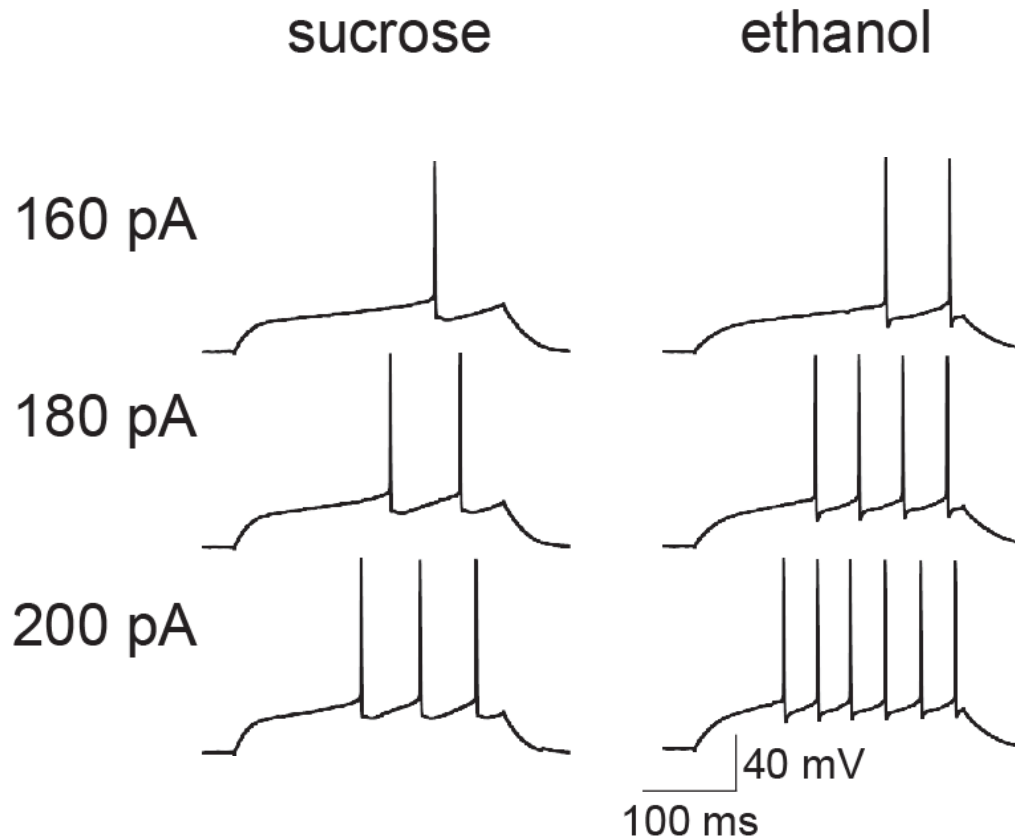
# Operant model of ethanol self-administration in adult Wistar rats



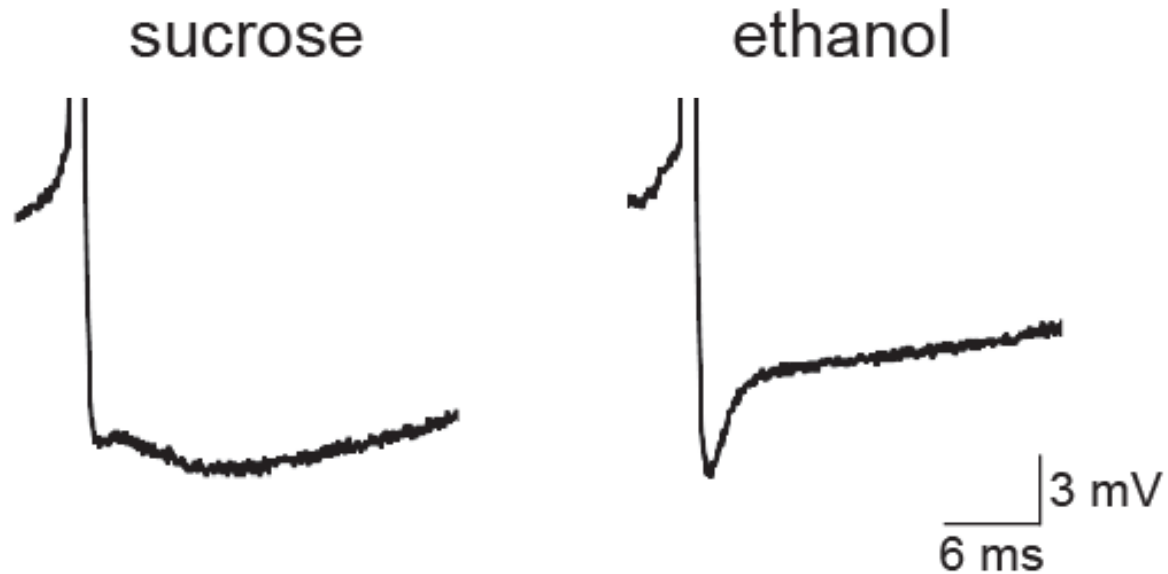
## Abstinence from ethanol significantly increases the motivation to lever press for ethanol



