Synaptic plasticity in the dopamine system: therapeutic implications for substance use disorders

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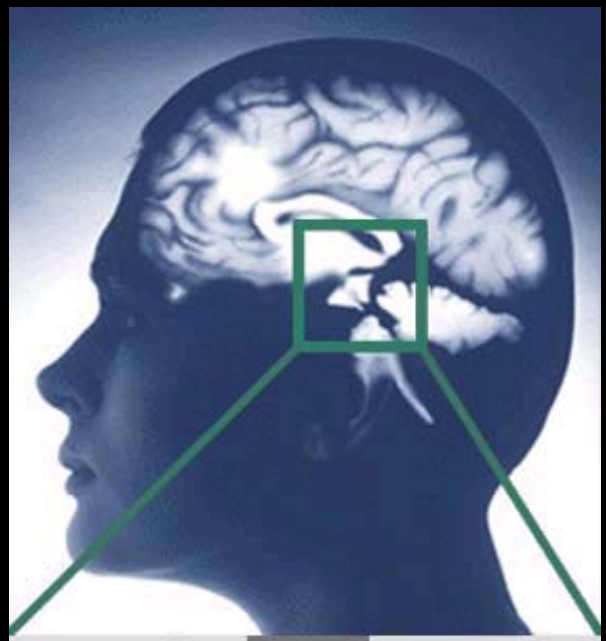
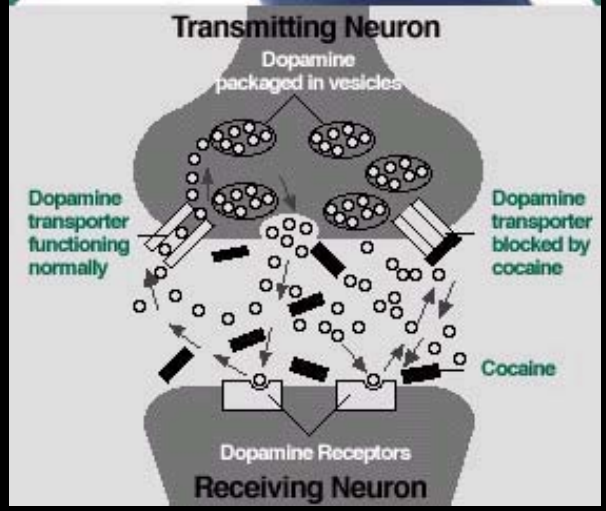
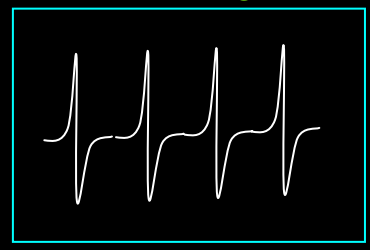
the general hypothesis:
Any addictive behavior depends on changes in electrical activity of specific brain regions

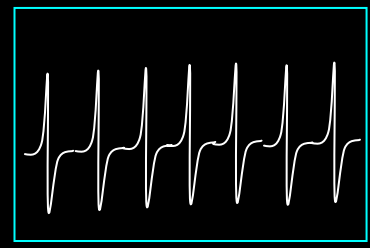




Genetic background



Environmental stimuli



Substance abuse

Why dopamine neurons?

