cocaine: from animal models to pharmaceutical targets

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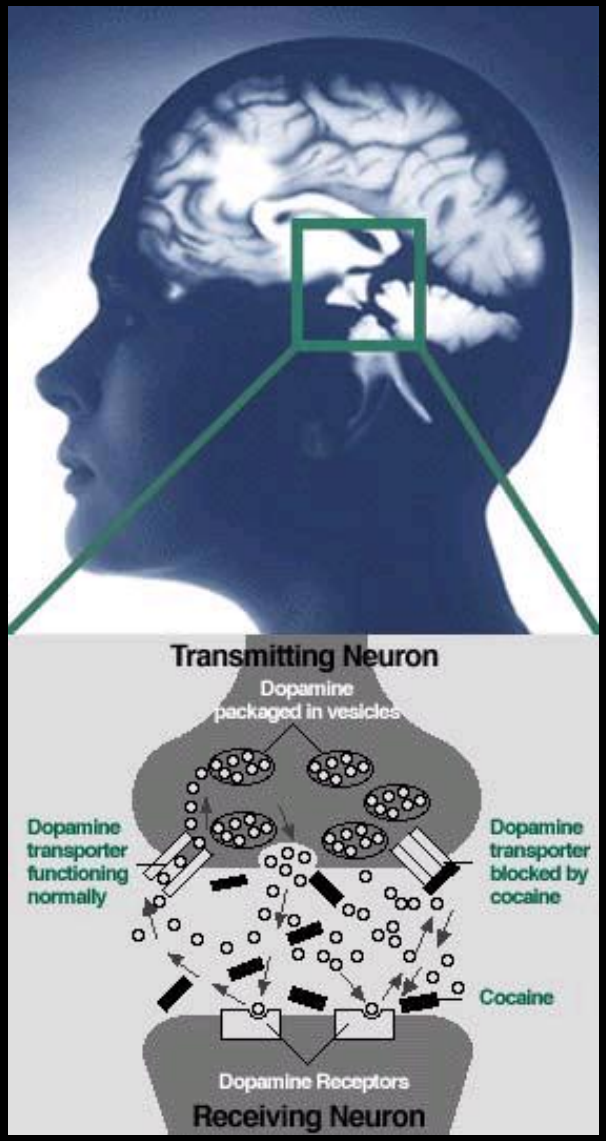
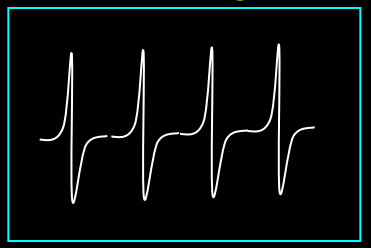
No conflict of interest

A simple hypothesis:
Any addictive behavior depends on changes in electrical activity of specific brain regions

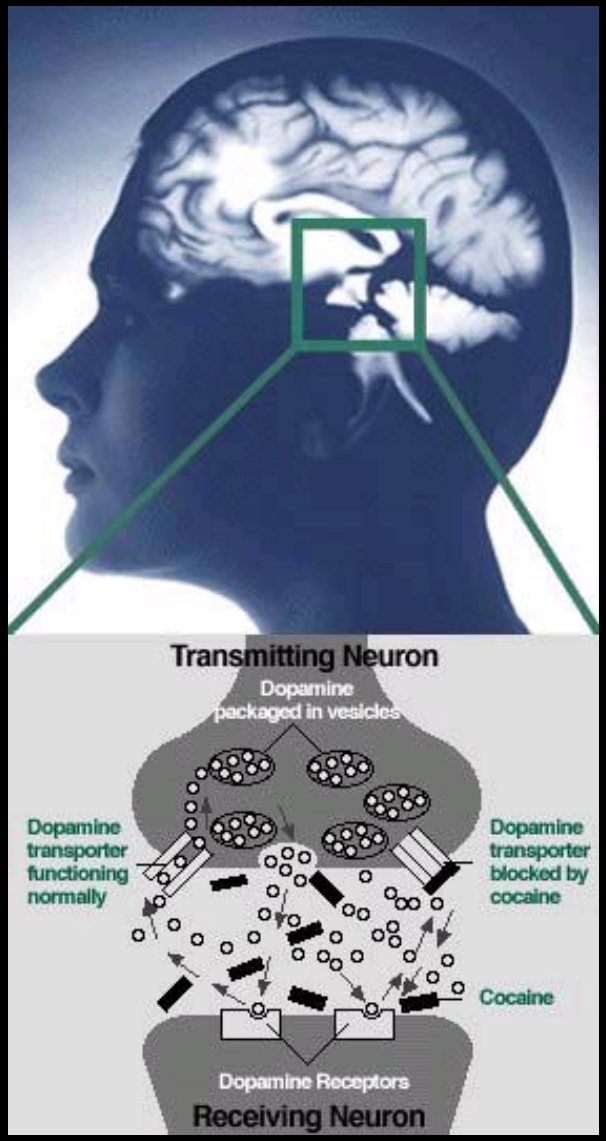


Genetic background

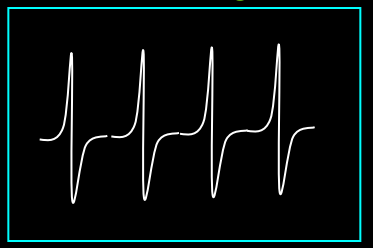


Environmental stimuli

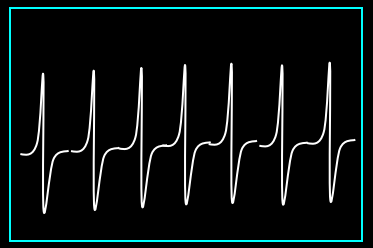
A simple hypothesis:
Any addictive behavior depends on changes in electrical activity of specific brain regions



Genetic background



Environmental stimuli



A simple hypothesis:
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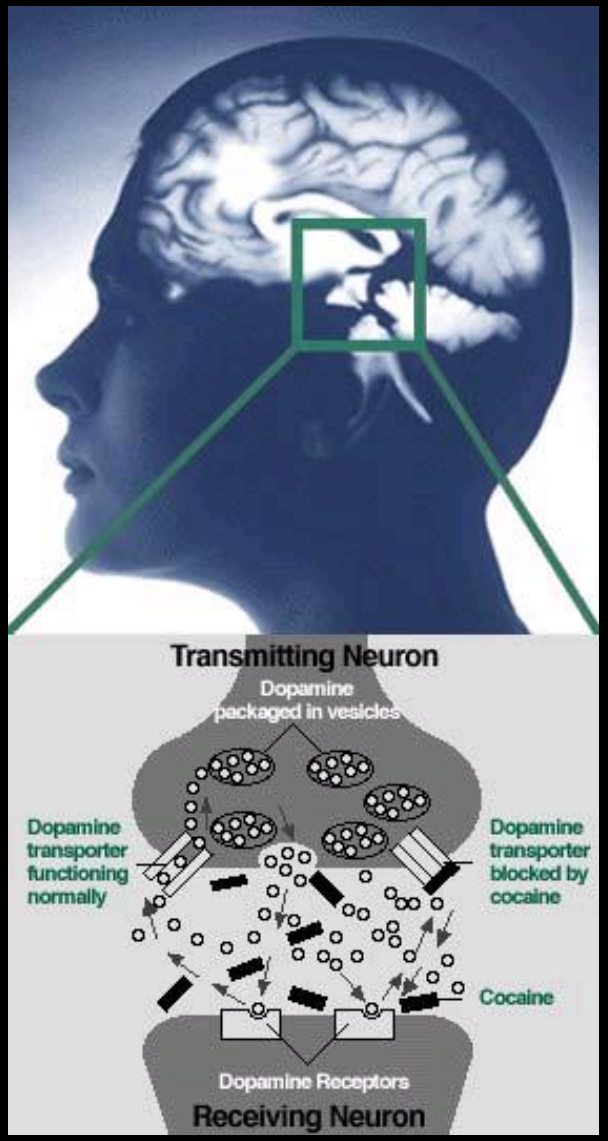
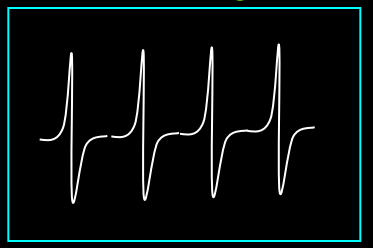
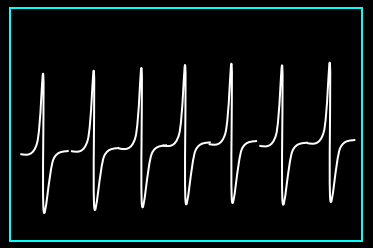


Genetic background



Environmental stimuli



Substance abuse

Why dopamine neurons?

Addiction

Apathy/motivation

Depression

Aggressive behaviors

Sexual, appetitive behaviors

Reward Deficiency Syndrome

Parkinson’s disease

ADHD

Schizophrenia

Dementias

Working memory

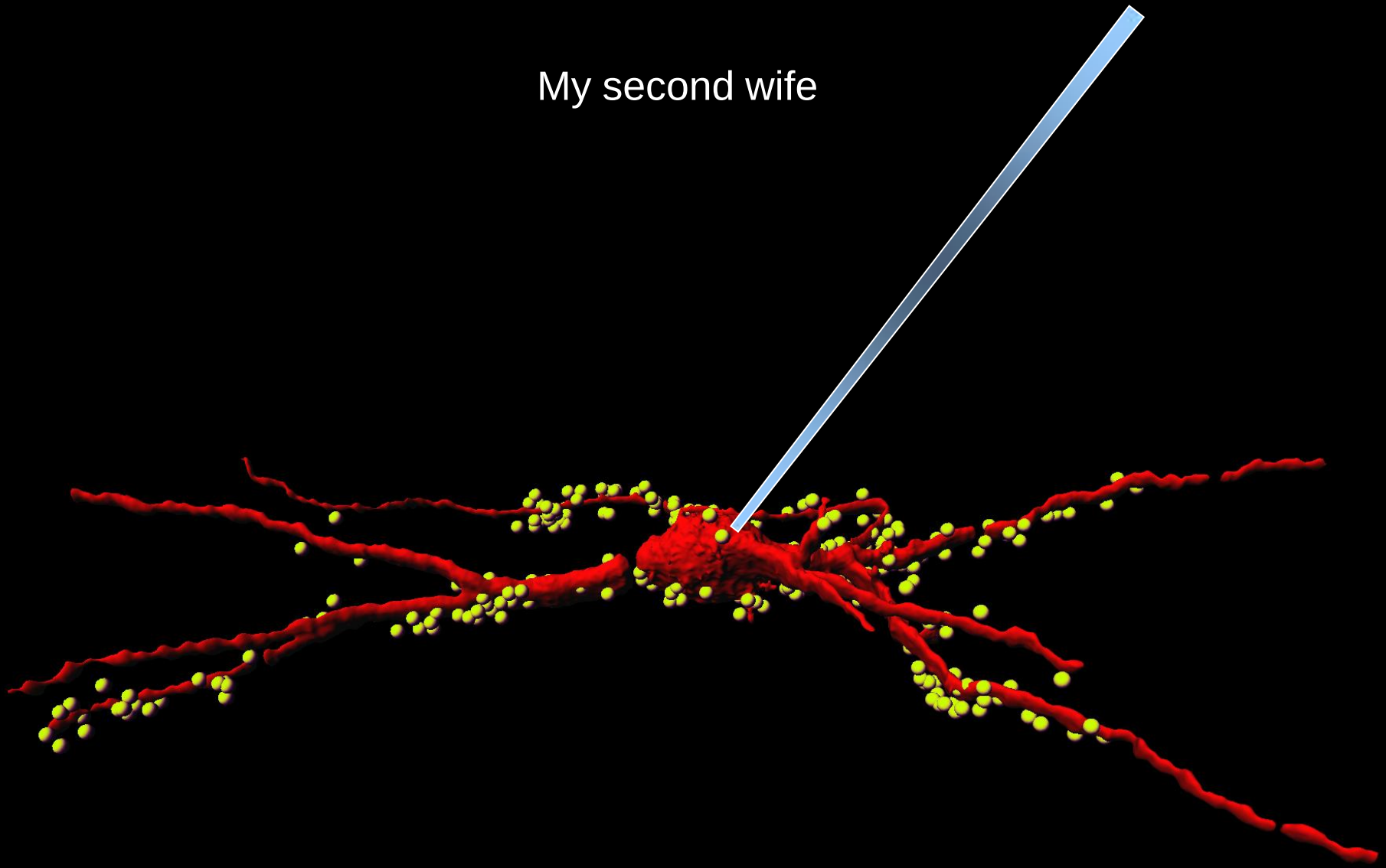
Behaviors produce by cocaine are modulated by dopamine neuron activity