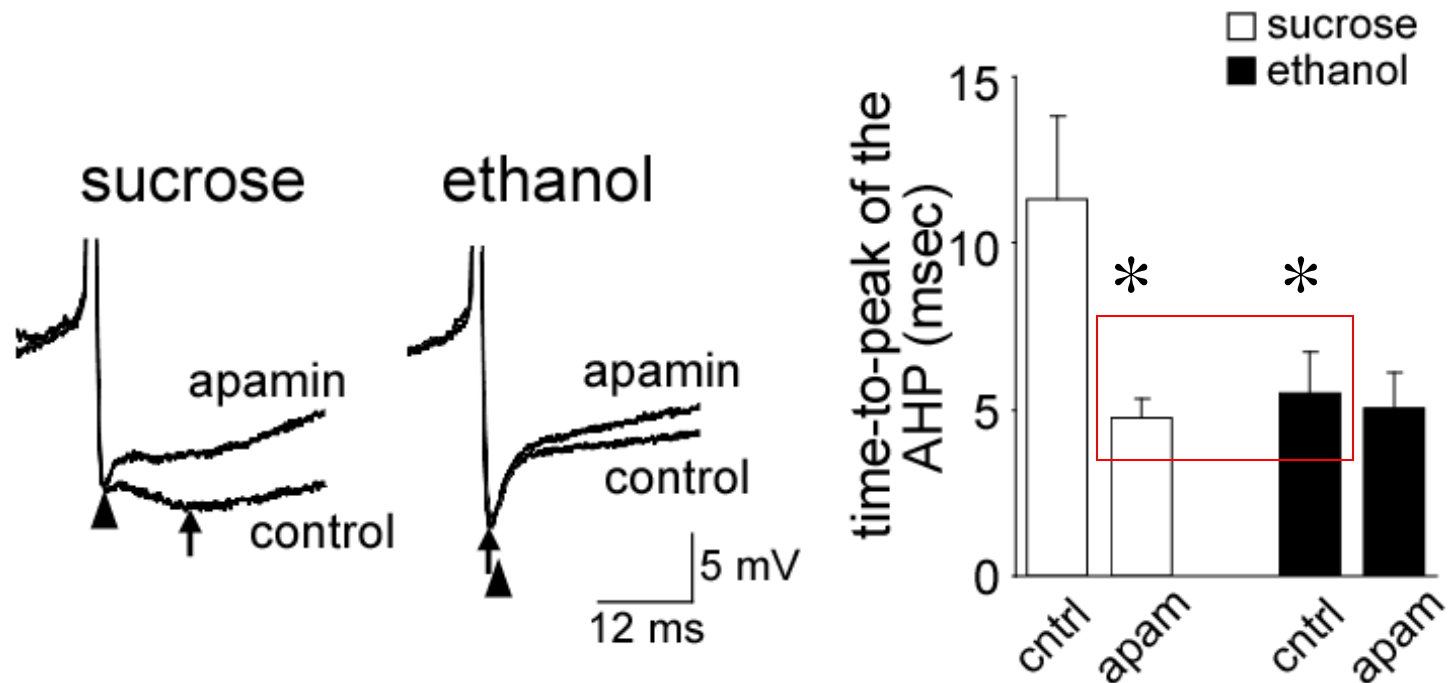
# **NAcb Core firing is significantly enhanced in ethanol animals at a time when the motivation for ethanol is elevated**



