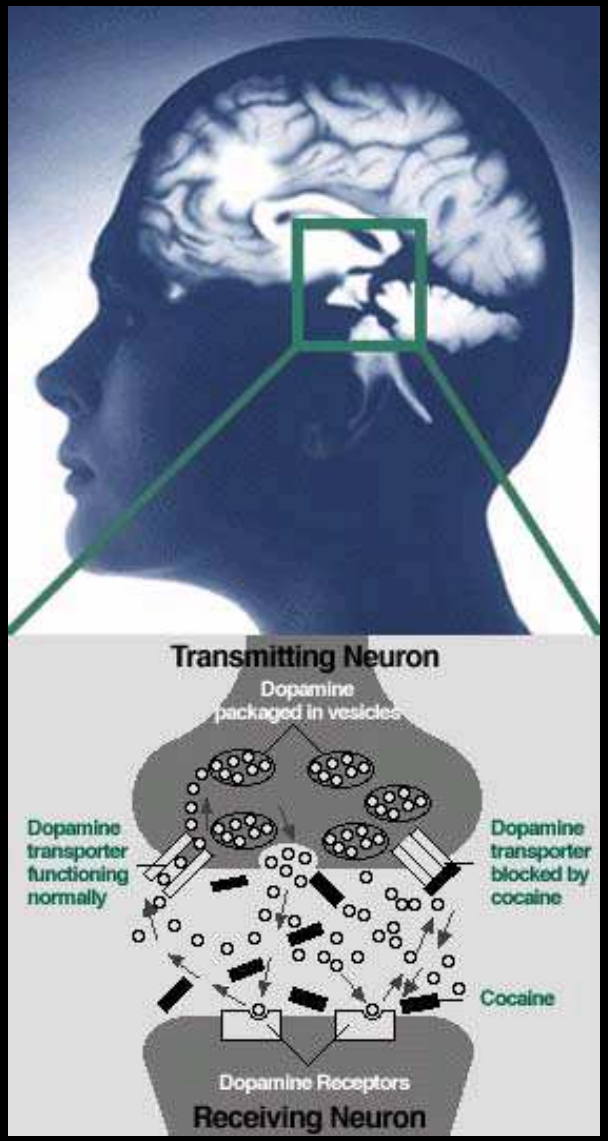
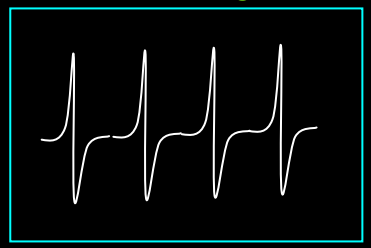
cocaine: from animal models to pharmaceutical targets

Antonello Bonci, M.D.
Gallo Center and Department of Neurology
UCSF, San Francisco, CA

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

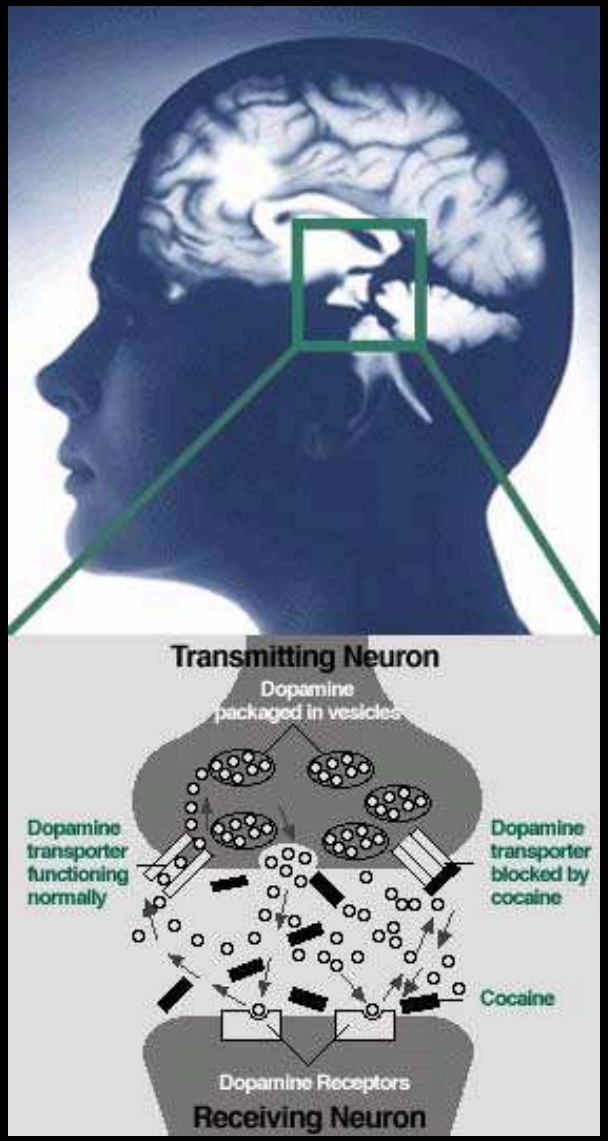


Genetic background

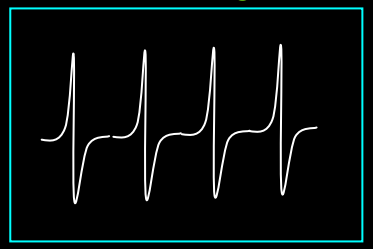


Environmental stimuli

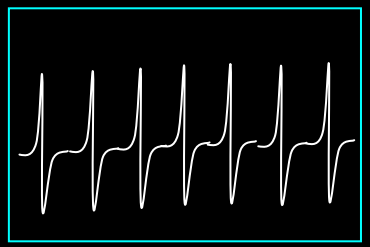
A simple hypothesis:
Any addictive behavior depends on changes in electrical activity of specific brain regions