Behavioral sensitization

Cocaine self-administration

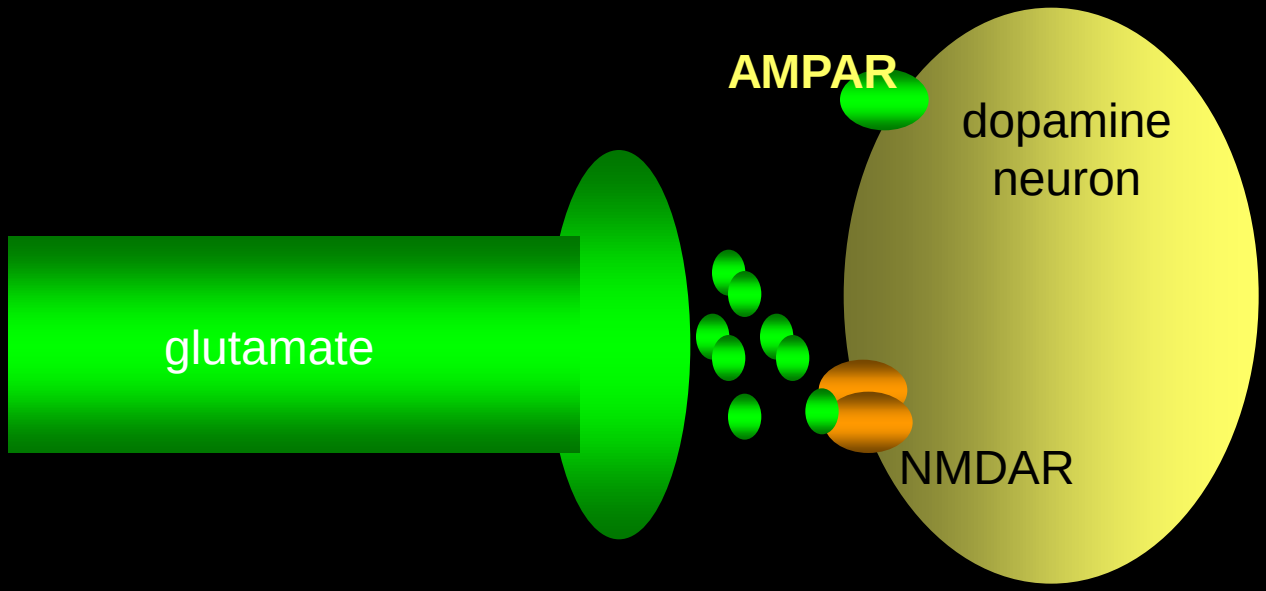
Relapse to cocaine seeking

My second wife

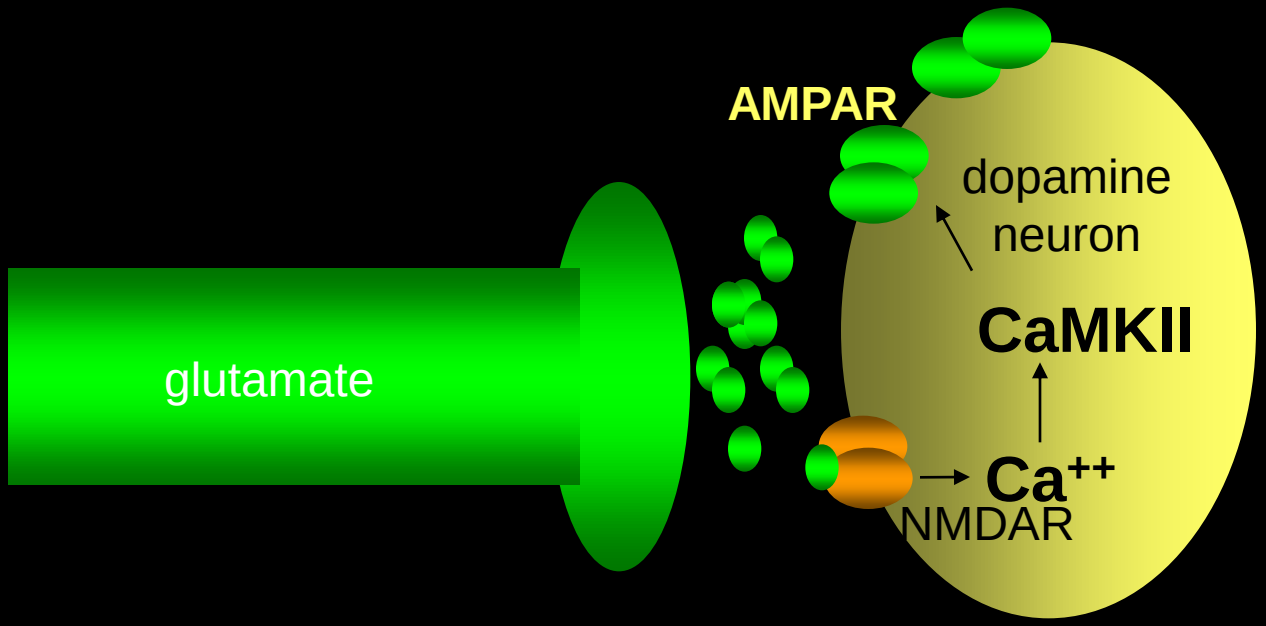


A fundamental cellular model of learning and memory: long-term potentiation (LTP)

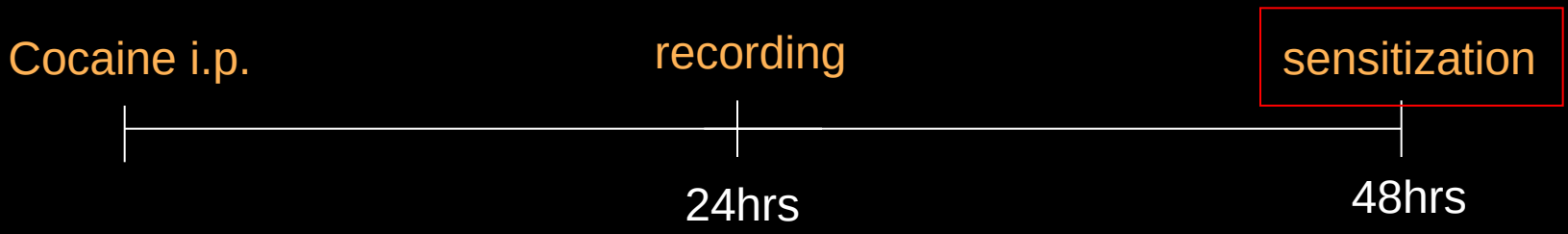
What is LTP?



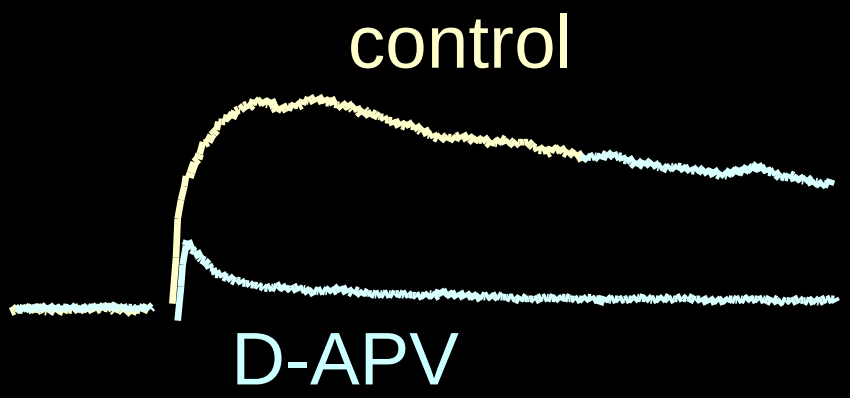
What is LTP?

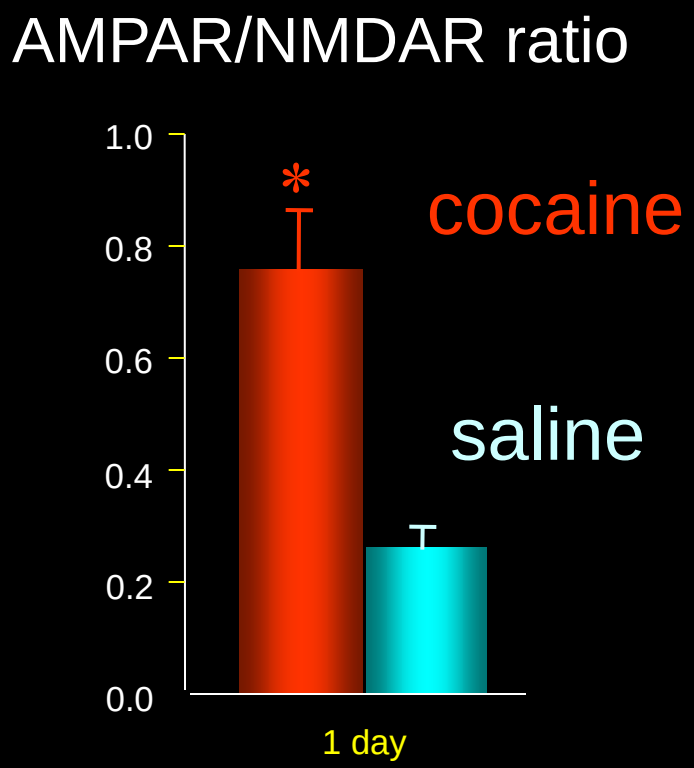


Are drugs of abuse capable of producing LTP?