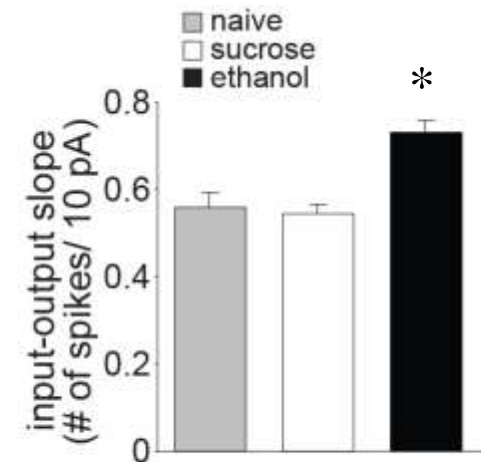
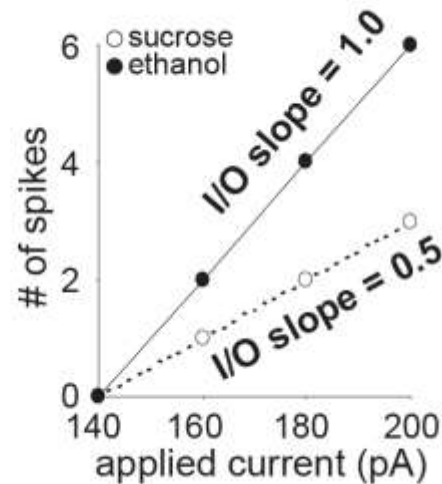
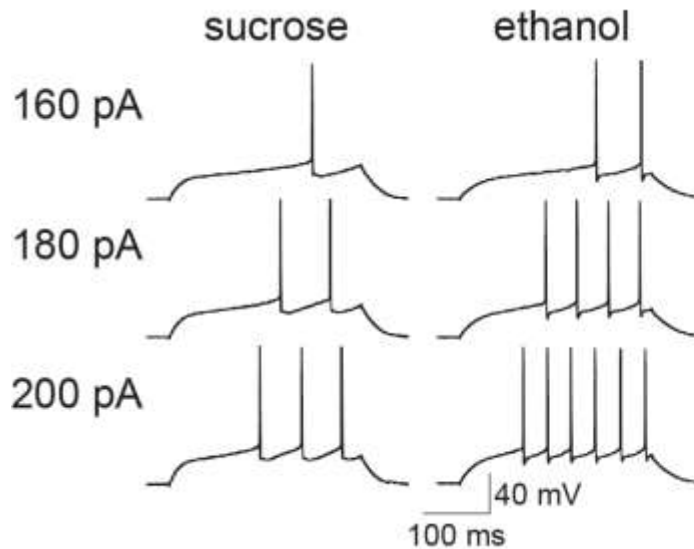
## The AHP in the NAcb Core is significantly reduced in ethanol animals