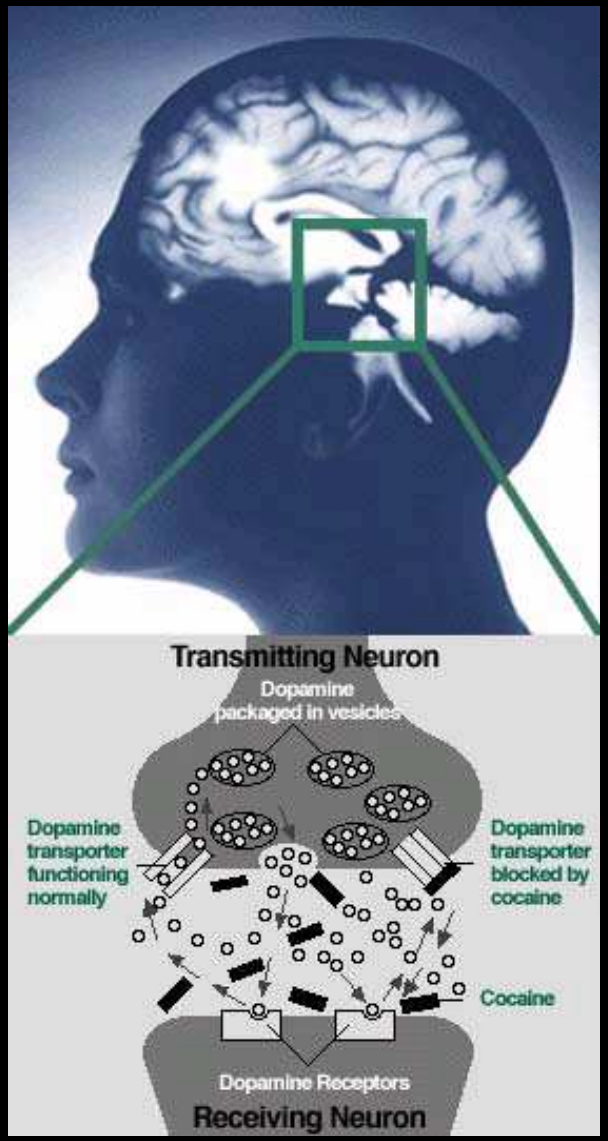
Genetic background



Environmental stimuli



The hypothesis:
Addictive behaviors depend on changes in electrical activity of specific brain regions



Genetic background

Environmental stimuli

Substance abuse

Why dopamine neurons?

Addiction

Apathy

Aggressive behaviors

Sexual, appetitive behaviors

Parkinson’s disease

Schizophrenia

Working memory

Depression

Reward Deficiency Syndrome

ADHD

Dementias

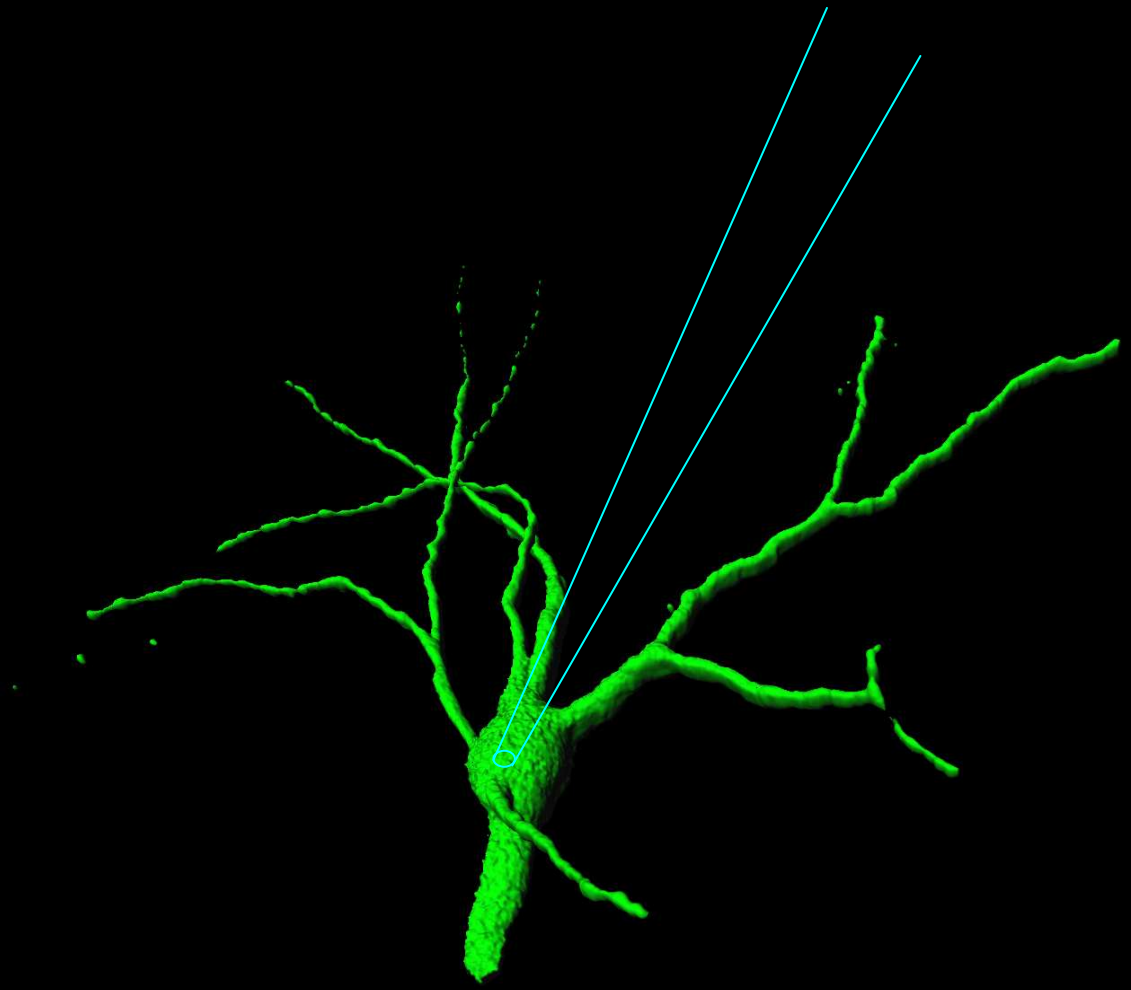
Behaviors produce by cocaine are modulated by dopamine neuron activity