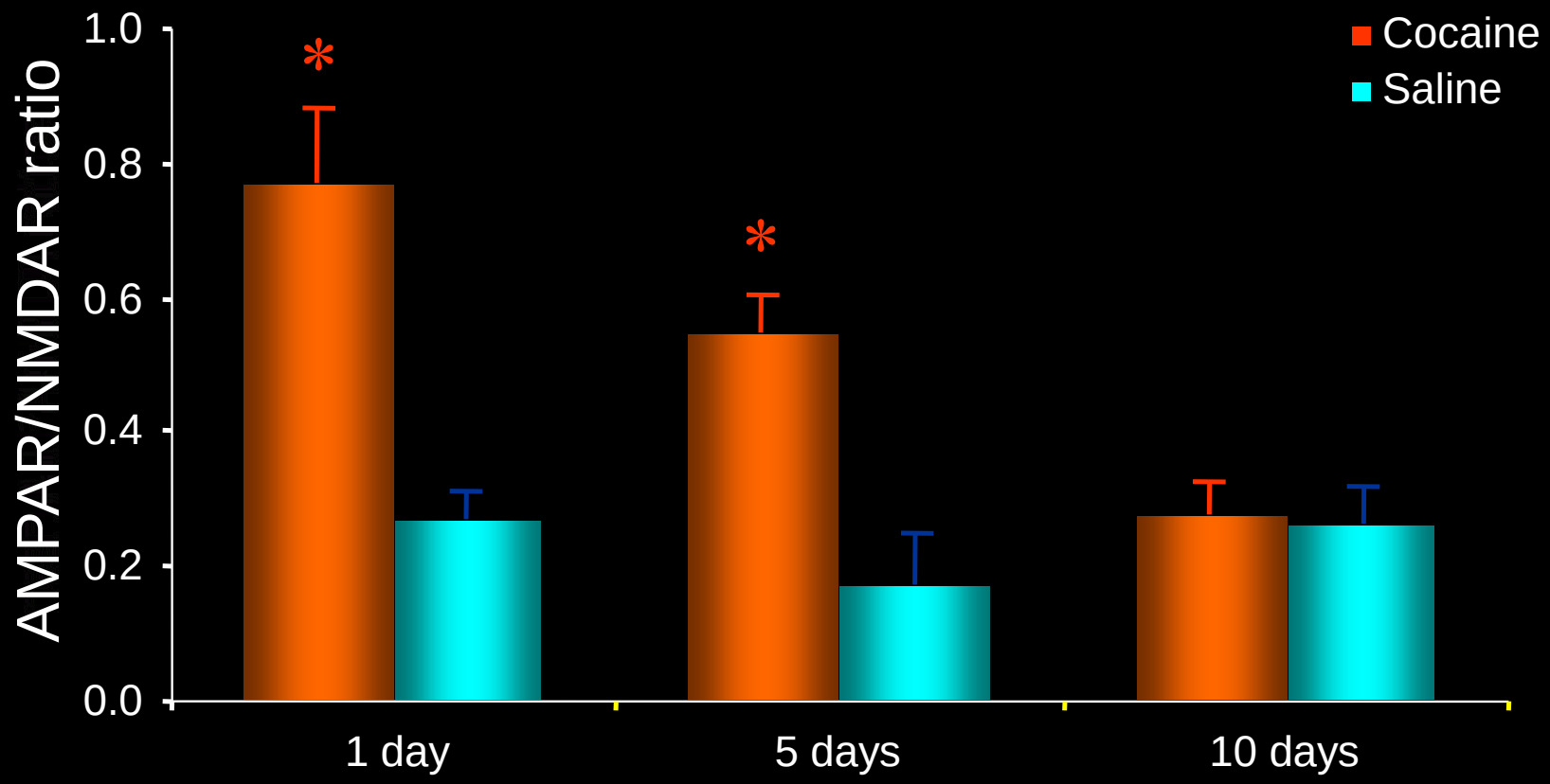
A single injection of cocaine increases the AMPAR/NMDAR ratio and produces LTP of AMPARs





Ungless et al., Nature (2001)

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

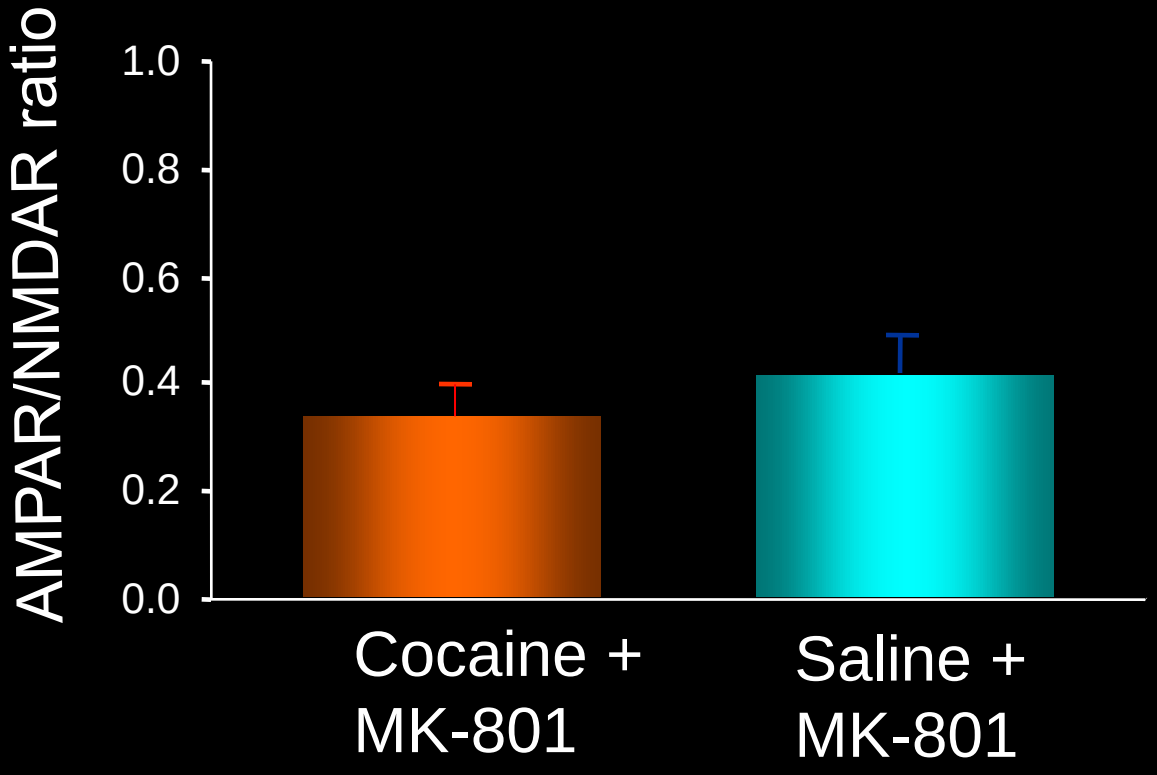


Ungless et al., Nature (2001)

Behavioral sensitization requires NMDAR activation
LTP requires NMDAR activation

May be LTP underlies behavioral sensitization

Co-administration of cocaine + NMDAR antagonist blocks increase of AMPAR/NMDAR ratio and behavioral sensitization

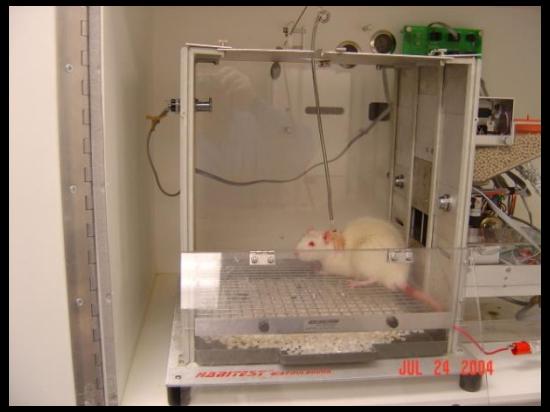


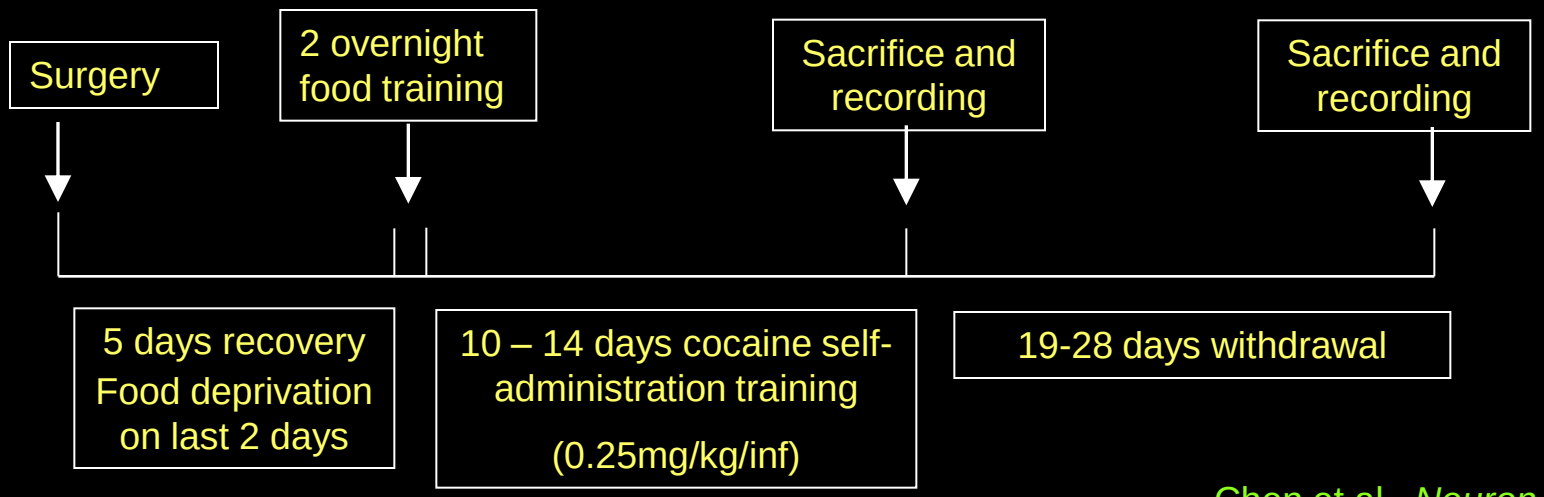
Ungless et al., Nature (2001)

Passive versus active choice of taking cocaine

4) What about cocaine self-administration?