## Apamin-sensitive SK currents are reduced in the NAcb Core in ethanol-exposed animals

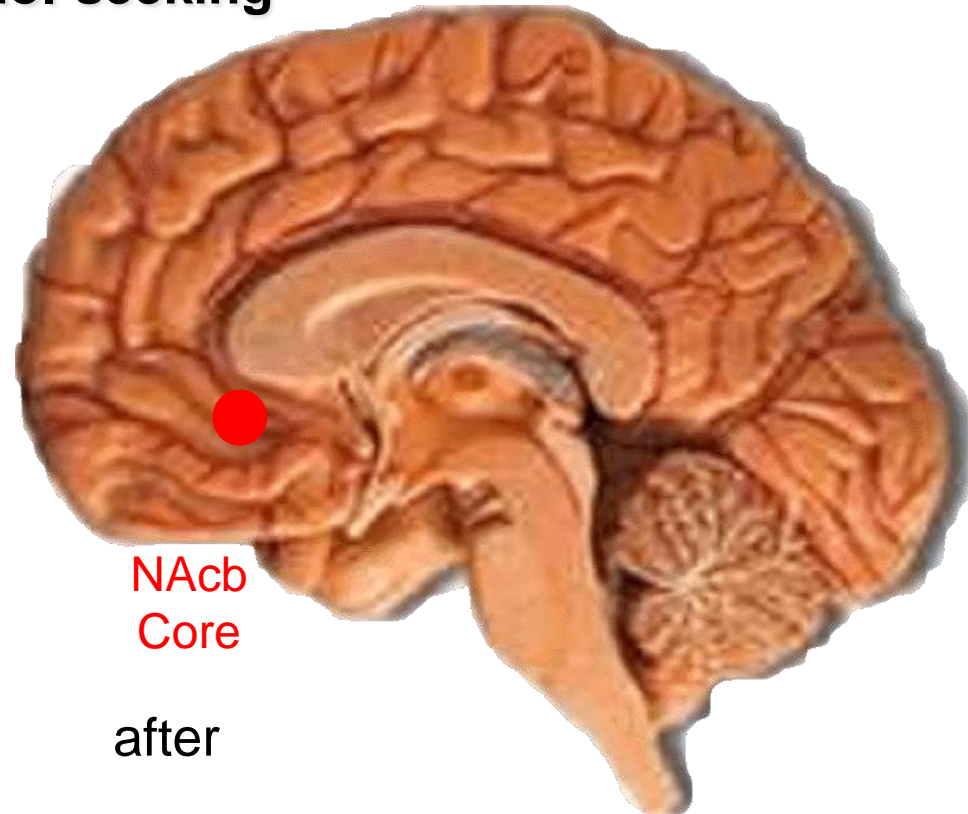


# The “input/output” slope is significantly increased after chronic ethanol exposure



## The bottom line:

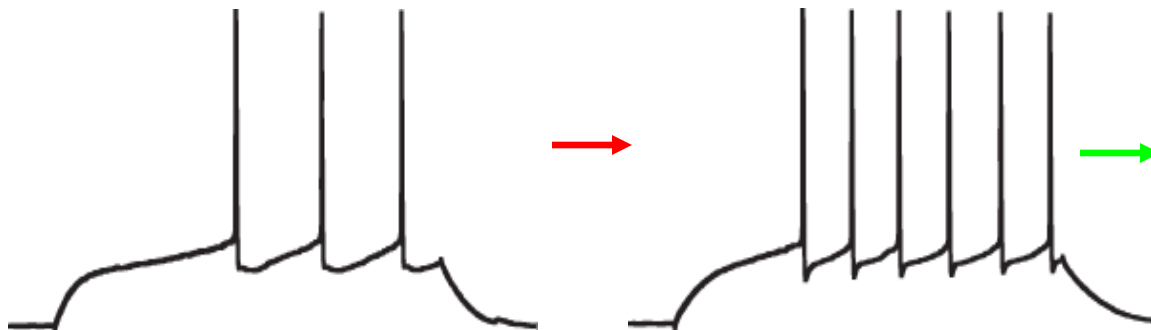
After protracted abstinence from ethanol, the core exhibits greater firing driving ethanol-seeking