Behavioral sensitization

Cocaine self-administration

Relapse to cocaine seeking

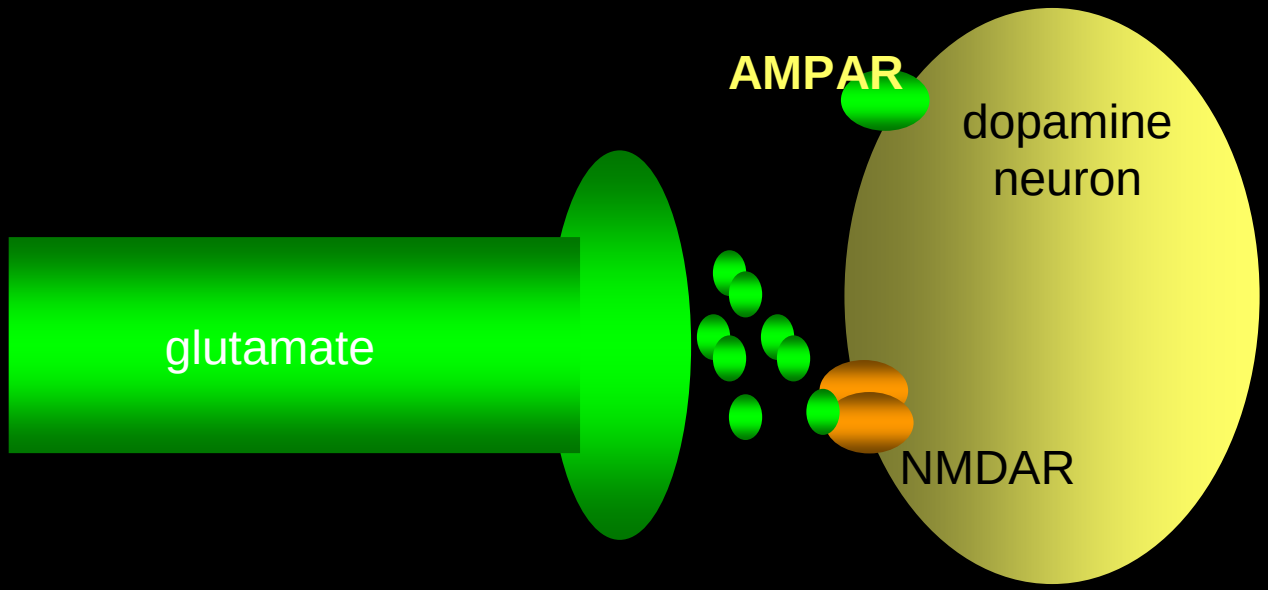
The approach: whole cell patch clamp recordings



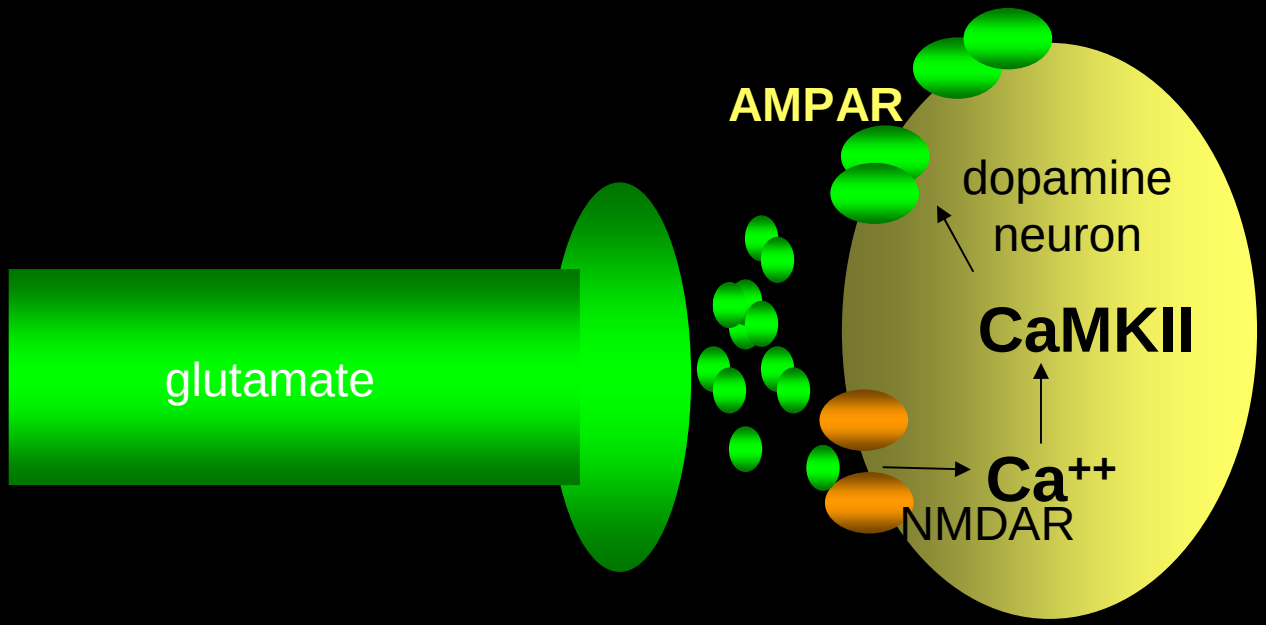
VTA dopamine neuron rendered in 3D

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

What is LTP?



What is LTP?

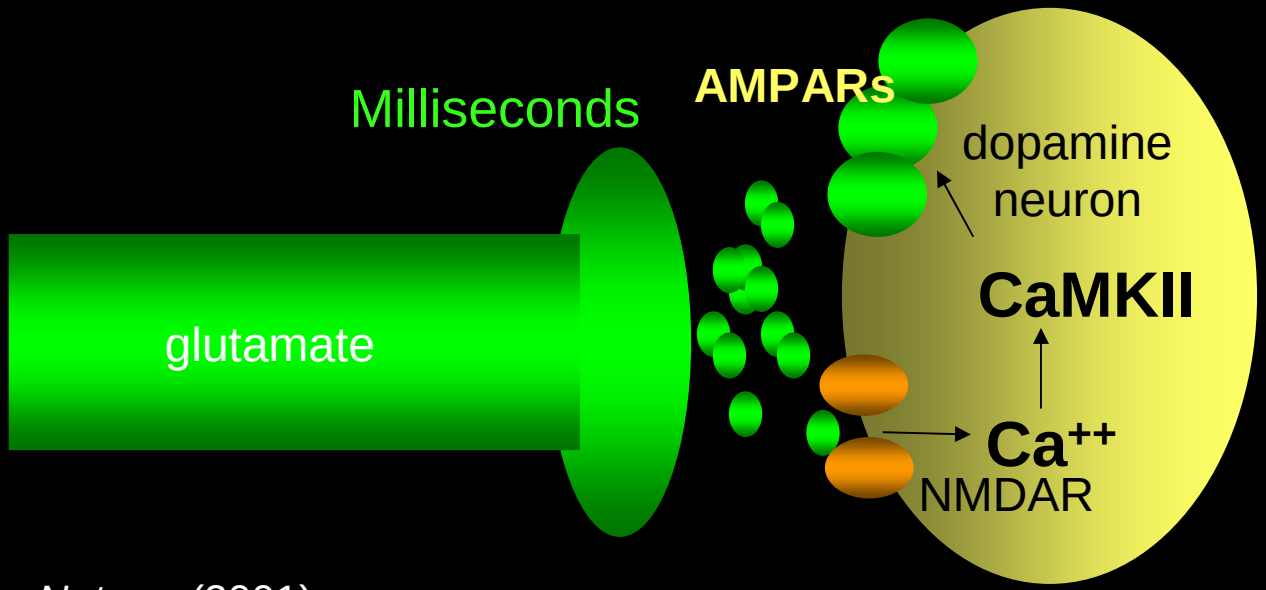


Why LTP?