Self-administration training and whole-cell recording schedule

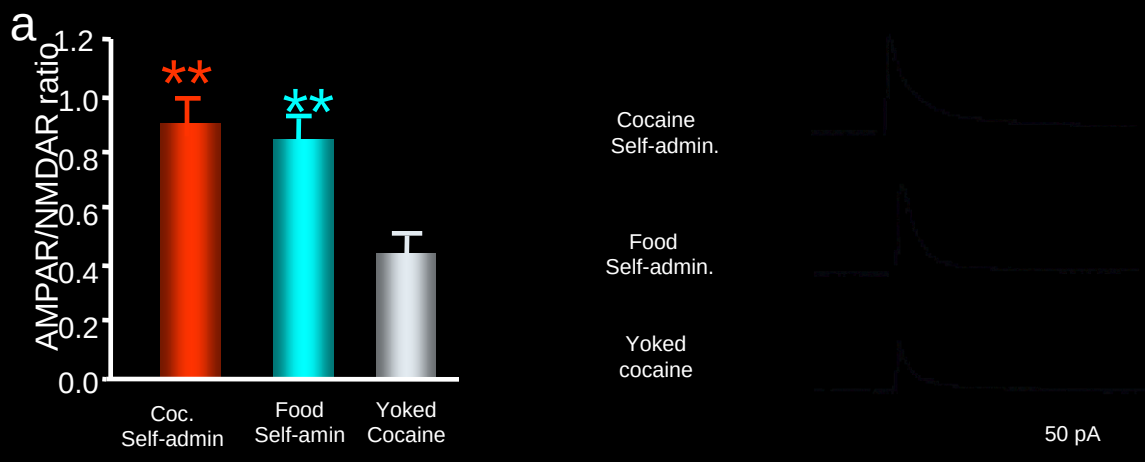




Chen et al., *Neuron (2008)*

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

1 day abstinence

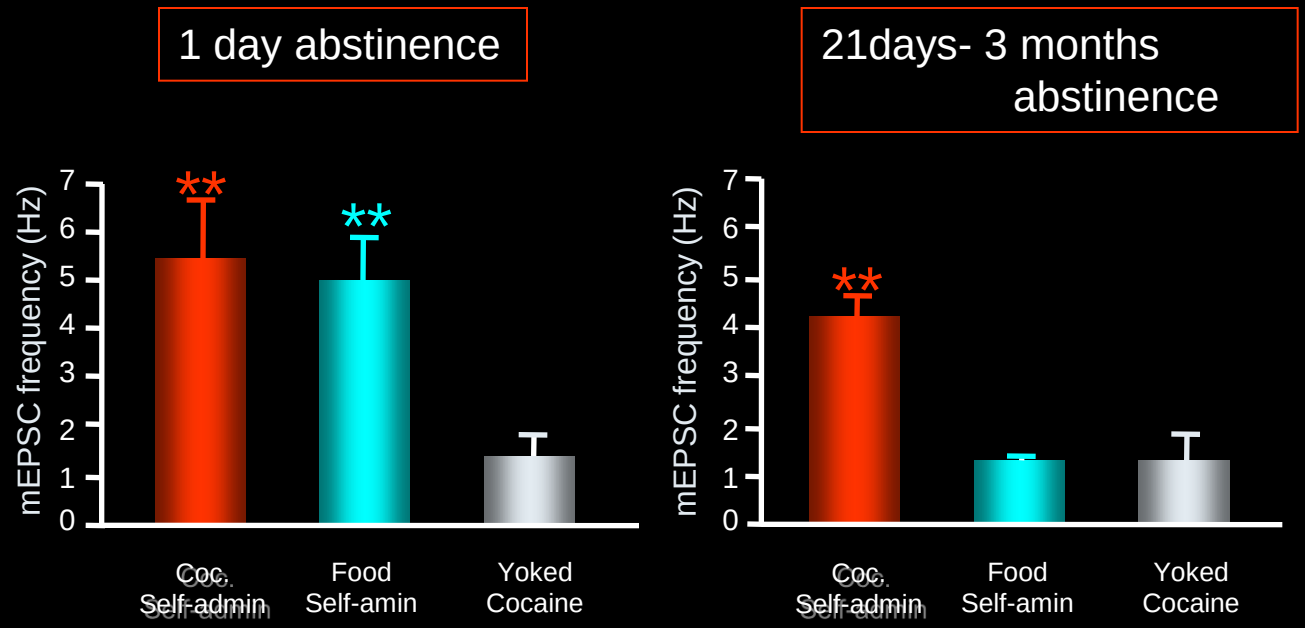


21 days-3 months

of abstinence

Chen et al., *Neuron (2008)*

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

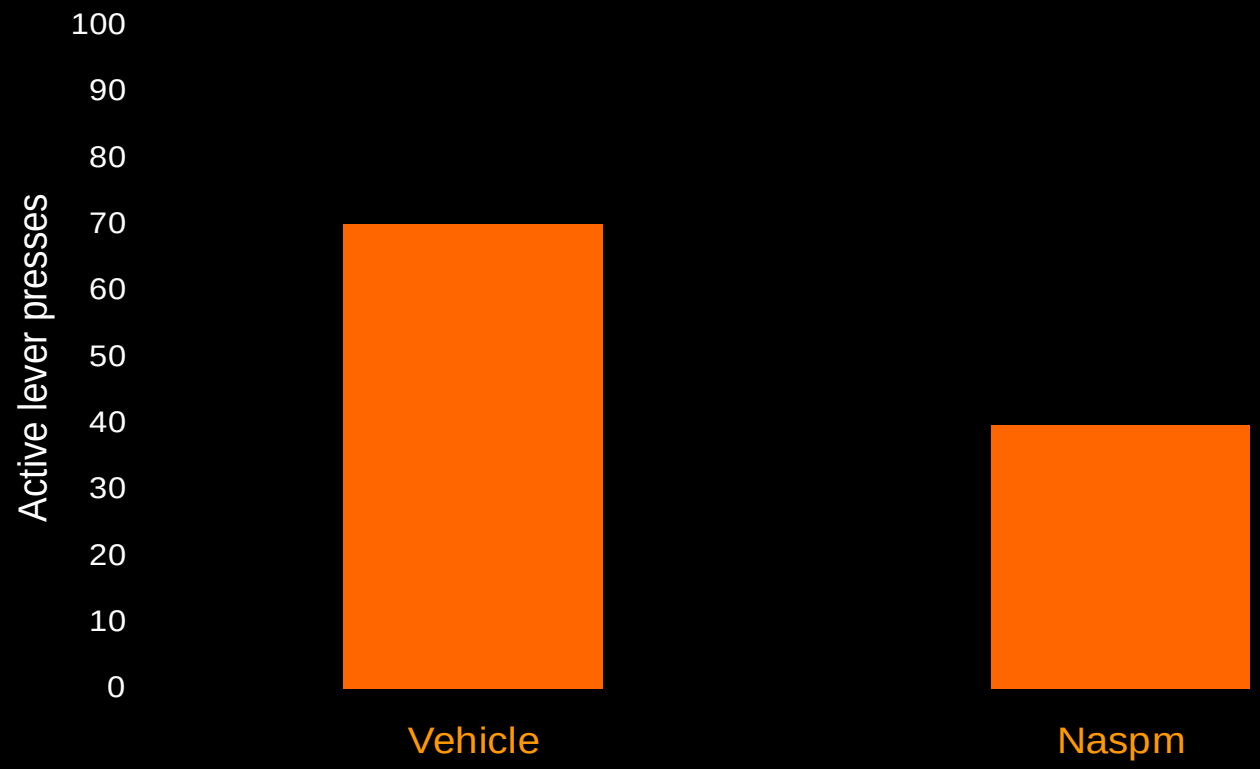


Chen et al., *Neuron (2008)*

Question:

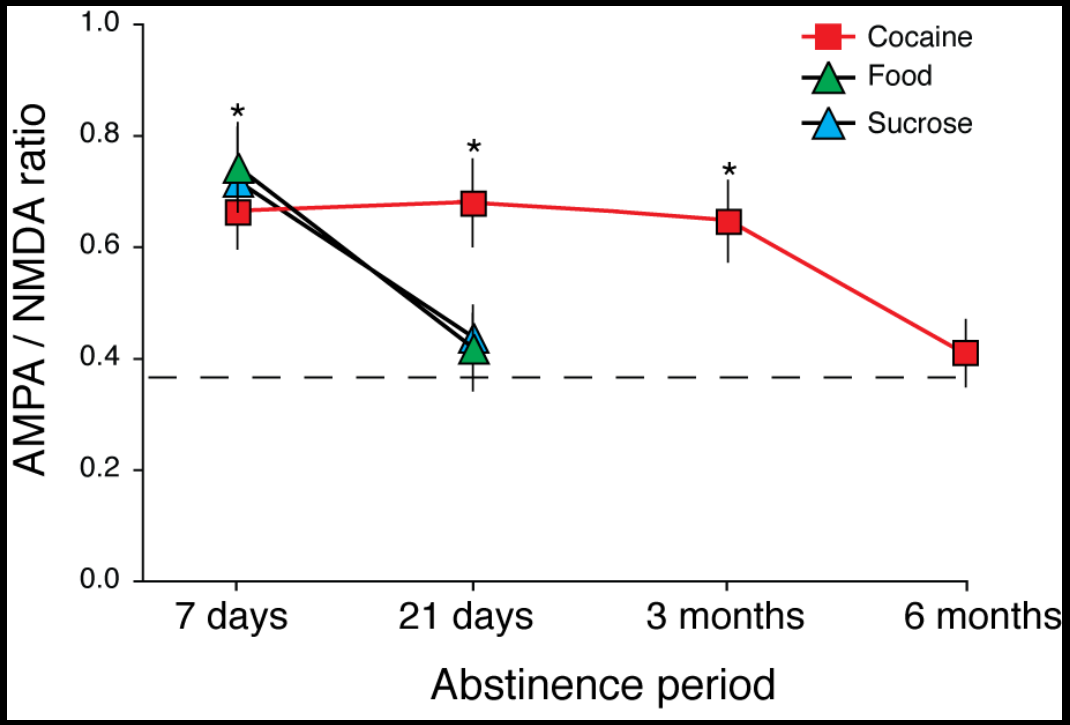
Can we reduce cocaine self-administration and thus synaptic plasticity?