NAcb  
Core

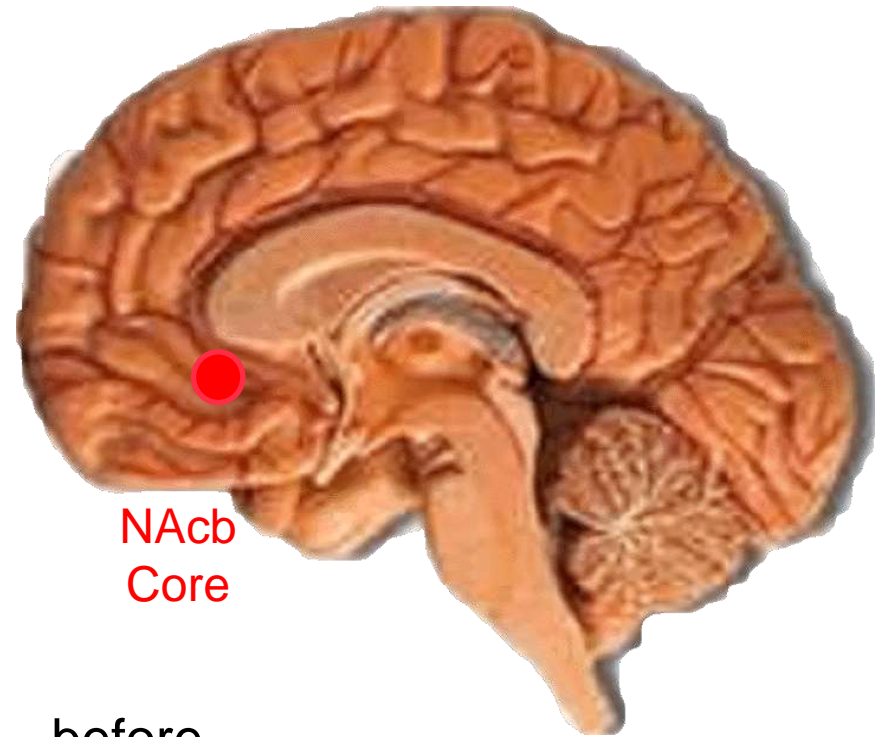
Before ethanol

after



Craving and relapse

# Can we re-activate SK channels and reduce motivation to consume ethanol?



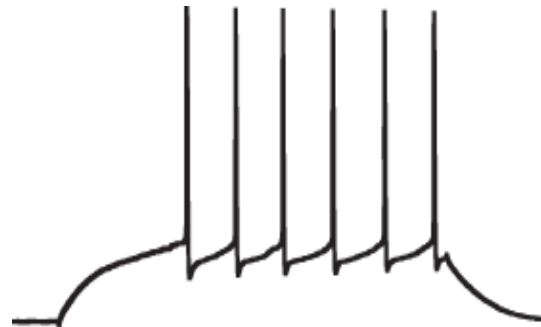
NAcb  
Core

After ethanol

before

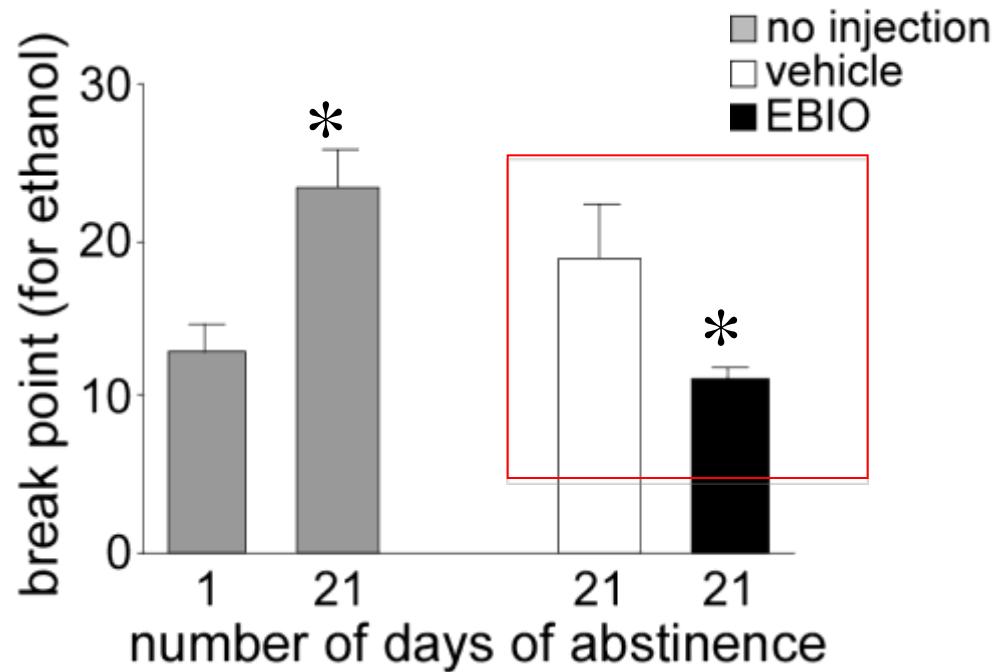
SK channel  
activator

→ No cravings and relapse?

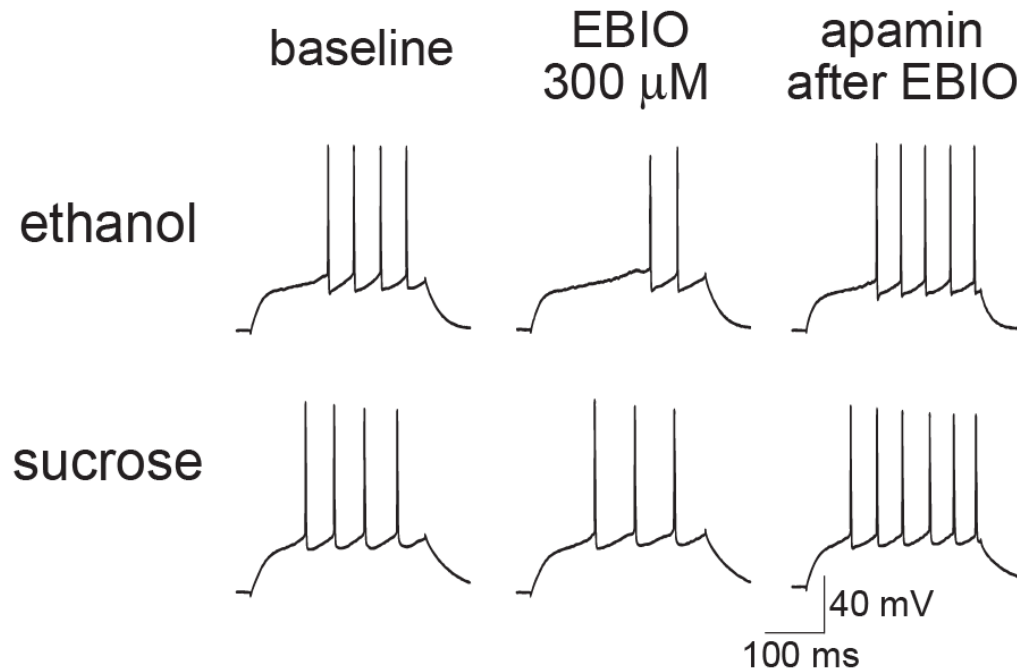




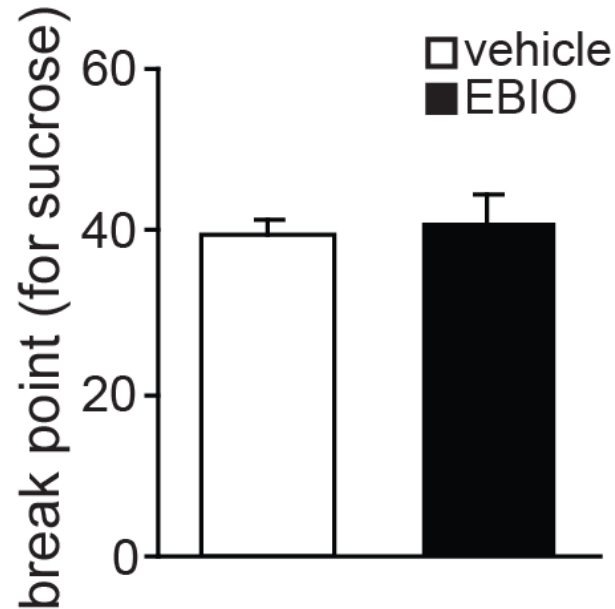
## Injecting EBIO into the NAcb Core reduces responding for ethanol