Addiction

Apathy/motivation

Aggressive behaviors

Sexual, appetitive behaviors

Parkinson’s disease

Schizophrenia

Working memory

Depression

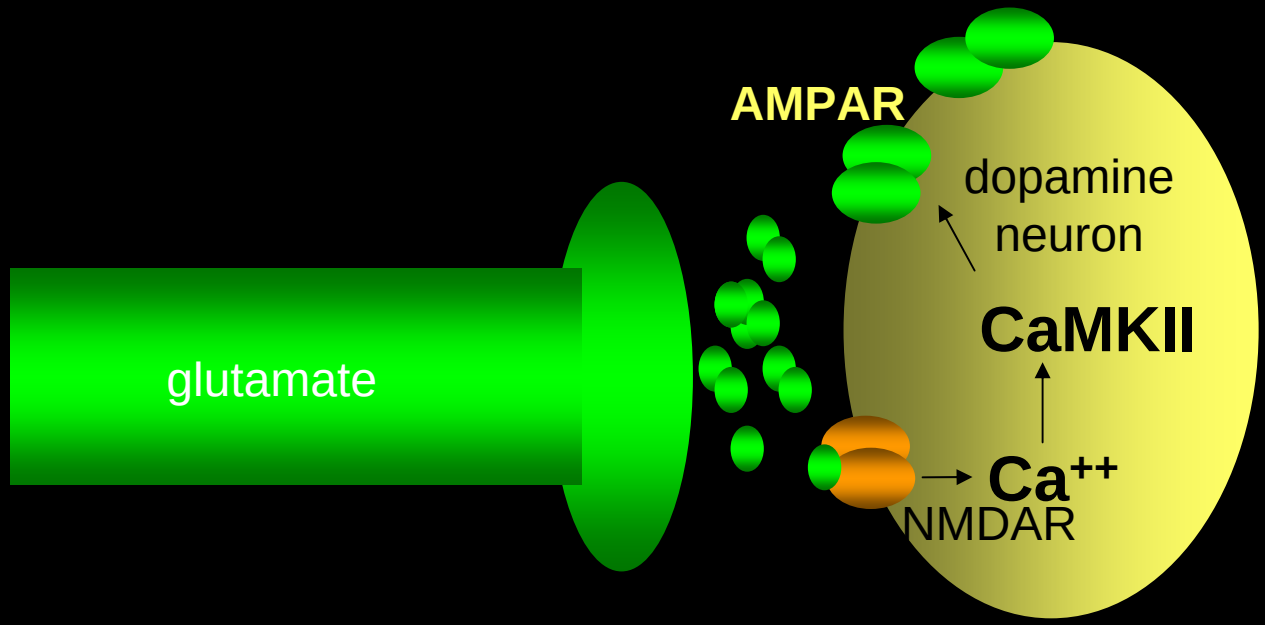
Reward Deficiency Syndrome

ADHD

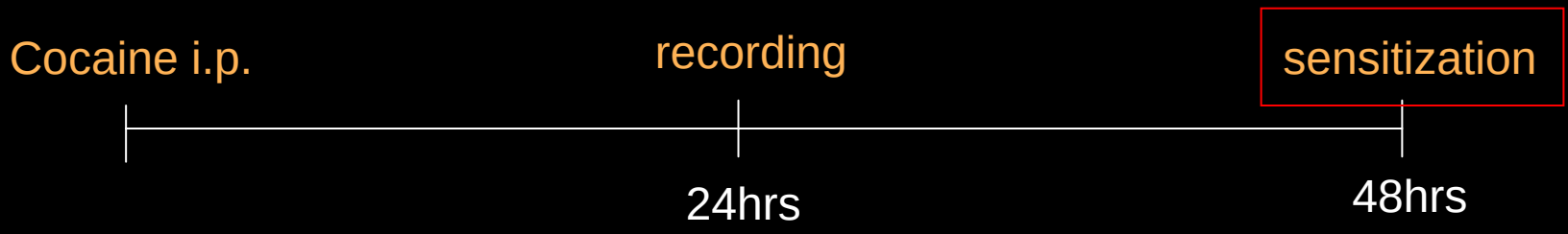
Dementias

My second wife

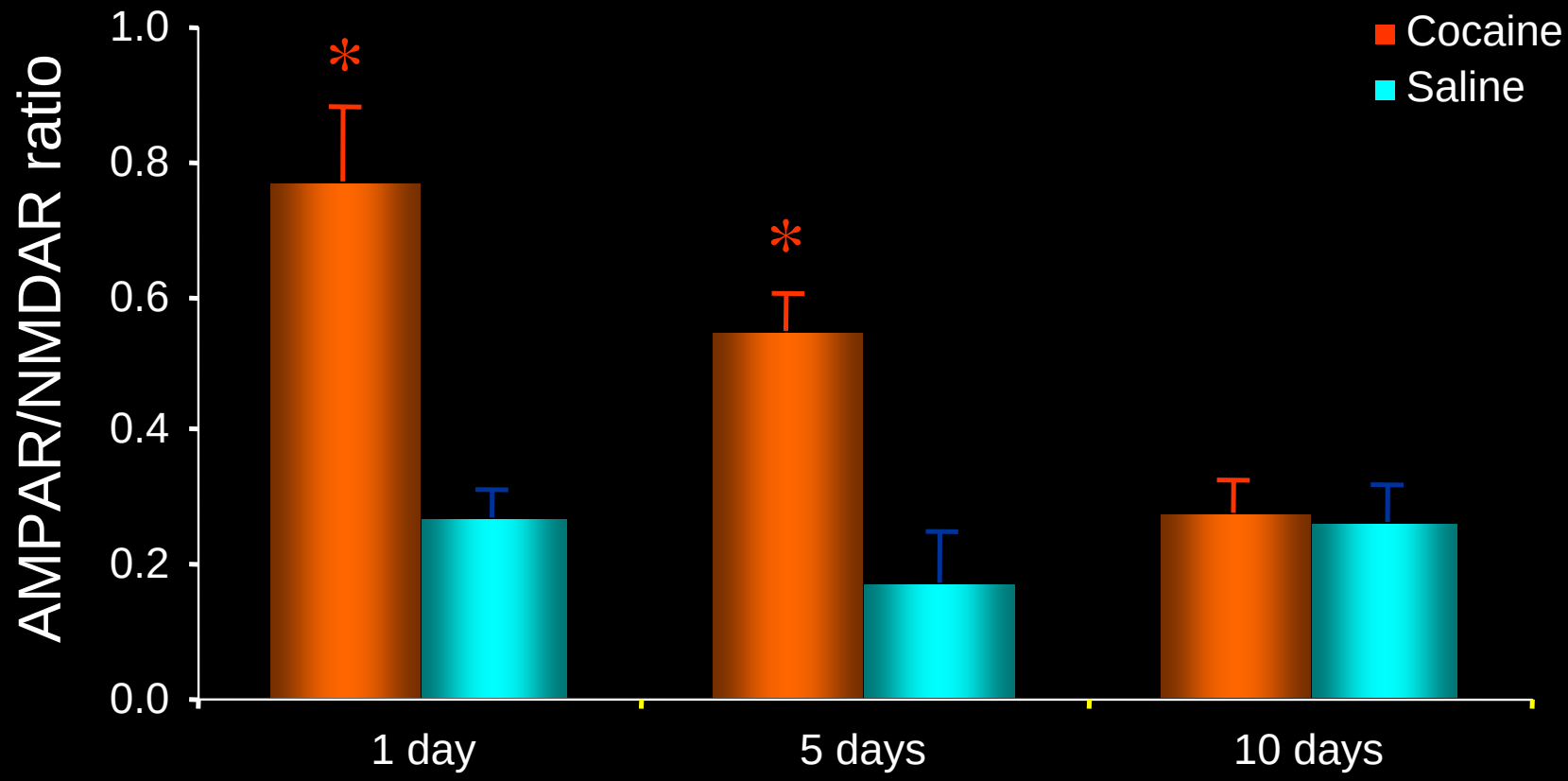
A fundamental cellular model of learning and memory: long-term potentiation (LTP)



Are drugs of abuse capable of producing LTP?