Hours, days, months

versus

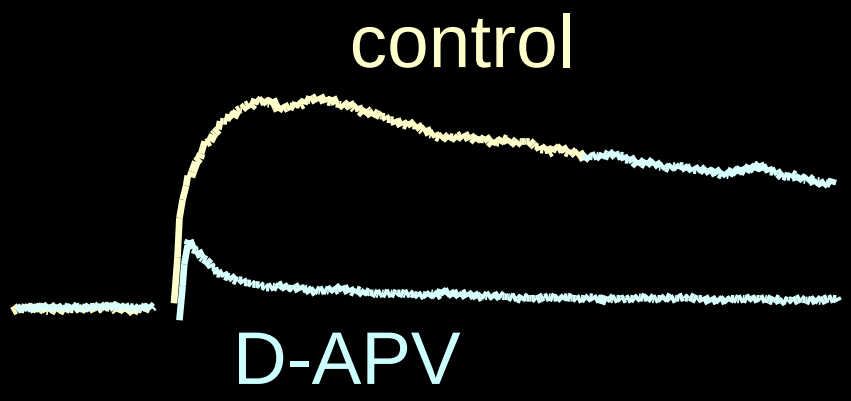
Milliseconds

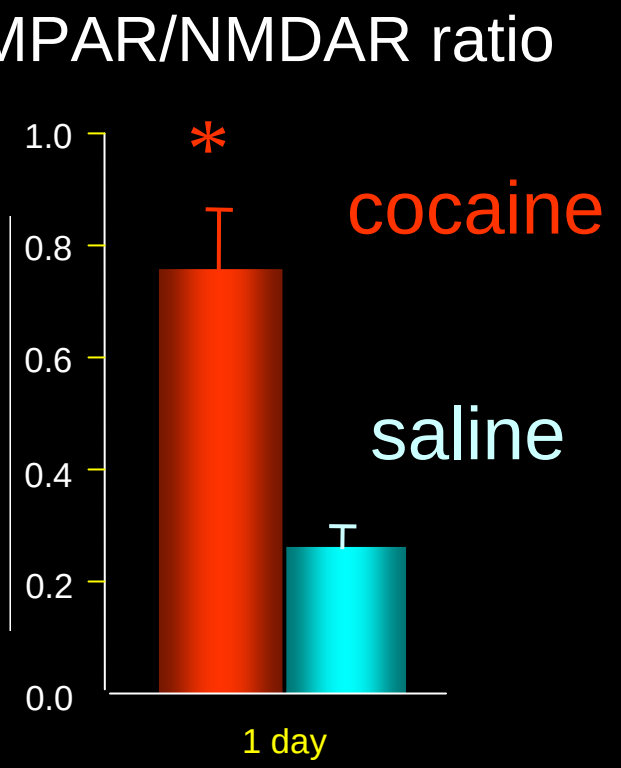


Ungless et al., *Nature* (2001)
Ungless et al., *Neuron* (2003)
Borgland et al. *J Neurosci* (2004)
Borgland et al., *Neuron* (2006)
Miquel et al., *Nature Neurosci* (2006)
Schilstrom et al., *J Neurosci* (2006)
Chen et al., Neuron (2008)
Stuber et al., Science (2008)

Are drugs of abuse capable of producing LTP?

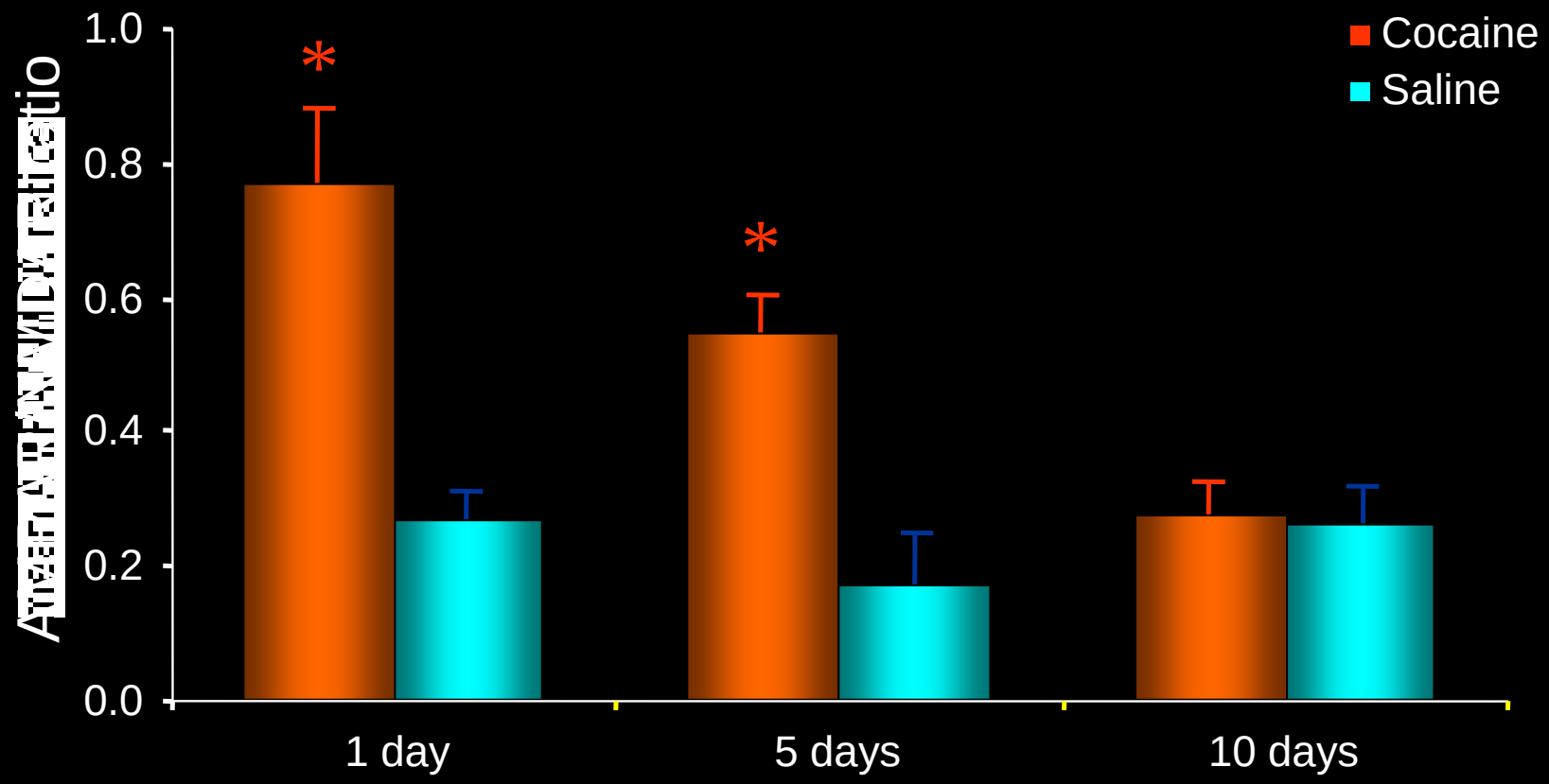
A single injection of cocaine produces a cellular memory