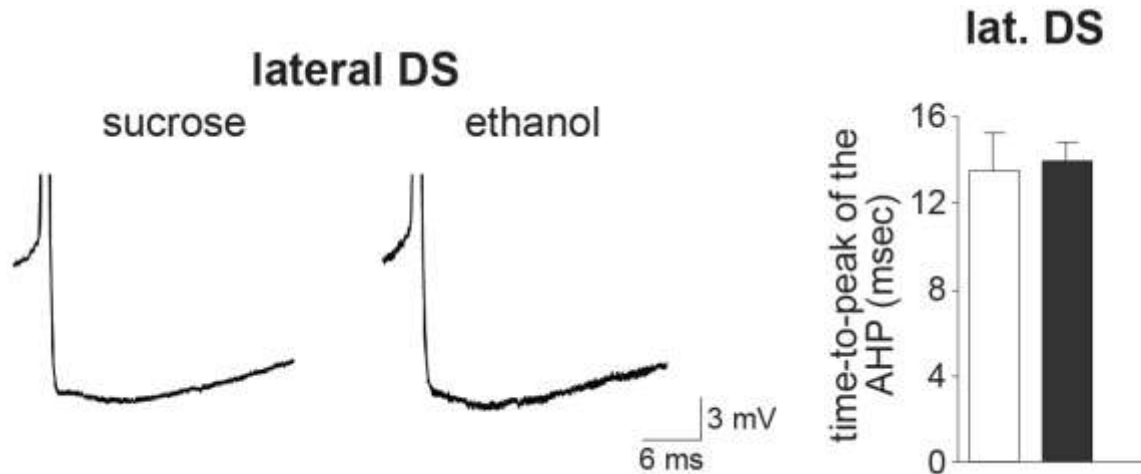
# EBIO activates SK channels and reduces firing in NAcb Core neurons.



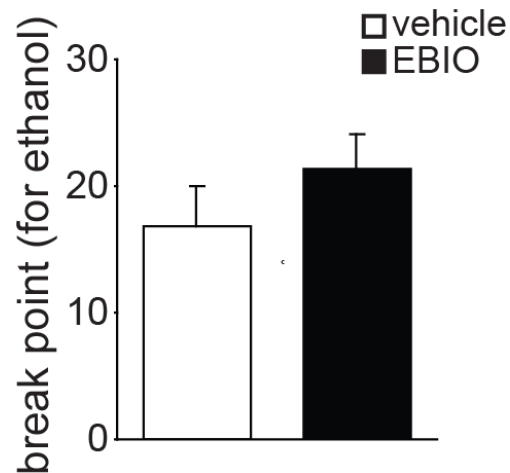
## Injecting EBIO into the NAc Core does not reduce responding for sucrose (after 21 days of abstinence from sucrose)