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

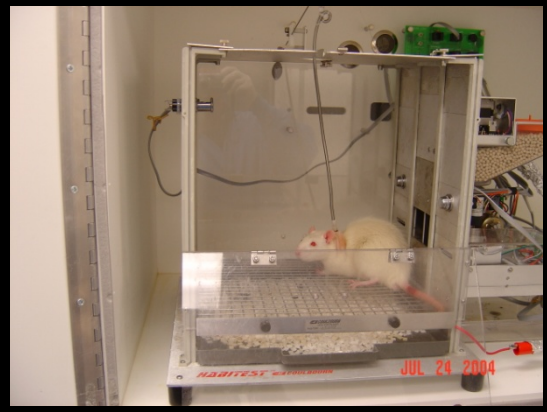


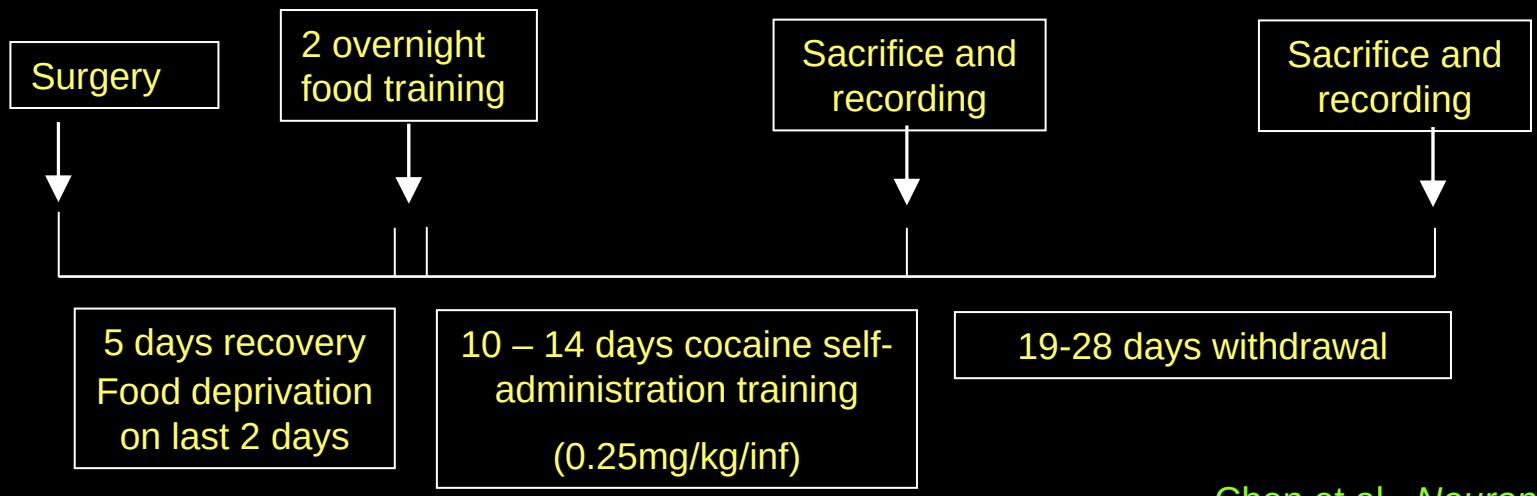
Ungless et al., Nature (2001)

Passive versus active choice of taking cocaine

4) What about cocaine self-administration?