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



Chen et al., in preparation

Cocaine-induced LTP in VTA is long-lasting but not permanent

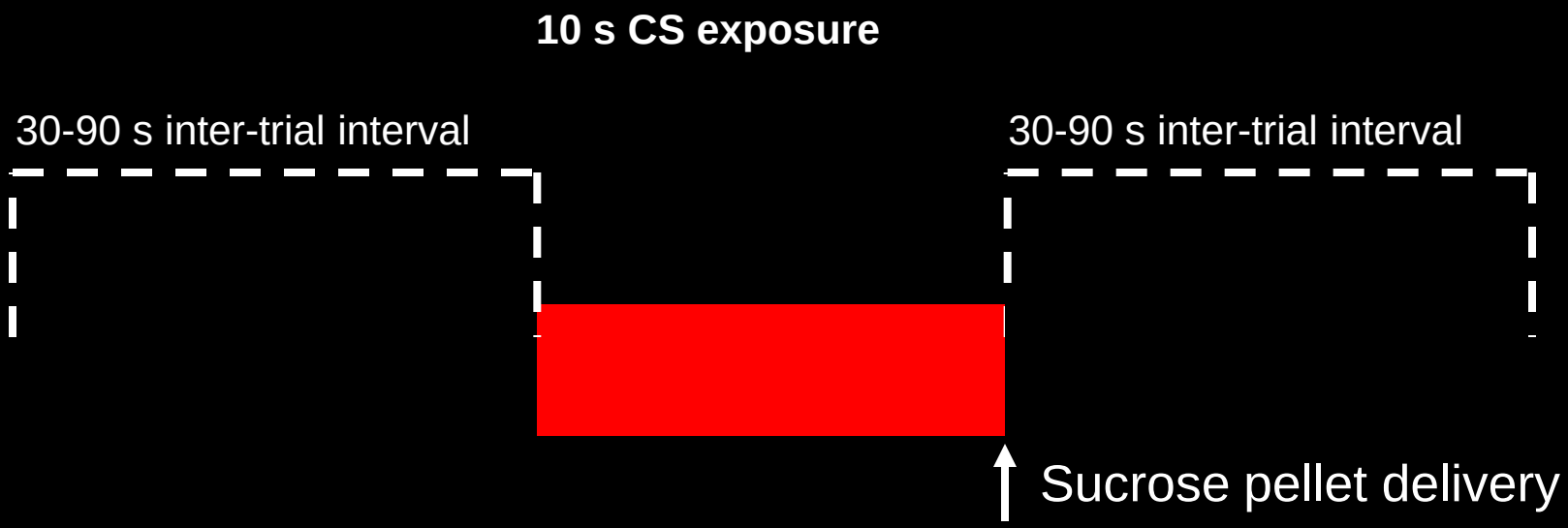


Chen et al., in preparation

Time course of natural reward versus cocaine

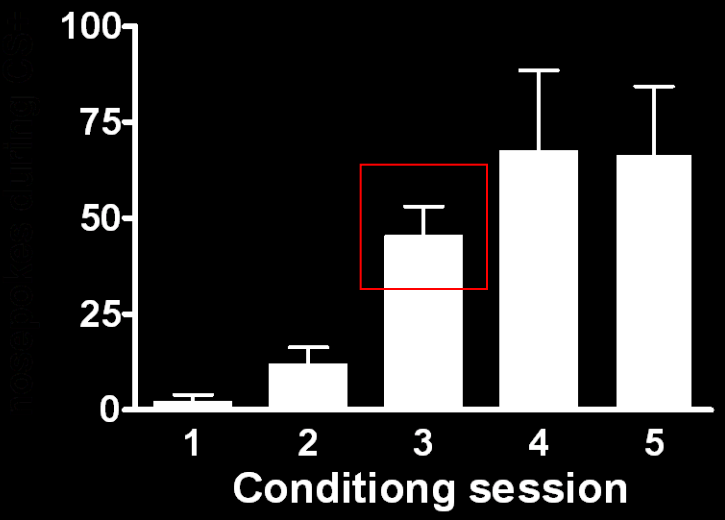
Behavioral Paradigm

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

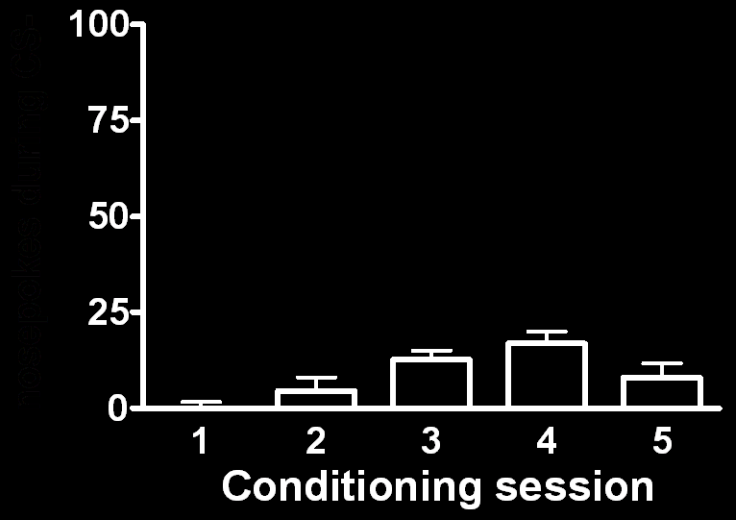


- All rats receive 32 trials per behavioral session