Ungless et al., Nature (2001)

Synaptic plasticity is long-lasting

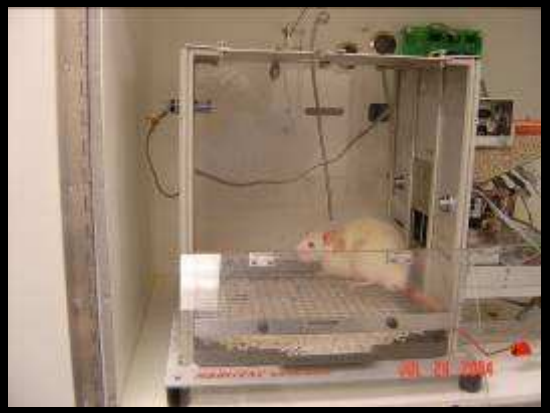


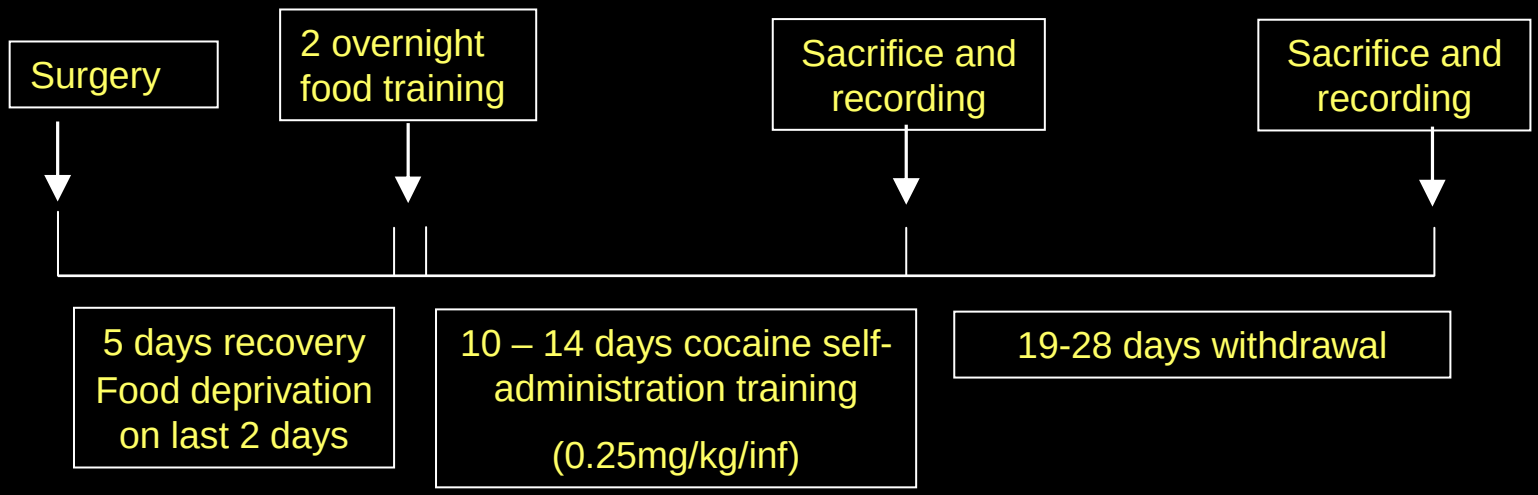
Ungless et al., Nature (2001)

Passive versus active choice of taking cocaine

4) What about cocaine self-administration?