Self-administration training and whole-cell recording schedule

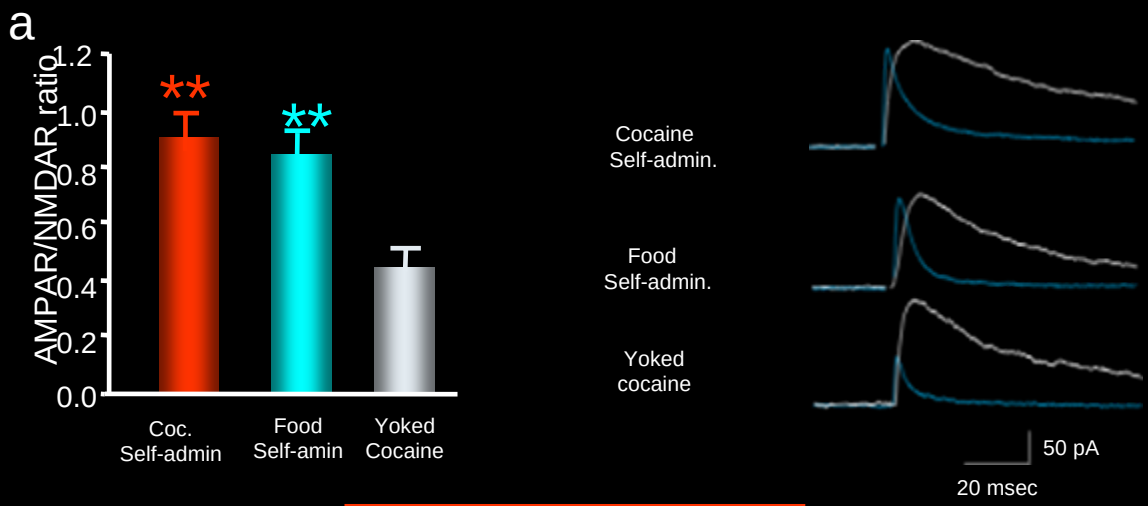




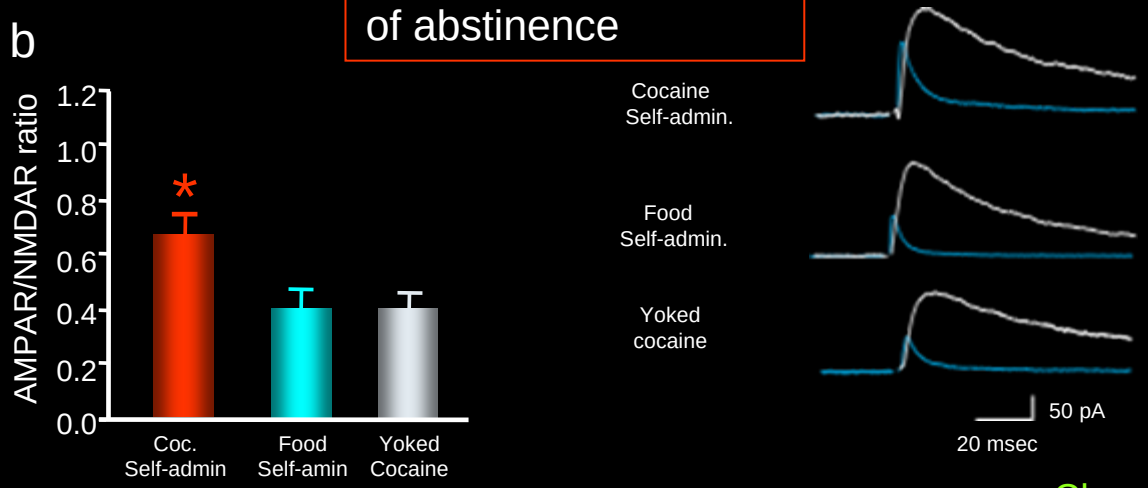
Chen et al., *Neuron (2008)*

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

1 day abstinence

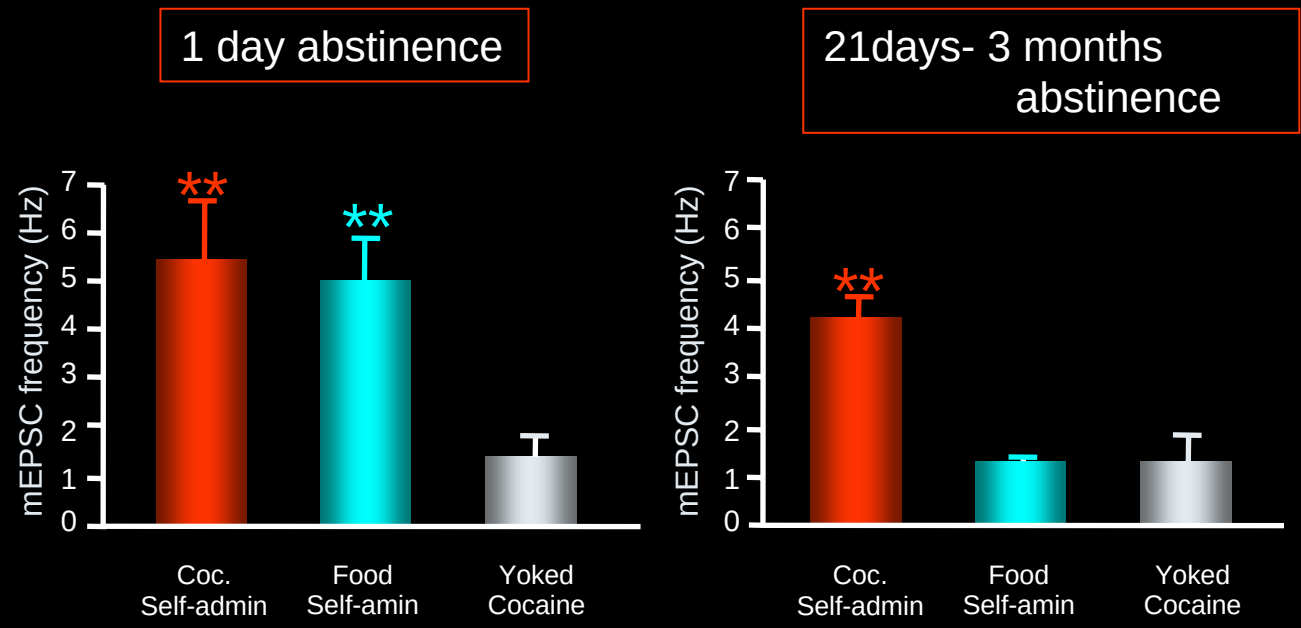


21 days-3 months of abstinence



Chen et al., *Neuron (2008)*

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

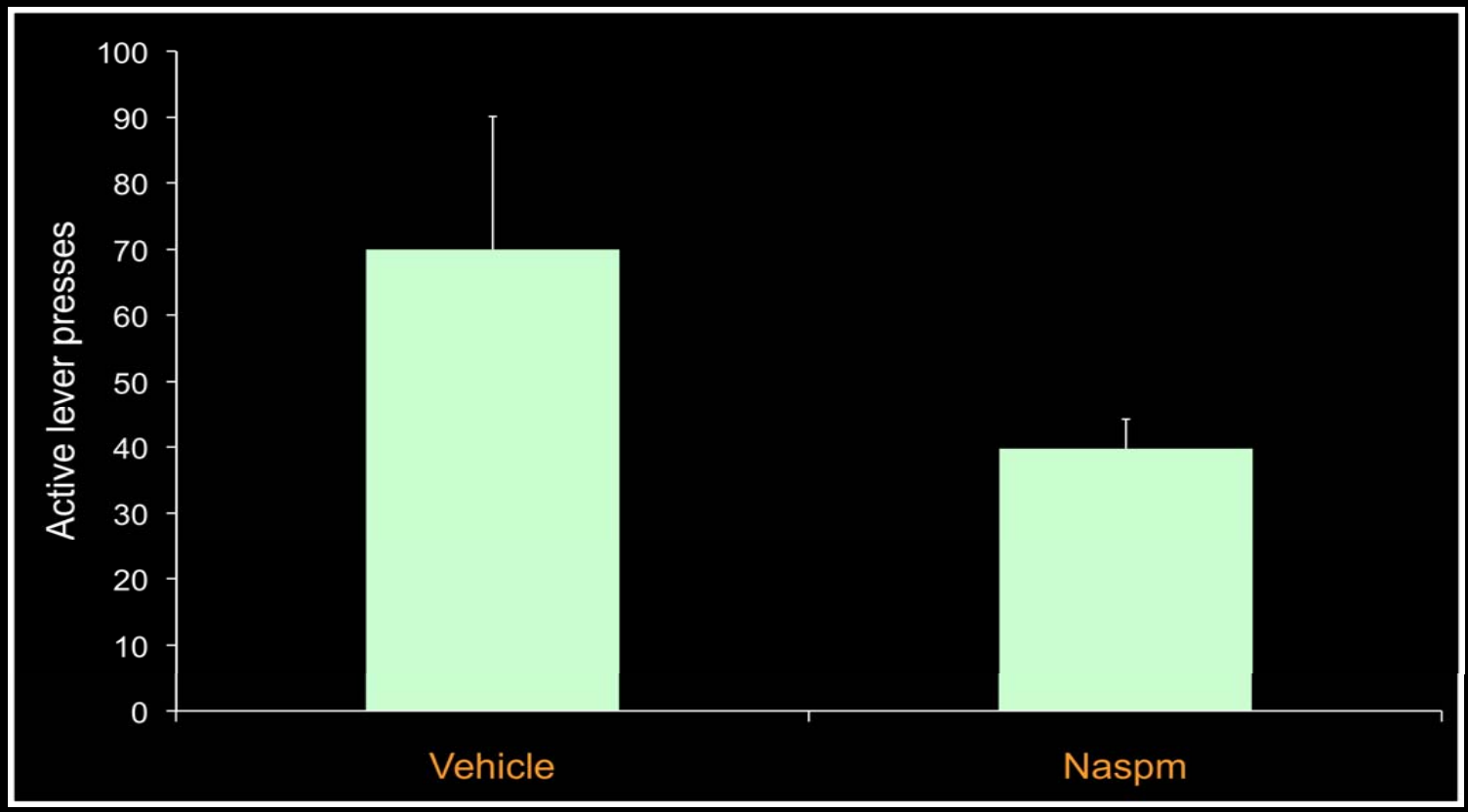


Chen et al., *Neuron (2008)*

Question:

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

Cue-induced relapse to cocaine is blocked by intra-VTA injection of selective inhibitor of AMPAR-GluR2-lacking subunits