- CS- rats receive the exact same exposure to stimuli and sucrose pellets except pellet delivery is not contingent upon CS presentation.

Cue-reward associations develop gradually over multiple conditioning sessions



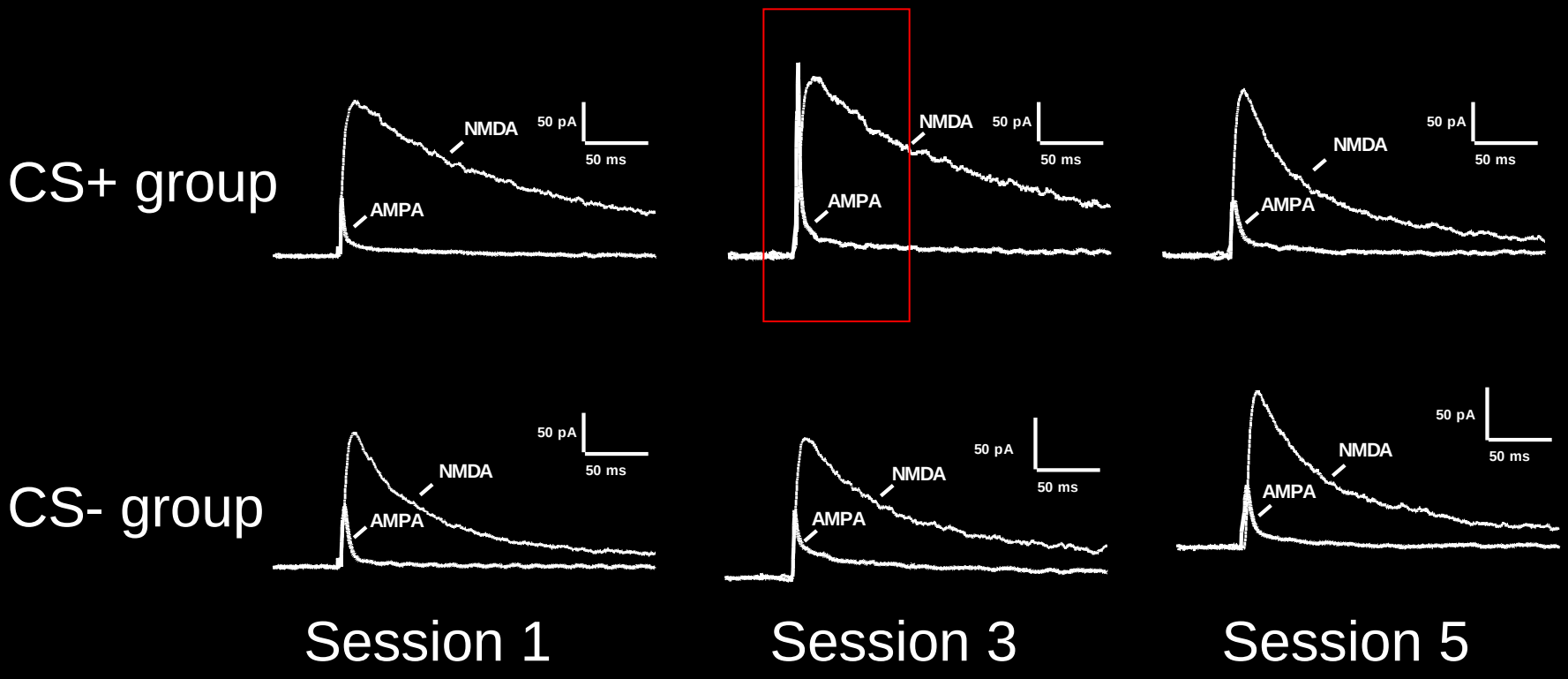
CS+ group



CS- group

Stuber et al., Science (2008)

AMPA/NMDA ratio is transiently elevated during reward learning



Stuber et al., Science (2008)

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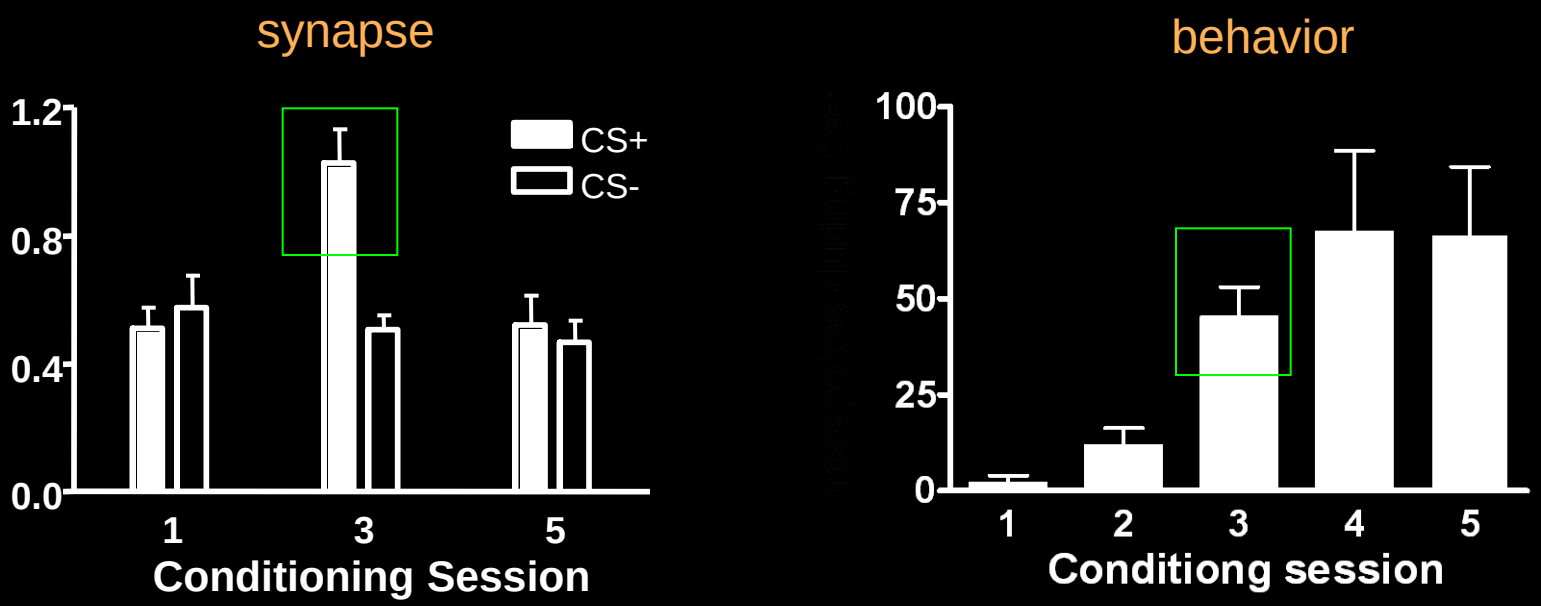
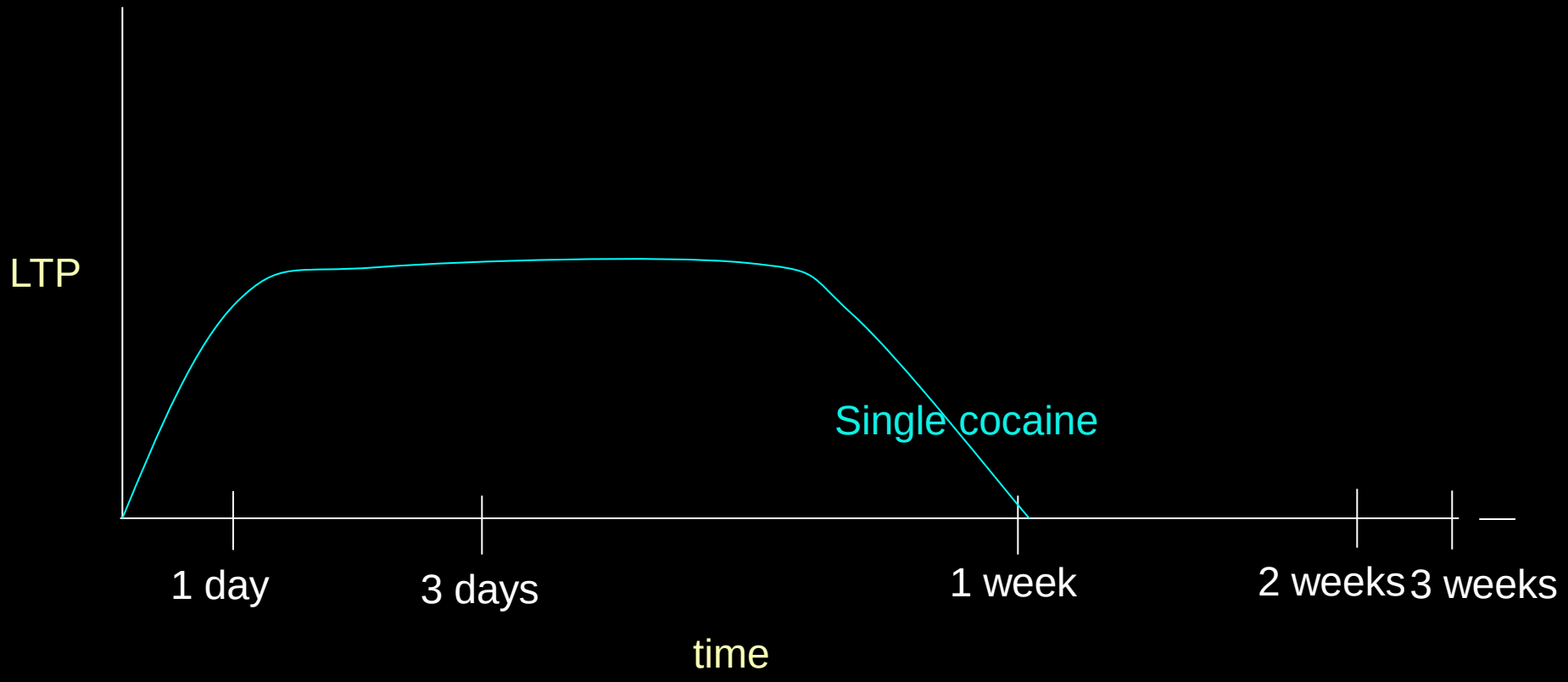
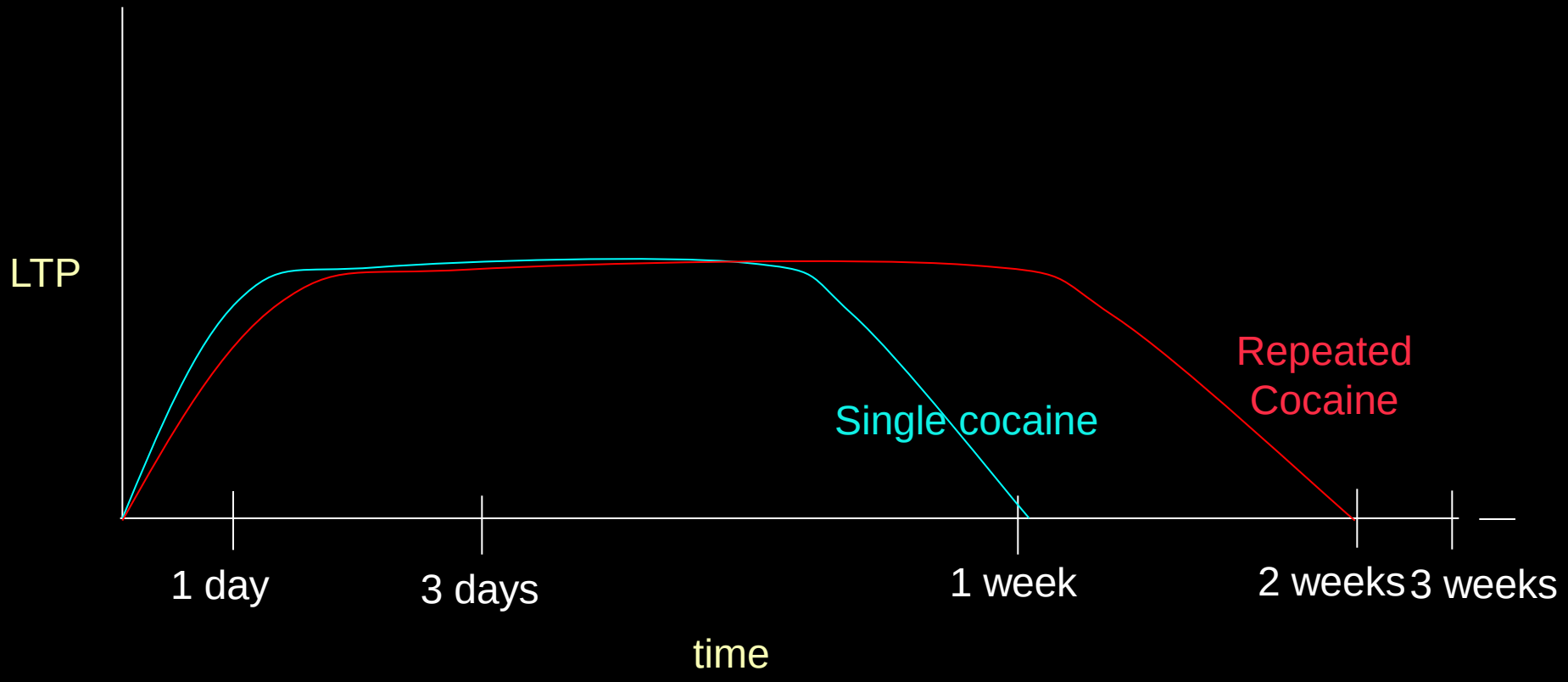