Self-administration training and whole-cell recording schedule

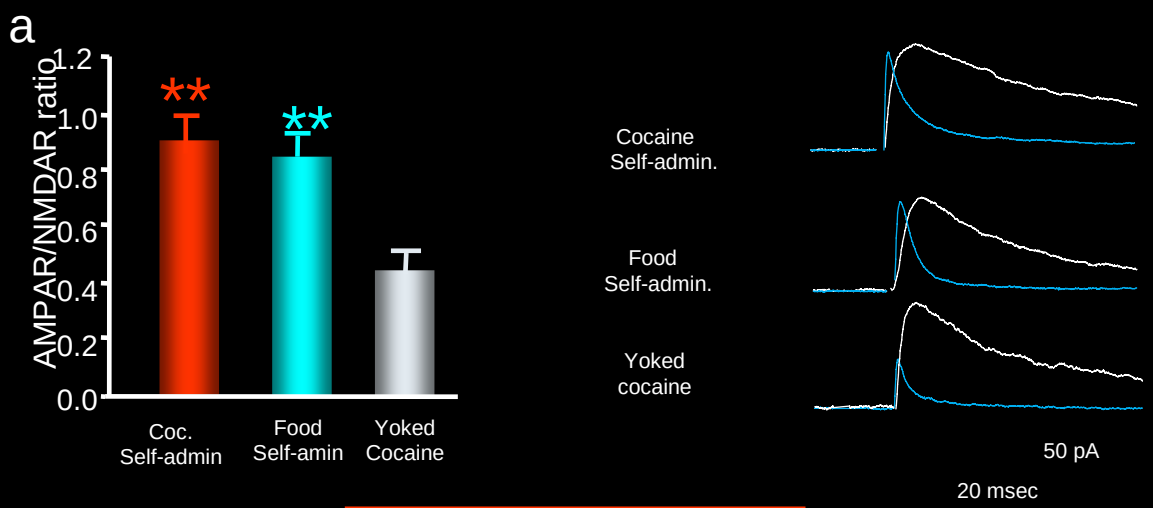




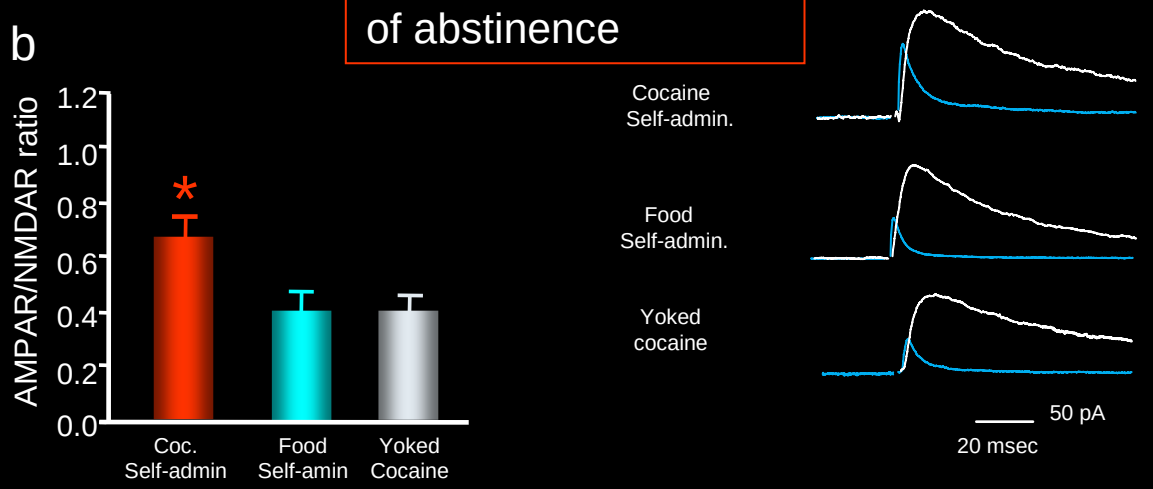
Chen et al., *Neuron (2008)*

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

1 day abstinence

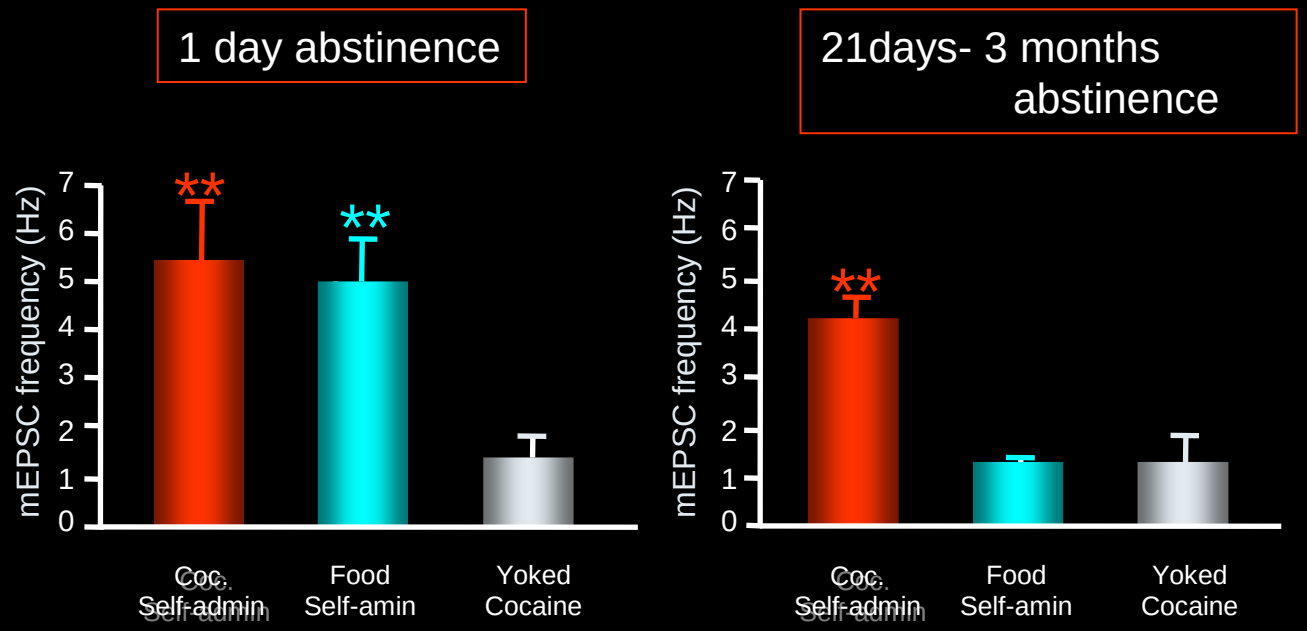


21 days-3 months of abstinence



Chen et al., *Neuron (2008)*

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

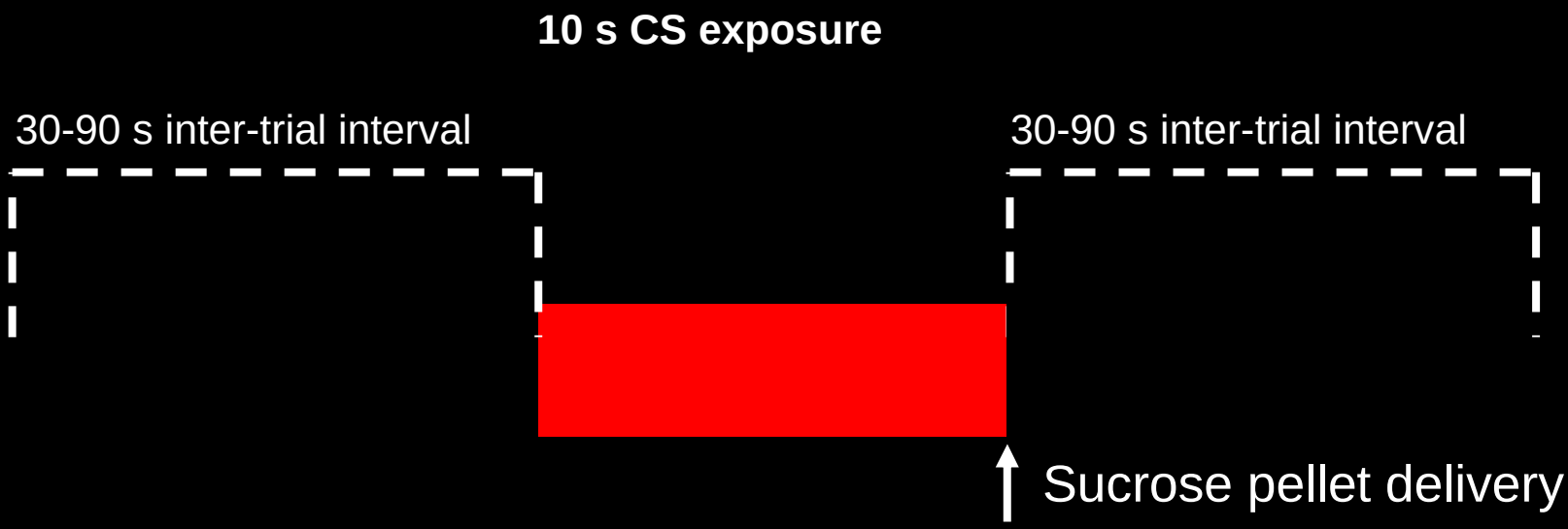