AMPAR antagonists are used in clinical trials

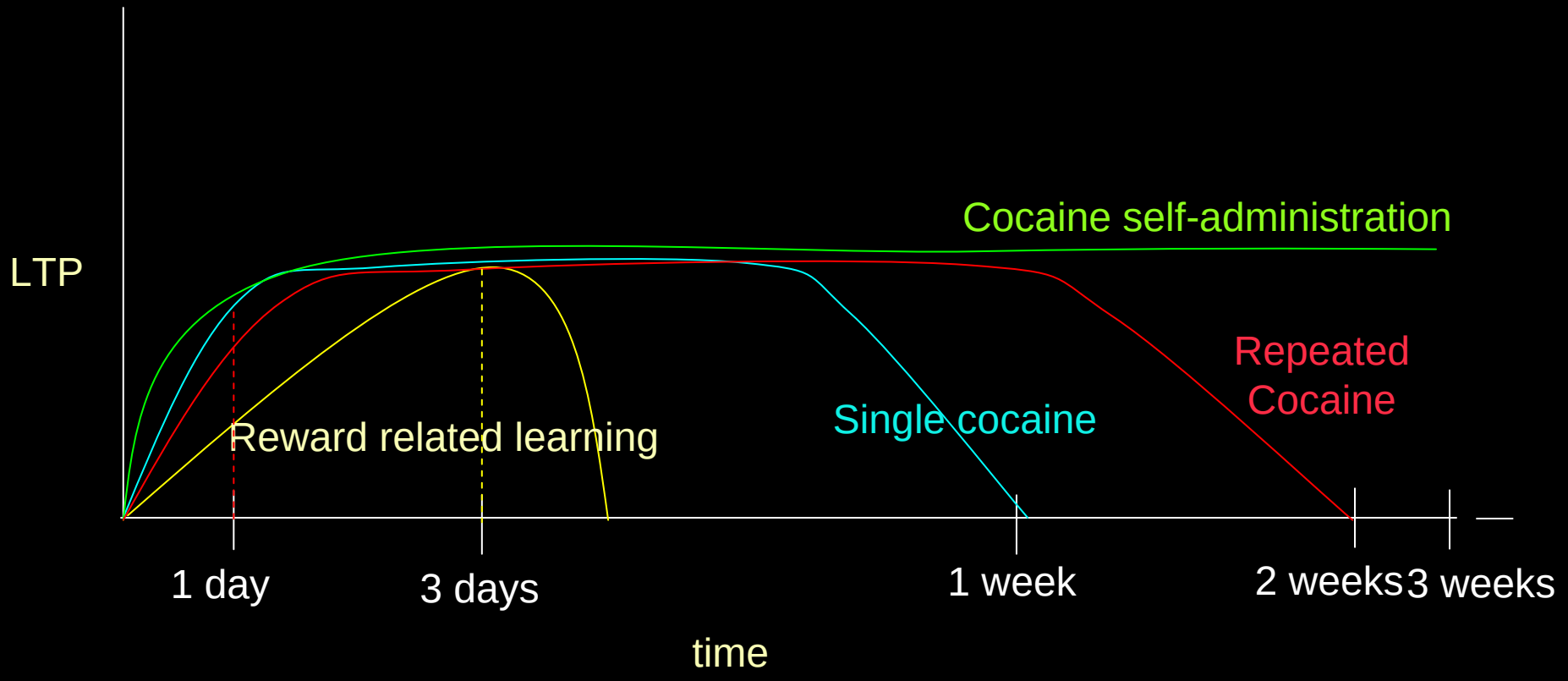
Table 2. Past and ongoing clinicl trials with selective AMPAR antagonists

Talampanel

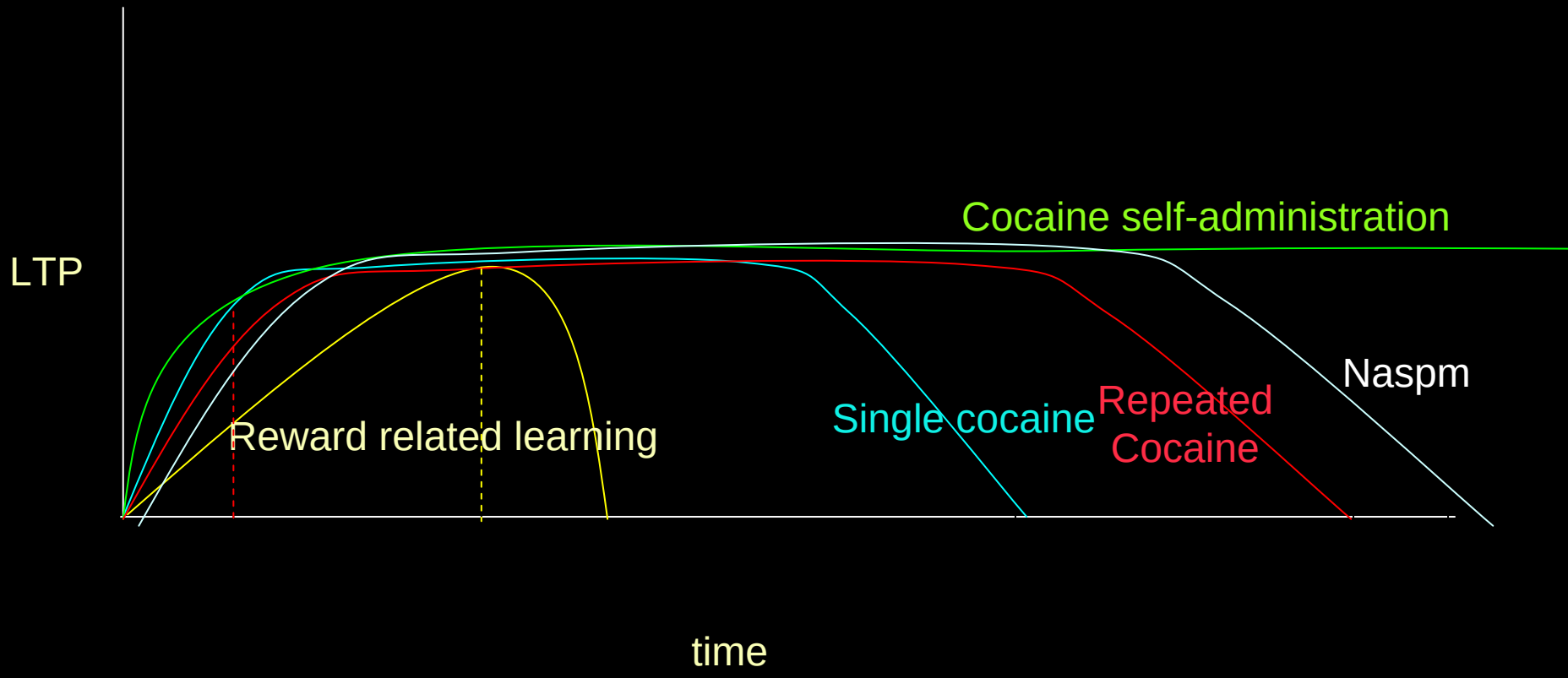
Status	Study	Condition	Intervention
Terminated	A Study to Investigate the Absorption, Metabolism and Excretion of Talampanel	Healthy	Drug: Talampanel (non-radiolabeled), [14C] Talampanel
Not yet recruiting	A Phase 1 Study to Investigate the Effects of Talampanel on the Heart Rhythm	Healthy	Drug: Talampanel; 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