## Lateral DS SK is not reduced in ethanol animals, and EBIO in the lateral DS does not alter ethanol-seeking

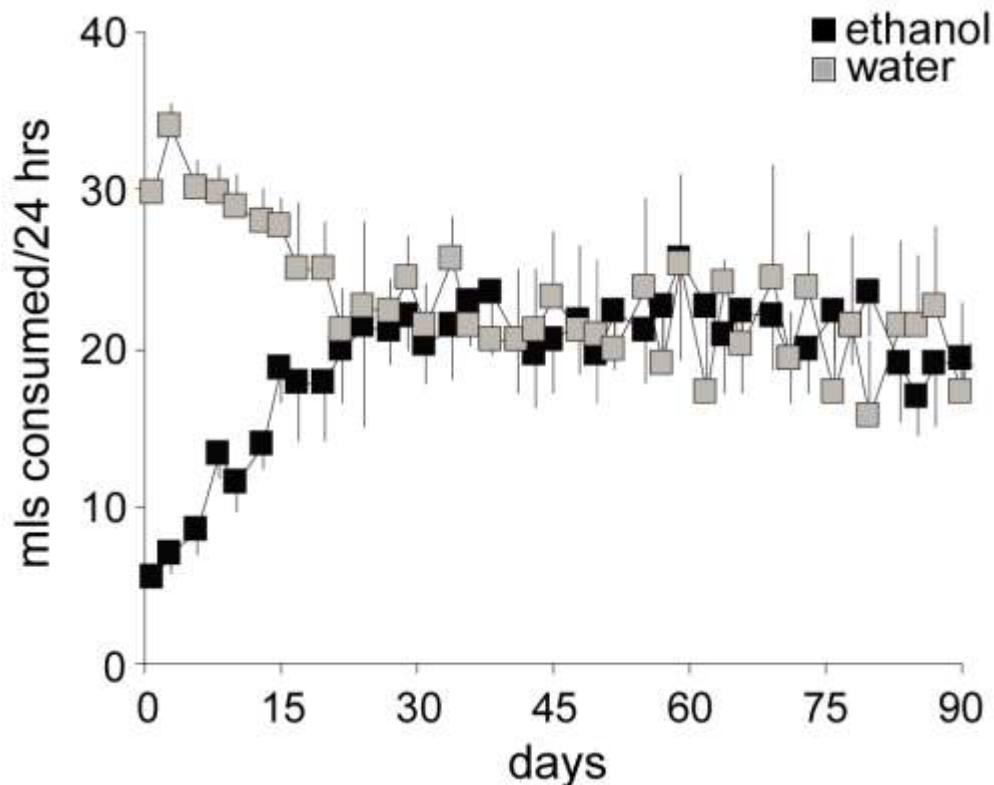


### SK activation in the lateral DS

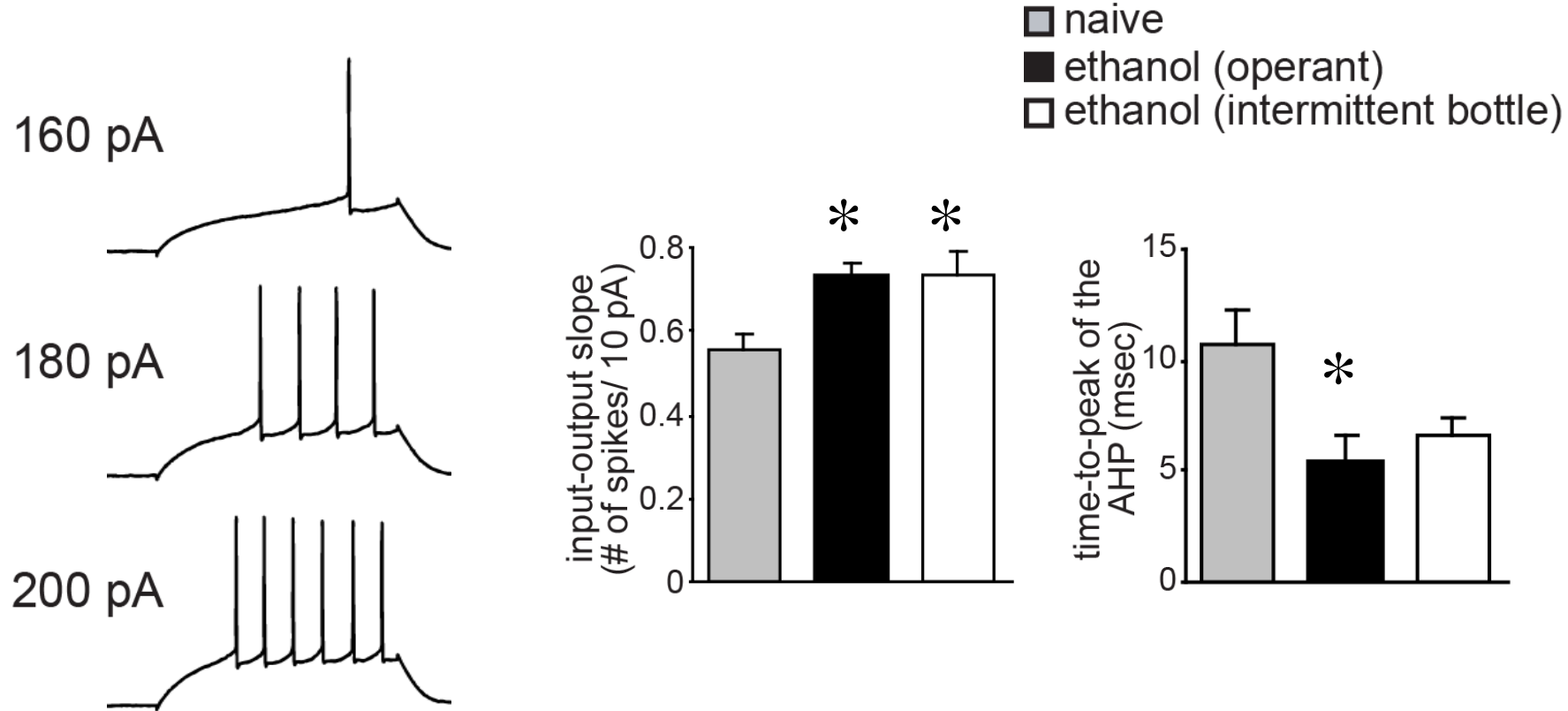


## Chronic intermittent ethanol access model

- Animals are allowed 24 hour access to 2 bottles (20% ethanol, water) across Monday, Wednesday, and Friday nights (Wise, 1973, Steensland et al., 2007).
  - Animals escalate intake across days to a plateau of ~8 g/kg/24 hrs.