Chen et al., *Neuron (2008)*

Time course of natural reward versus cocaine

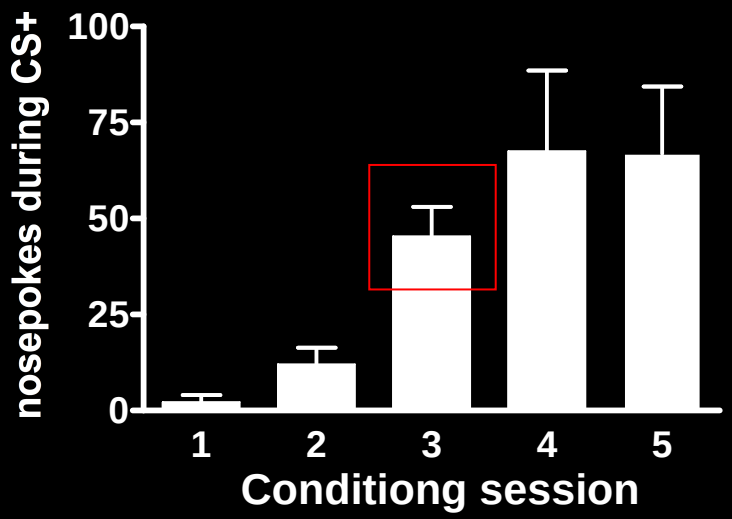
Behavioral Paradigm

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

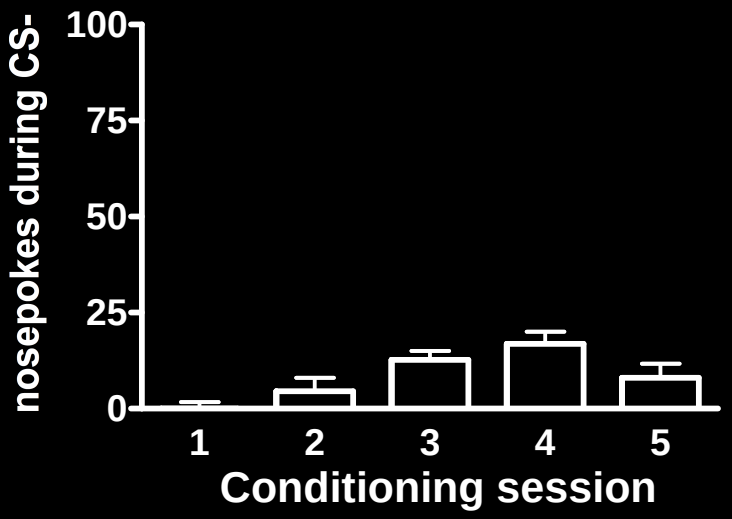


- All rats receive 32 trials per behavioral session
- CS- rats receive the exact same exposure to stimuli and sucrose pellets except pellet delivery is not contingent upon CS presentation.