Bowers, Chen and Bonci. Neuron, invited review

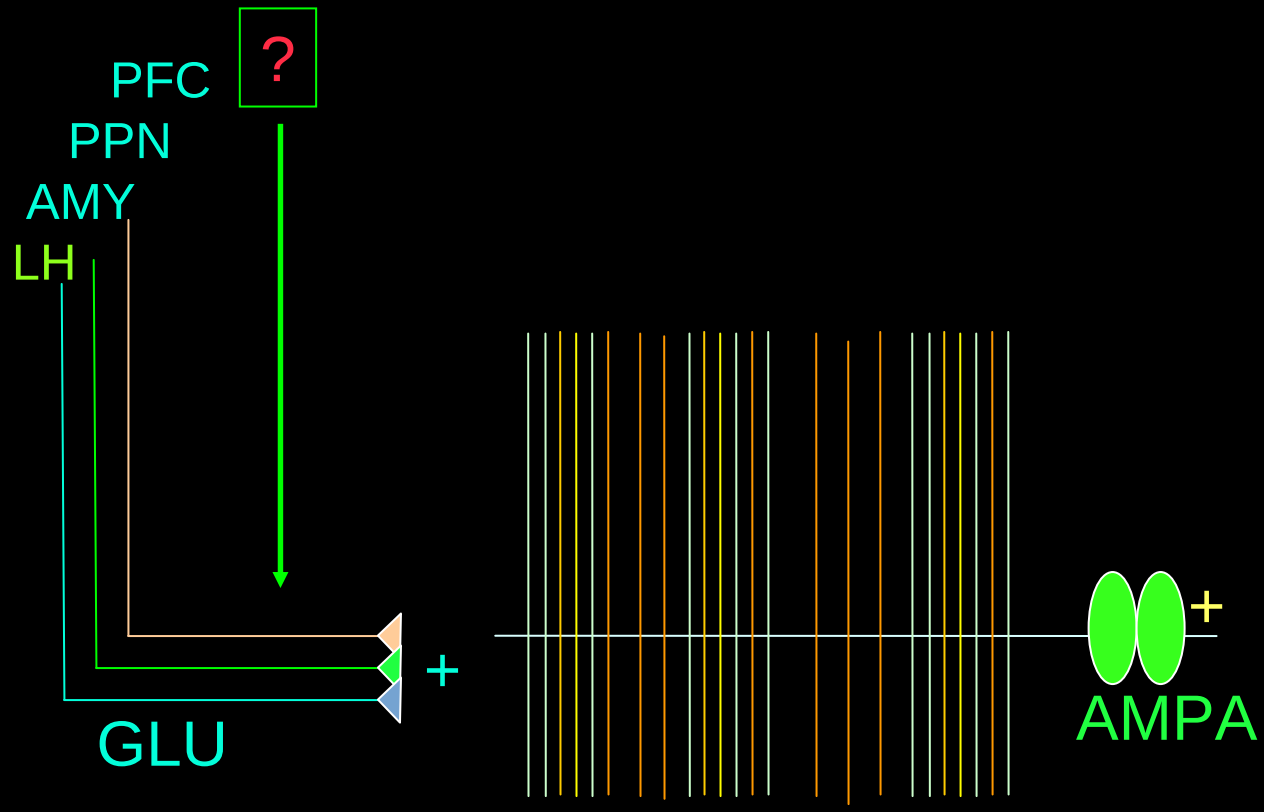
The time course of LTP



The time course of LTP



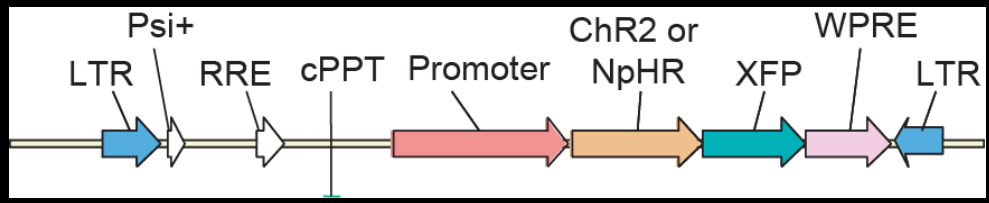
Functional consequences of increased AMPAR activity