Stuber et al., Science (2008)

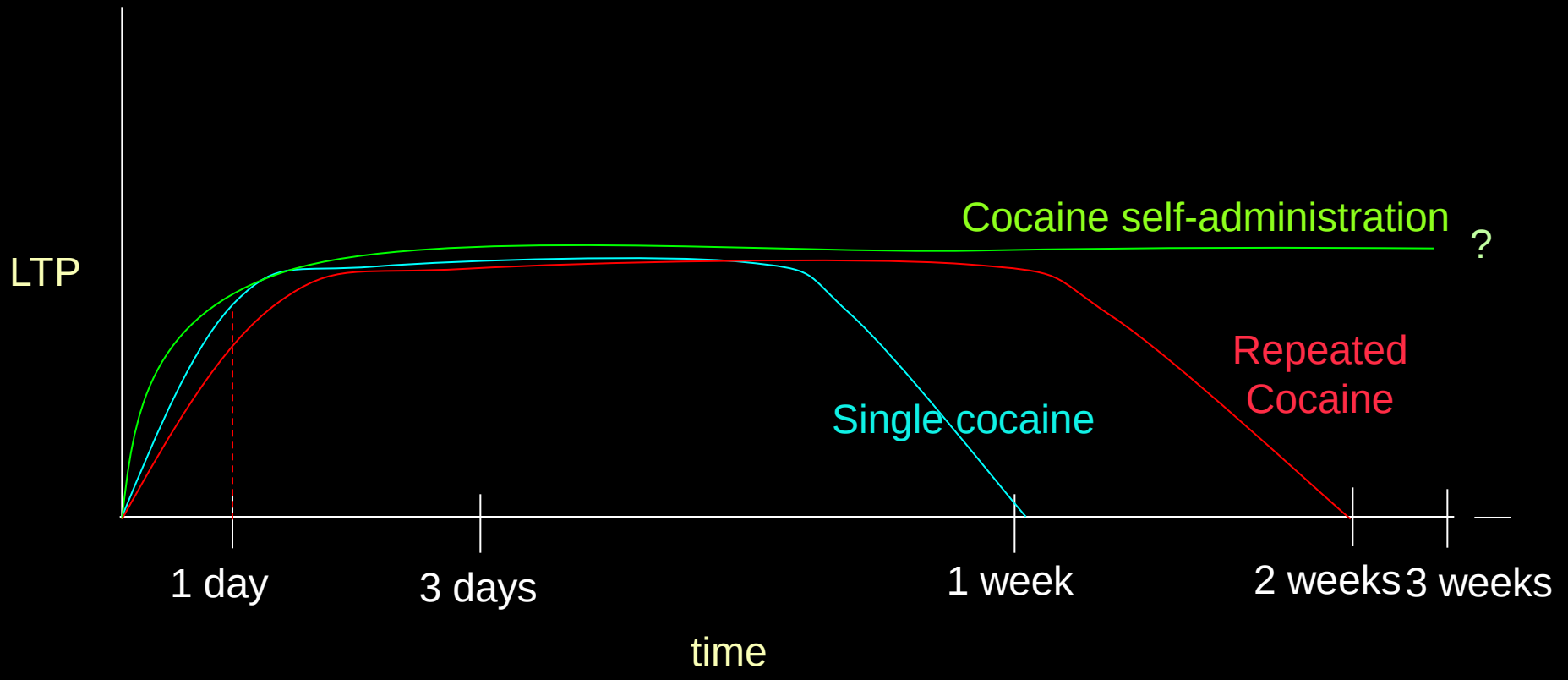
The time course of LTP



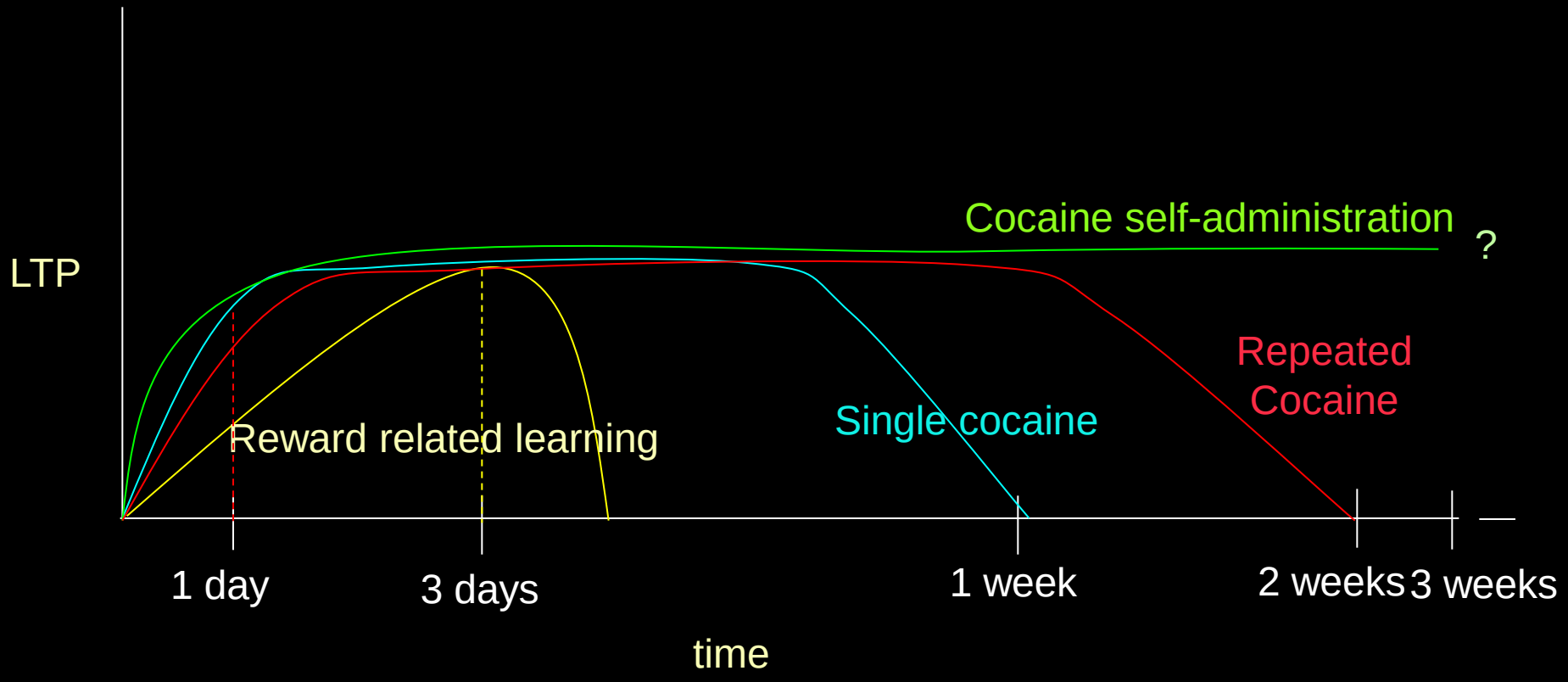
The time course of LTP



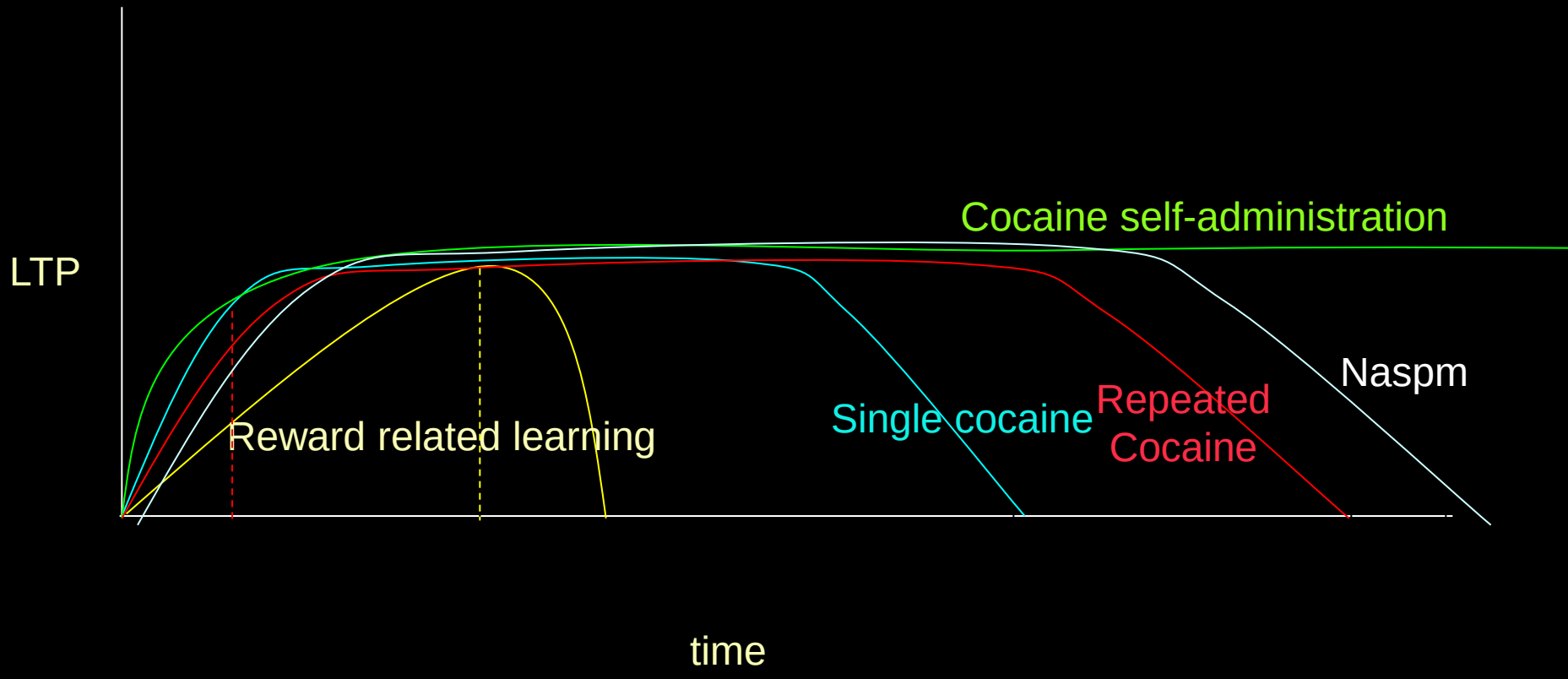
The time course of LTP



The time course of LTP

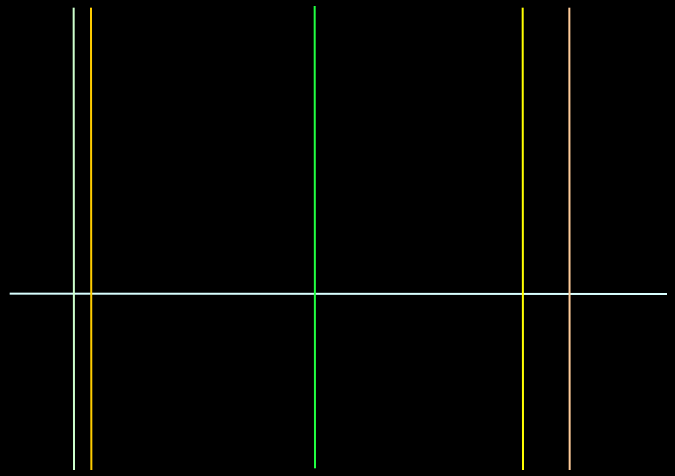


The many faces of LTP in the VTA



How acute cocaine affects DA neuron activity

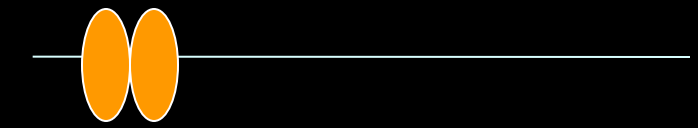
No cocaine



VTA neuron

How cocaine affects DA neuron activity

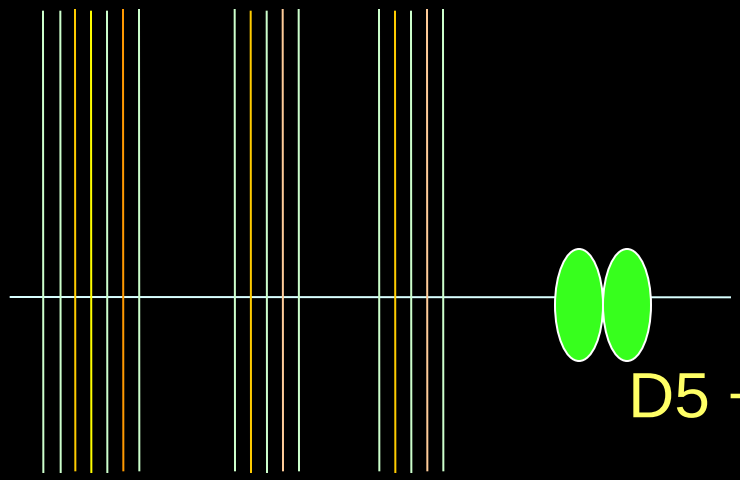
Acute cocaine



VTA neuron

How cocaine affects DA neuron activity

Acute cocaine

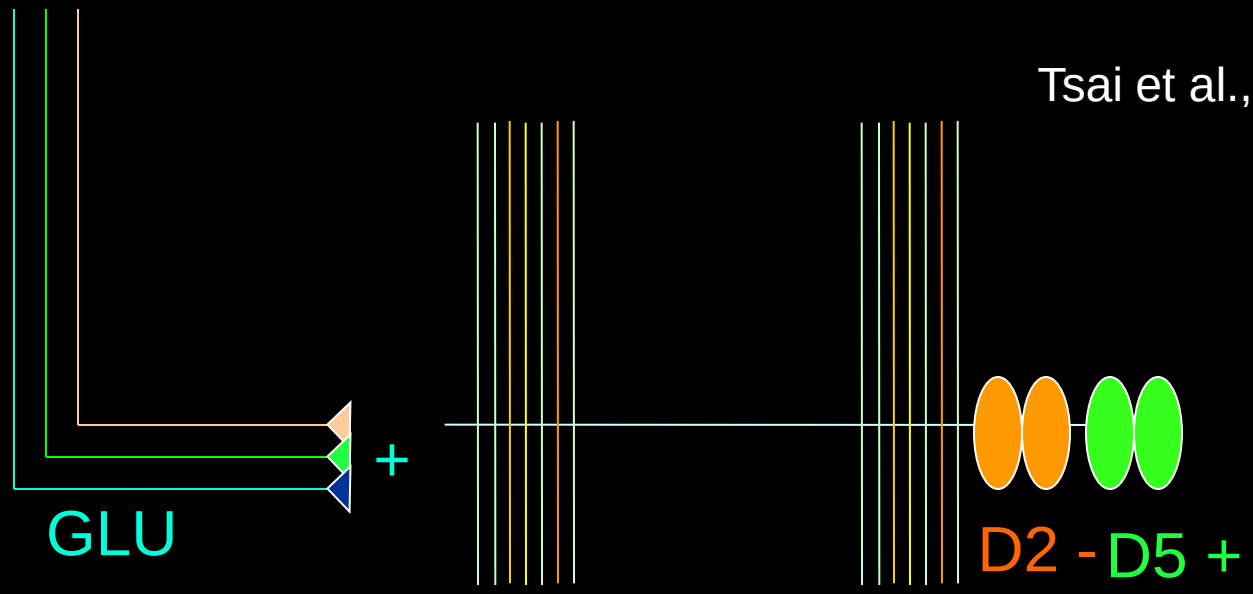


VTA neuron

How cocaine affects DA neuron activity

PFC
PPN
AMY

Acute cocaine

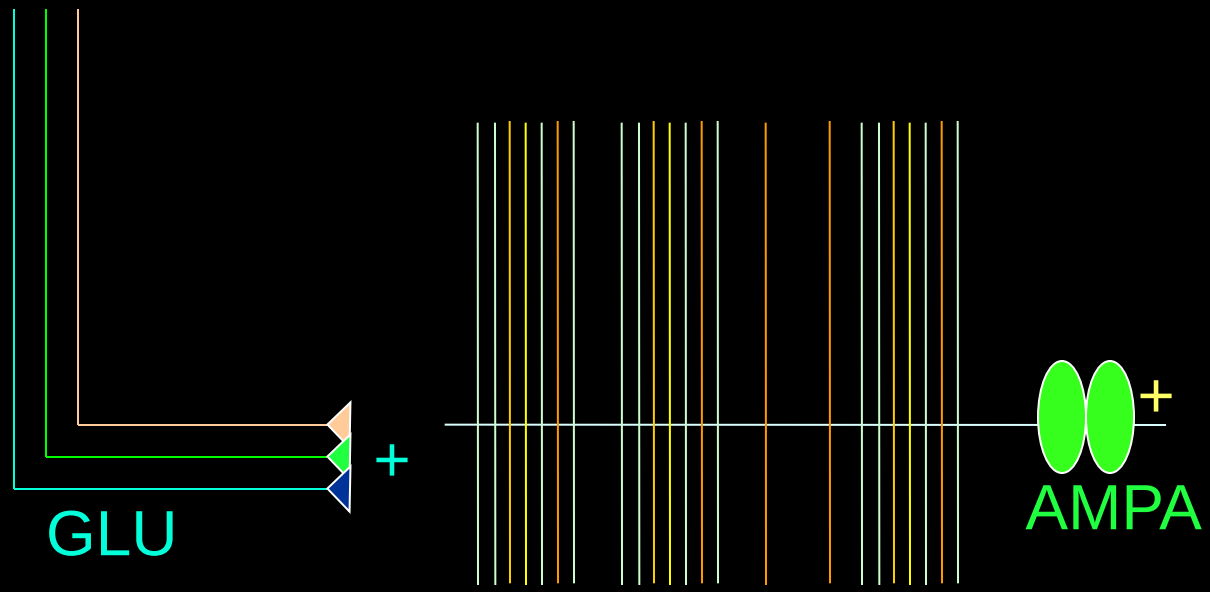


Tsai et al., Science (2009)