# Chronic intermittent ethanol intake reduces SK function in the NAcb Core

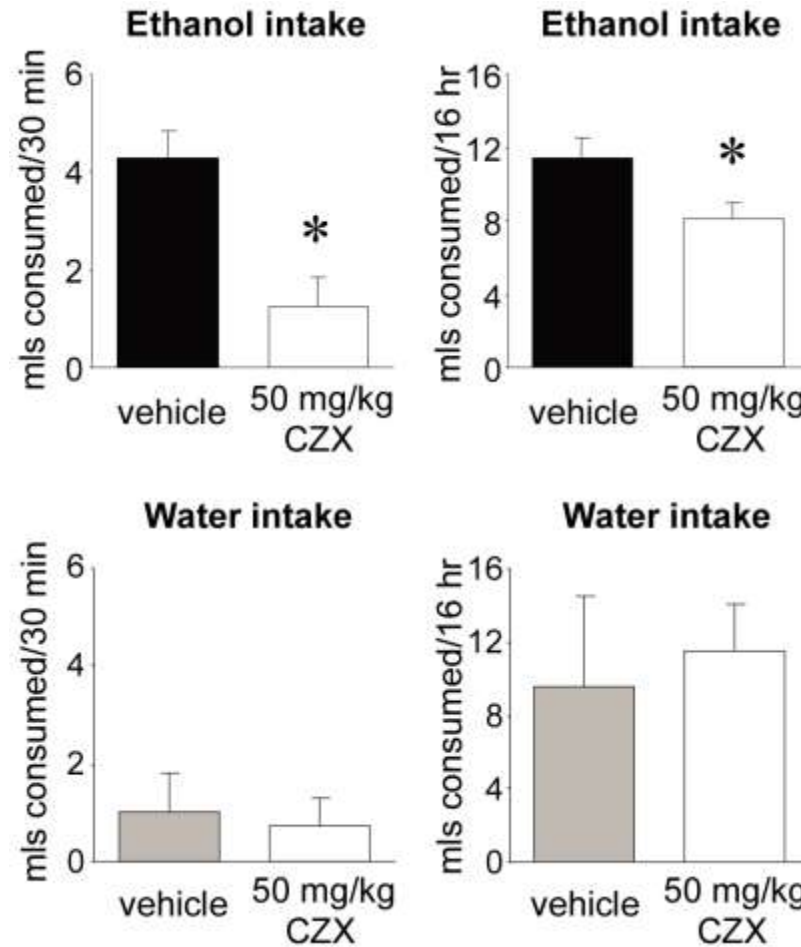


# Chlorzoxazone: an SK agonist and the progenitor of a novel therapeutic agents against alcoholism?



- A “centrally acting muscle relaxant”  
(**Paraflex, Parafon Forte, Relaxazone, Remular-S**)
- Used to treat a variety of conditions involving muscle pain or spasticity

# Chlorzoxazone significantly reduces ethanol but not water intake in the chronic intermittent access model





# Conclusions

- Long-term, voluntary ethanol self-administration alters NAcb core firing (tested against two very different drinking models).
- Pharmacological reversal of the SK channel inhibition in the NAcb Core firing reduces ethanol drinking.
- SK agonists represent a novel, promising target against alcoholism

# Acknowledgements

## Lab Members

(ex)

**Mark Ungless (ICL)**

**Stephanie Borgland (UBC)**

**Garret Stuber (UNC)**

Scott Bowers (VCU)

(current)

**Billy Chen**

Jon Britt

Said Kourrich

Hau Jie Yau

Ikue Kusumoto

Ross McDevitt

Nathan Marchant

Tim Galfin

Yang Zheng

Janice Koo

Christina Hatch

Stephanie Older

## Collaborations

### Extramural

Robert C. Malenka

Karl Deisseroth

Feng Zhang

Howard Fields

Luis deLecea

### Intramural

Jean Lud Cadet

Roy Wise

Brandon Harvey

Marisela Morales

Bruce Hope

Yavin Shaham

Sergi Ferre'

Thanks to NIDA, DoD and  
State of California