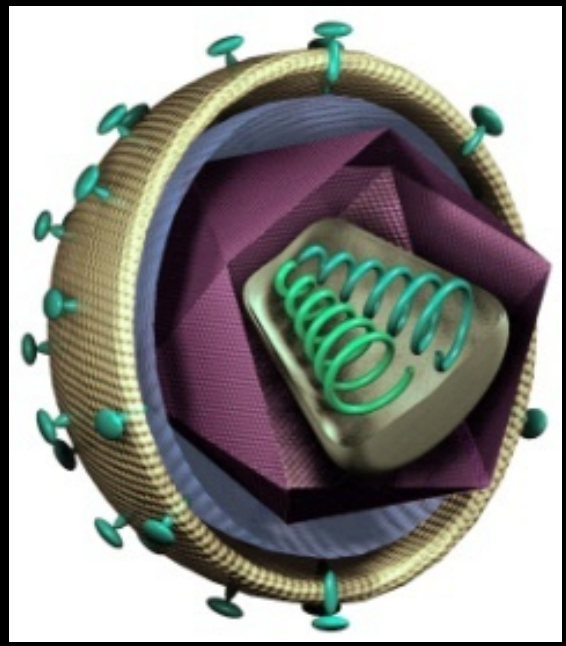


Engineering Light-sensitive Neurons

Lentiviral Gene Transfer

Lentivirus Vector

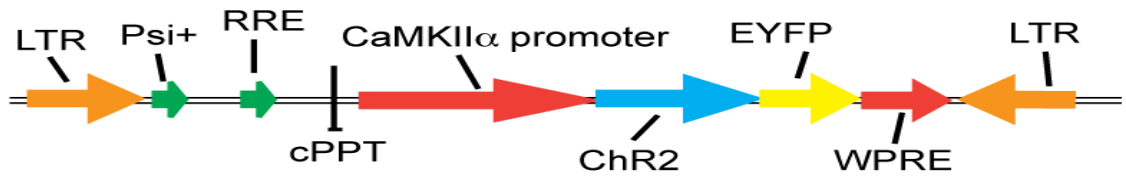




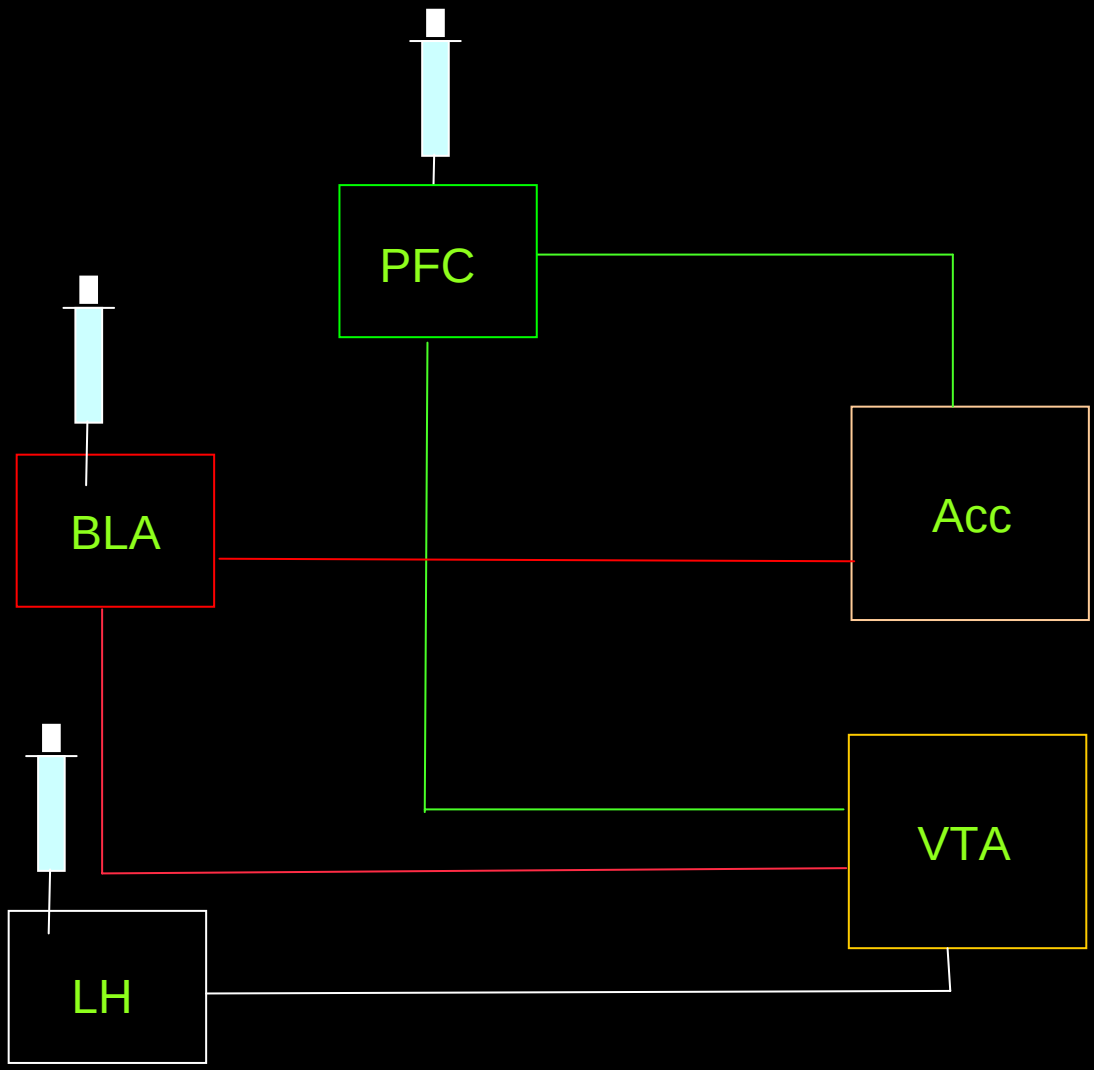
Courtesy of Feng Zhang, KD Lab

Pathway specific control of glutamate afferents

AAV-CaMKIIa-ChR2-EYFP:



ChR2 expressing neurons



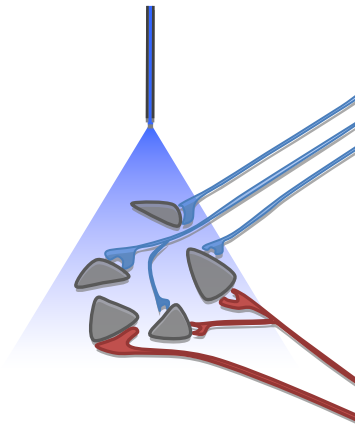
Garret Stuber

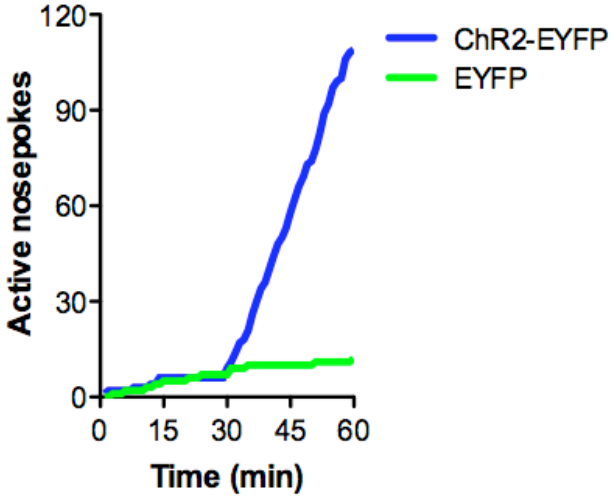
3. Record or perform *in vivo* expp.