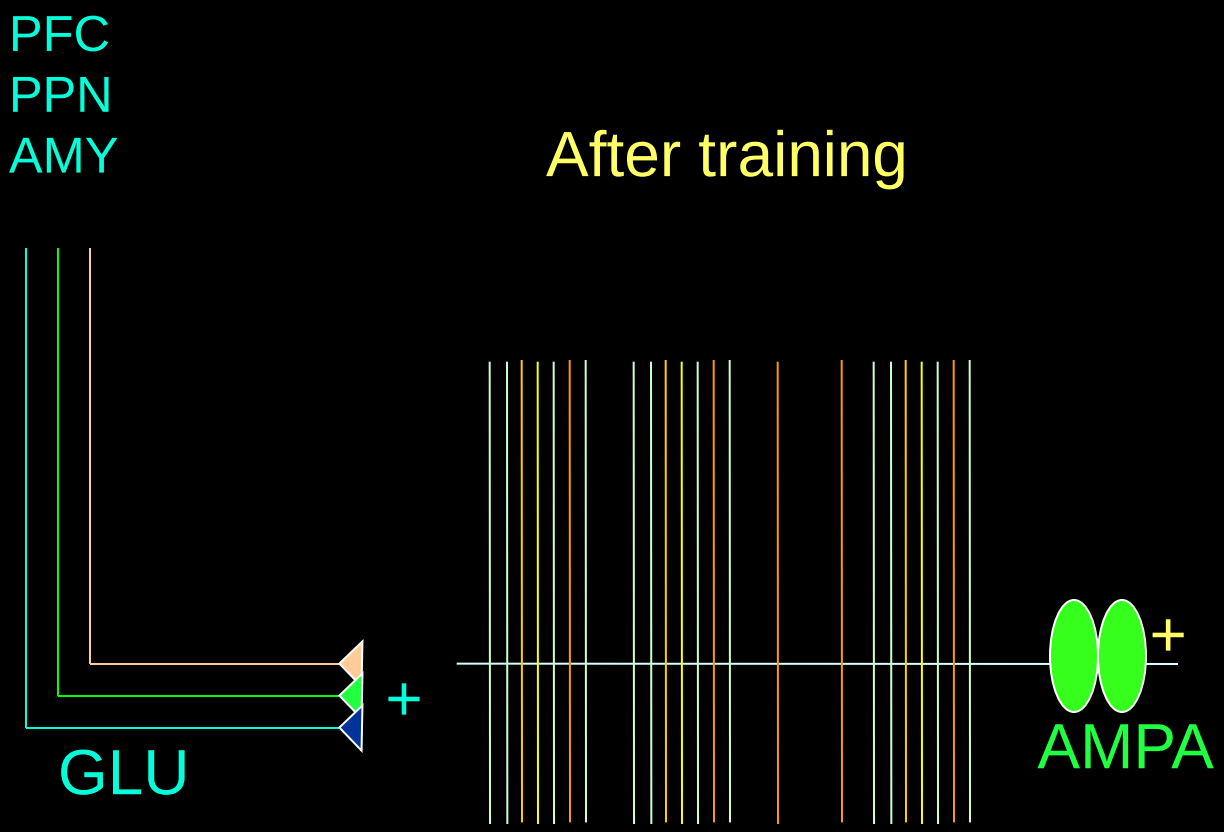
How cocaine affects DA neuron activity

PFC
PPN
AMY

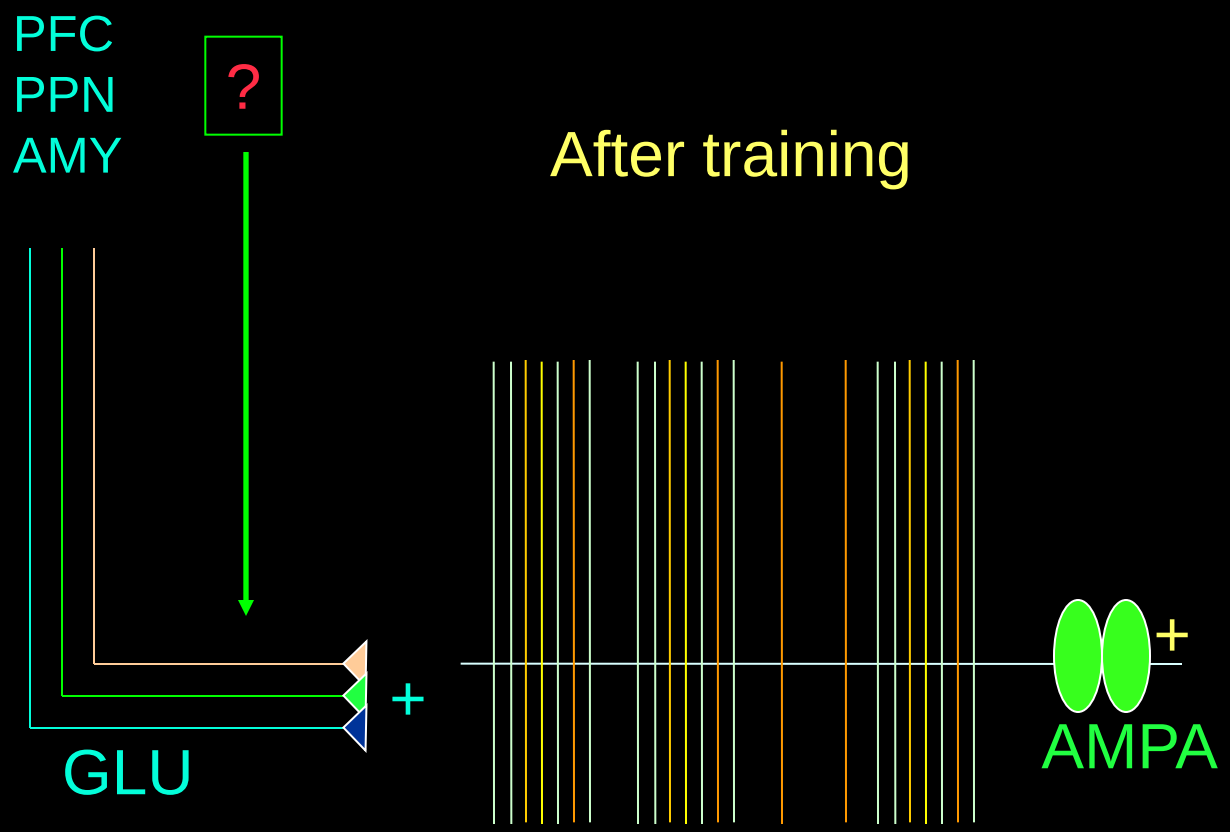
After chronic cocaine



How natural rewards affects DA neuron activity

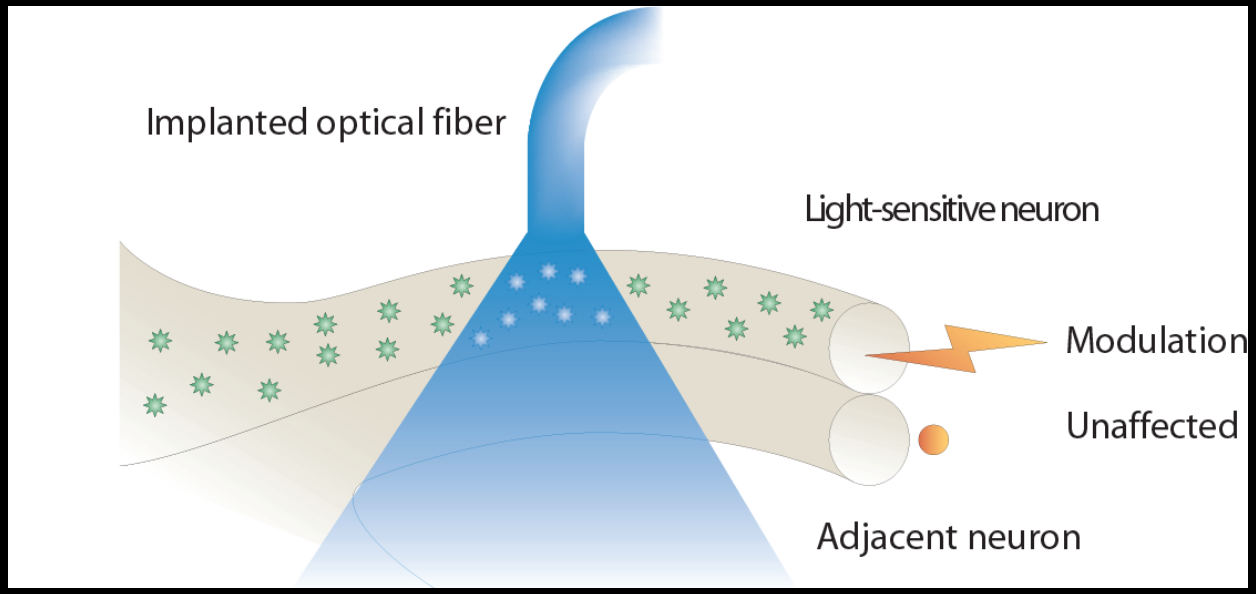


How natural rewards affects DA neuron activity



Optogenetic Neuromodulation

Genetic targeting of neuron subtypes using light-sensitive proteins.

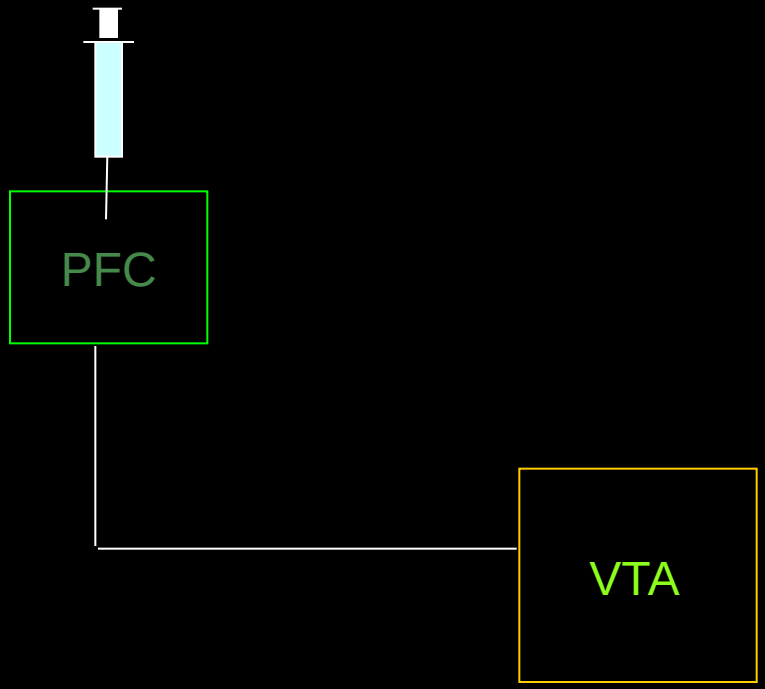


- http://www.stanford.edu/group/dlab/optogenetics/index.html

- Application in rodent models
- Targeted expression in specific cell types

Feng Zhang, KD lab

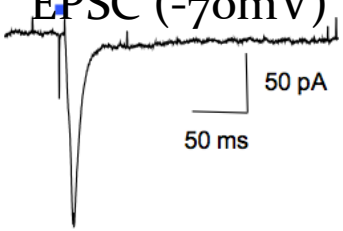
ChR2 expressing neurons can provide an answer



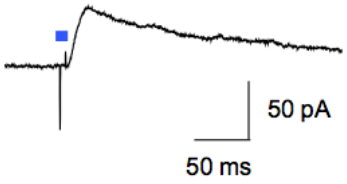
Garret Stuber, Feng Zhang

EPSCs can be readily evoked by light at accumbens and VTA synapses

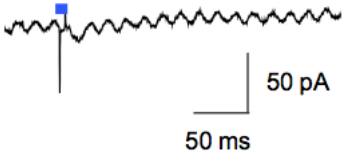
AMPAR-mediated EPSC (-70mV)



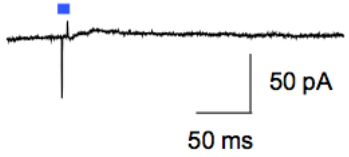
NMDAR-mediated EPSC (+40mV)



Blocked by 10 µM CNQX



Blocked by 50 µM AP5



Garret Stuber, Emanuela Argilli, Wieke Van Leeuwen, Manouk Baches

Conclusions

-*in vivo* exposure to cocaine produces LTP in VTA DA neurons

- Voluntary versus passive drug exposure produces longer lasting LTP

-Longer time course of cocaine LTP versus natural rewards

-AMPAR antagonists as therapeutic agents against cocaine consumption

Conclusions

- Long-term potentiation (LTP) is a long-lasting increase in synaptic activity

- LTP represents a fundamental cellular phenomenon underlying normal learning and memory processes

- A single cocaine exposure produces LTP, lasting about a week

-Natural rewards (food, sucrose) produce short-lasting LTP (1-3 days)

-Cocaine self-administration produces persistent LTP in dopamine neurons (3 months)

Acknowledgements

Lab Members

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Bob Messing
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