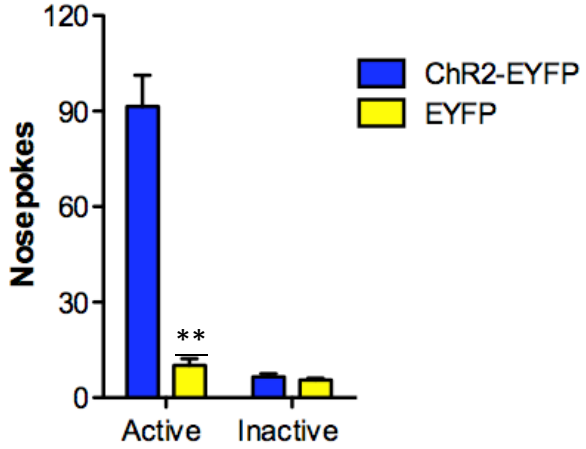
1. Inject the AAV containing the CaMKIIα promoter

Garret Stuber

Acquisition of BLA-to-NAc Optical ICSS in freely moving mice



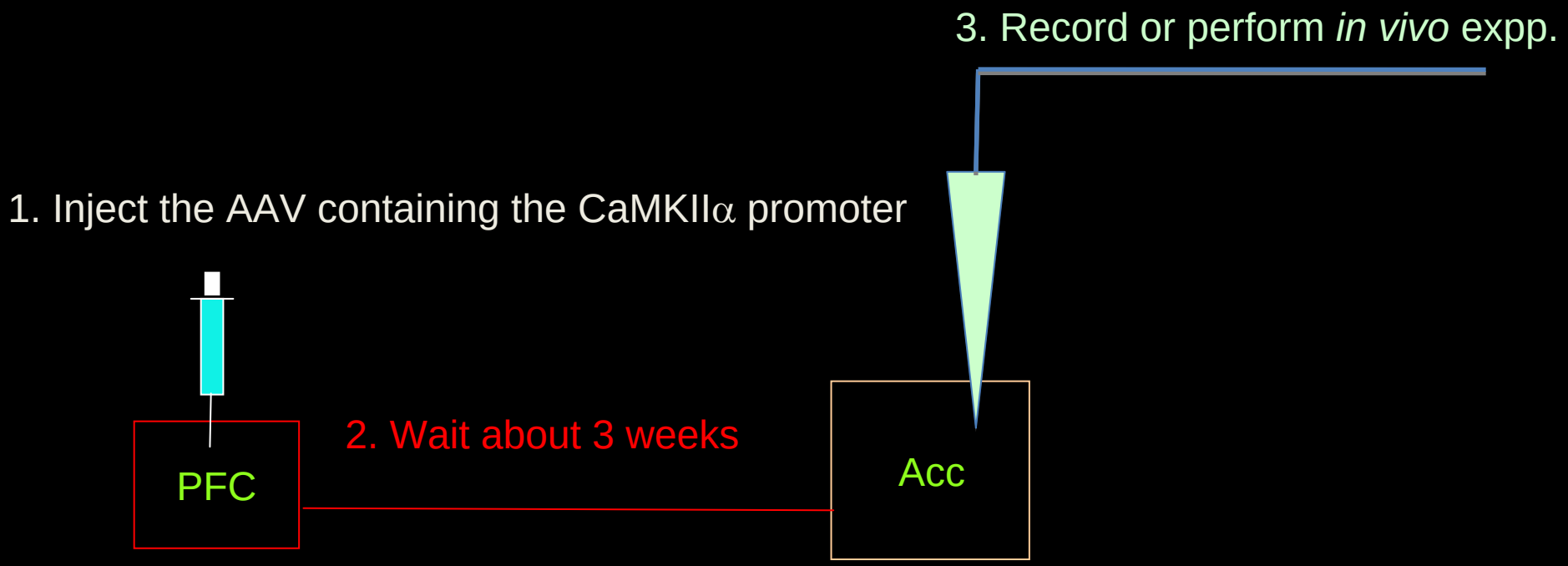




Mice readily learn to nosepoke for optical stimulation in a single 1 hr session.

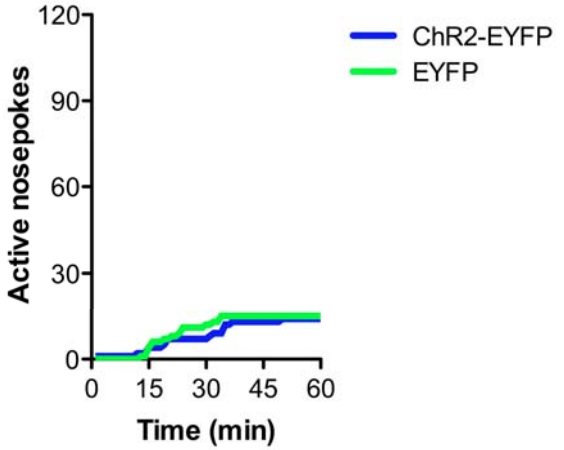
Stuber et al., under revision

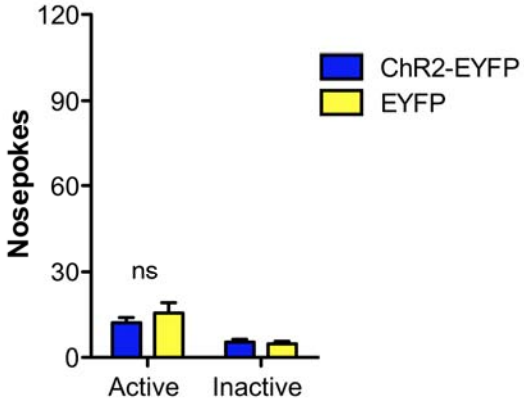
PFC to BLA stimulation

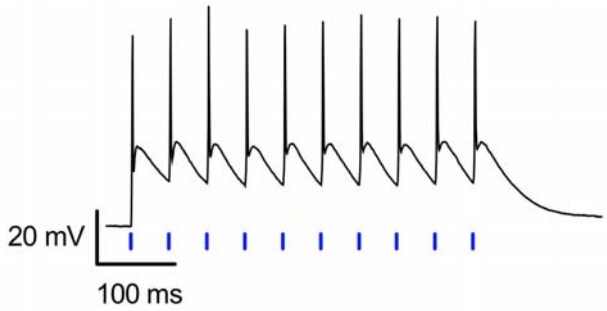


Kim Kempadoo, Garret Stuber

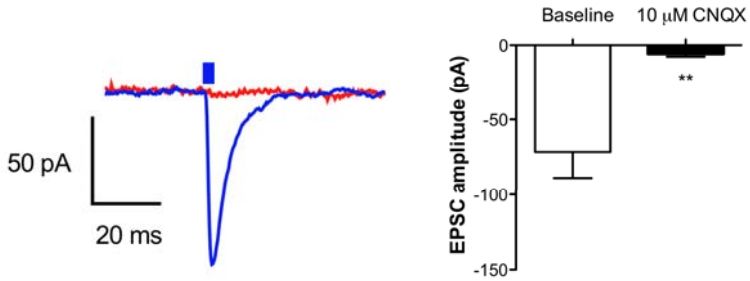
mPFC-to-NAc transmission is not reinforcing







ChR2-mediated firing in mPFC



Glutamate mediated EPSCs can be evoked directly under guide cannula in the NAc

Stuber et al.,under revision

Acknowledgements

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