Cue-reward associations develop gradually over multiple conditioning sessions



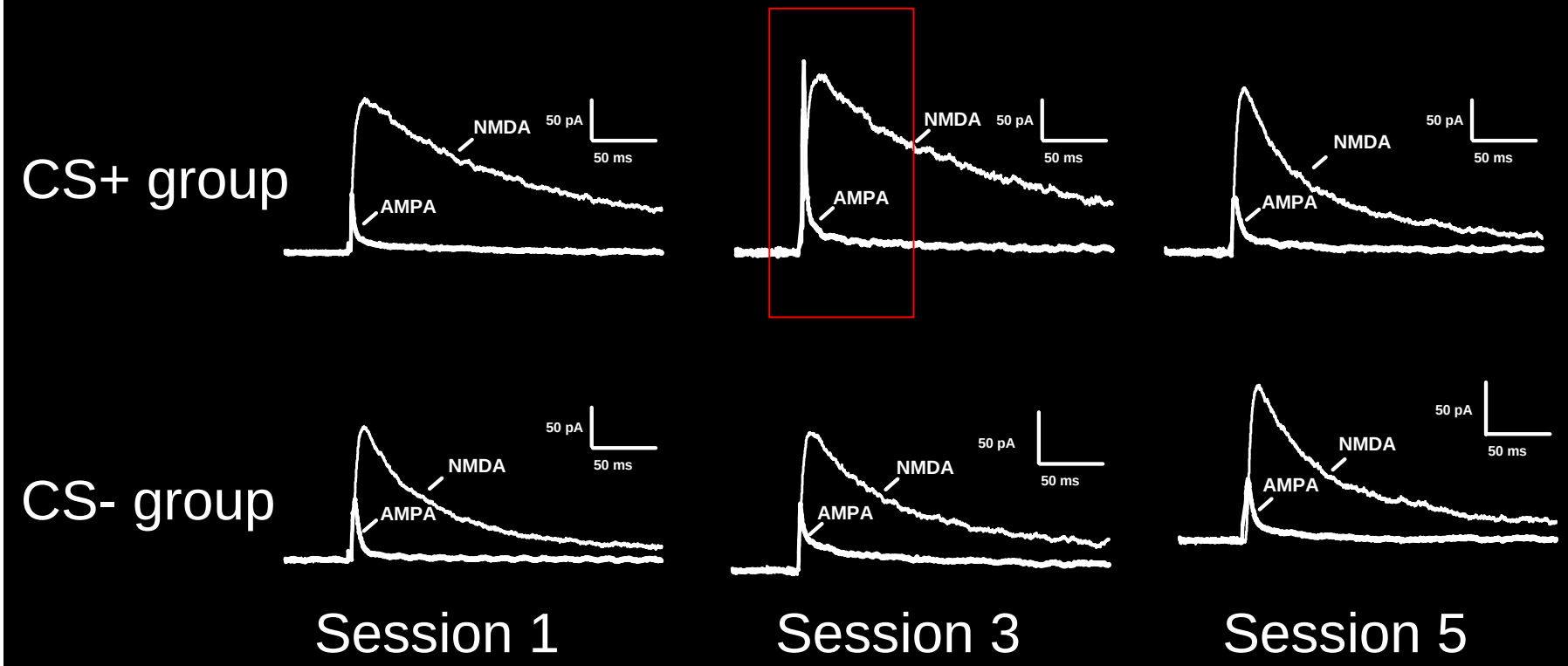
CS+ group



CS- group

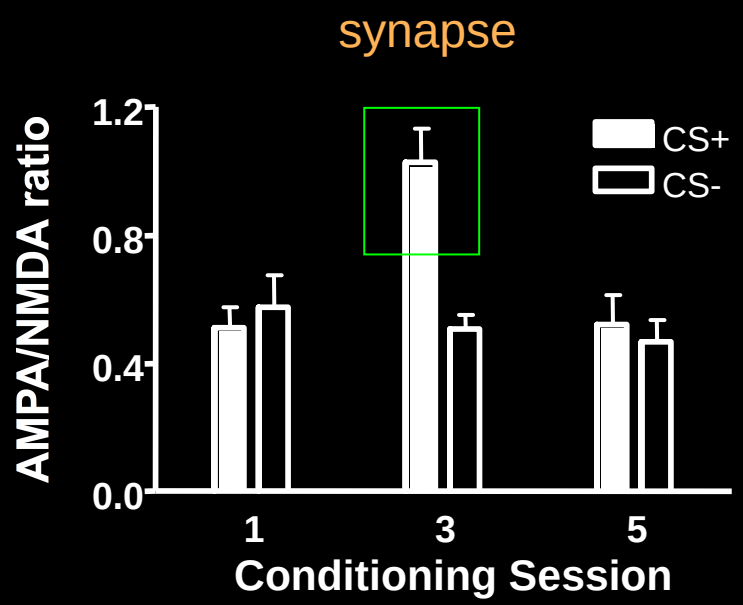
Stuber et al., Science (2008)

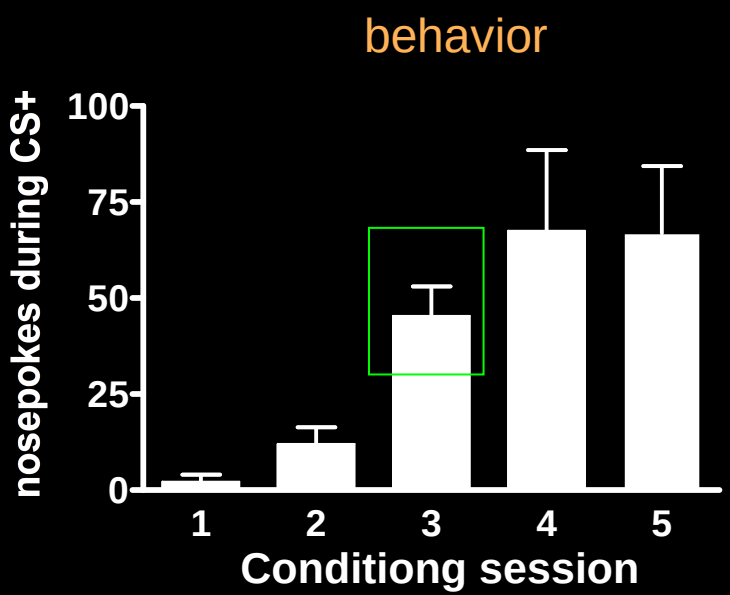
AMPA/NMDA ratio is transiently elevated during reward learning



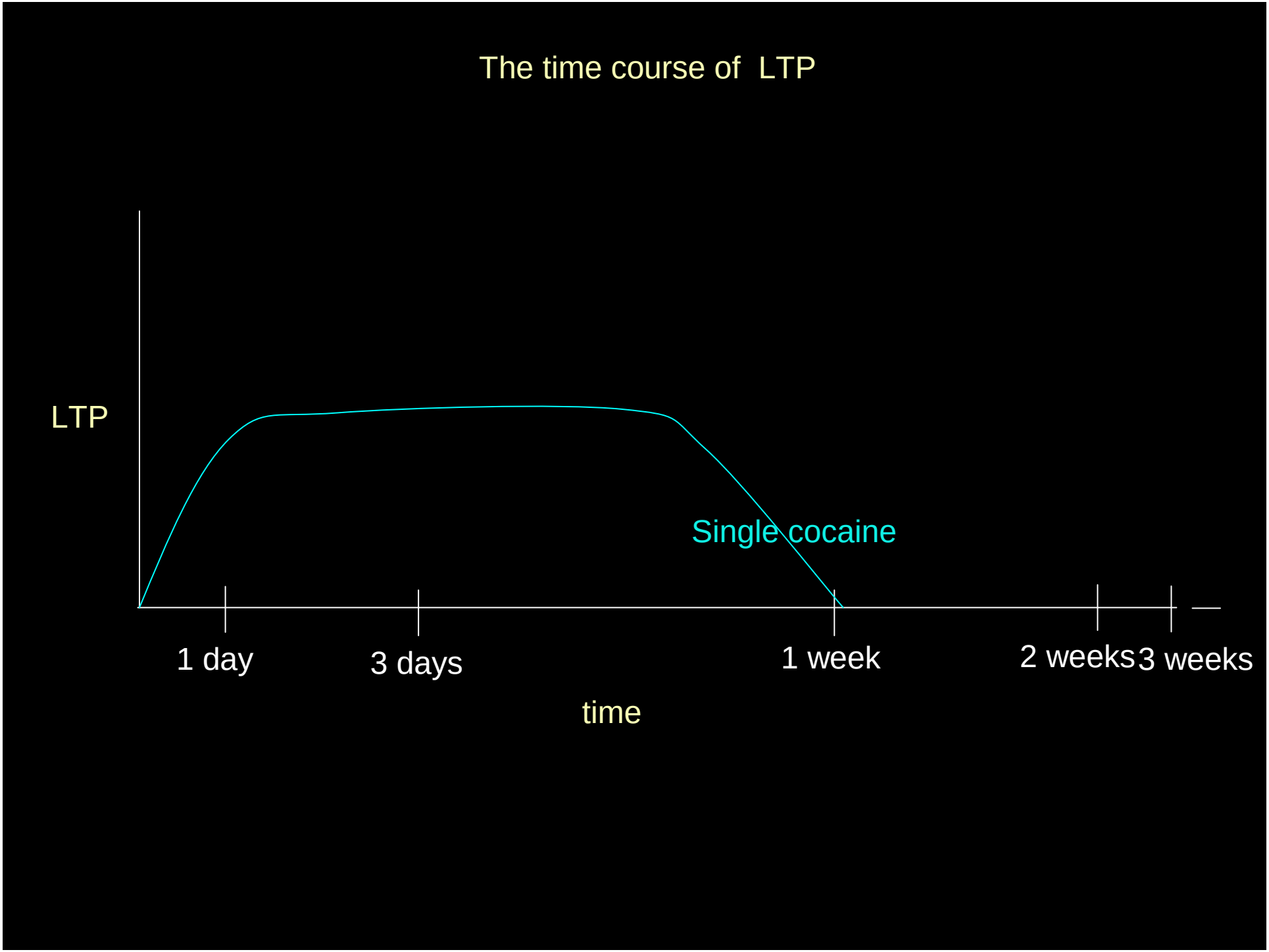
Stuber et al., Science (2008)

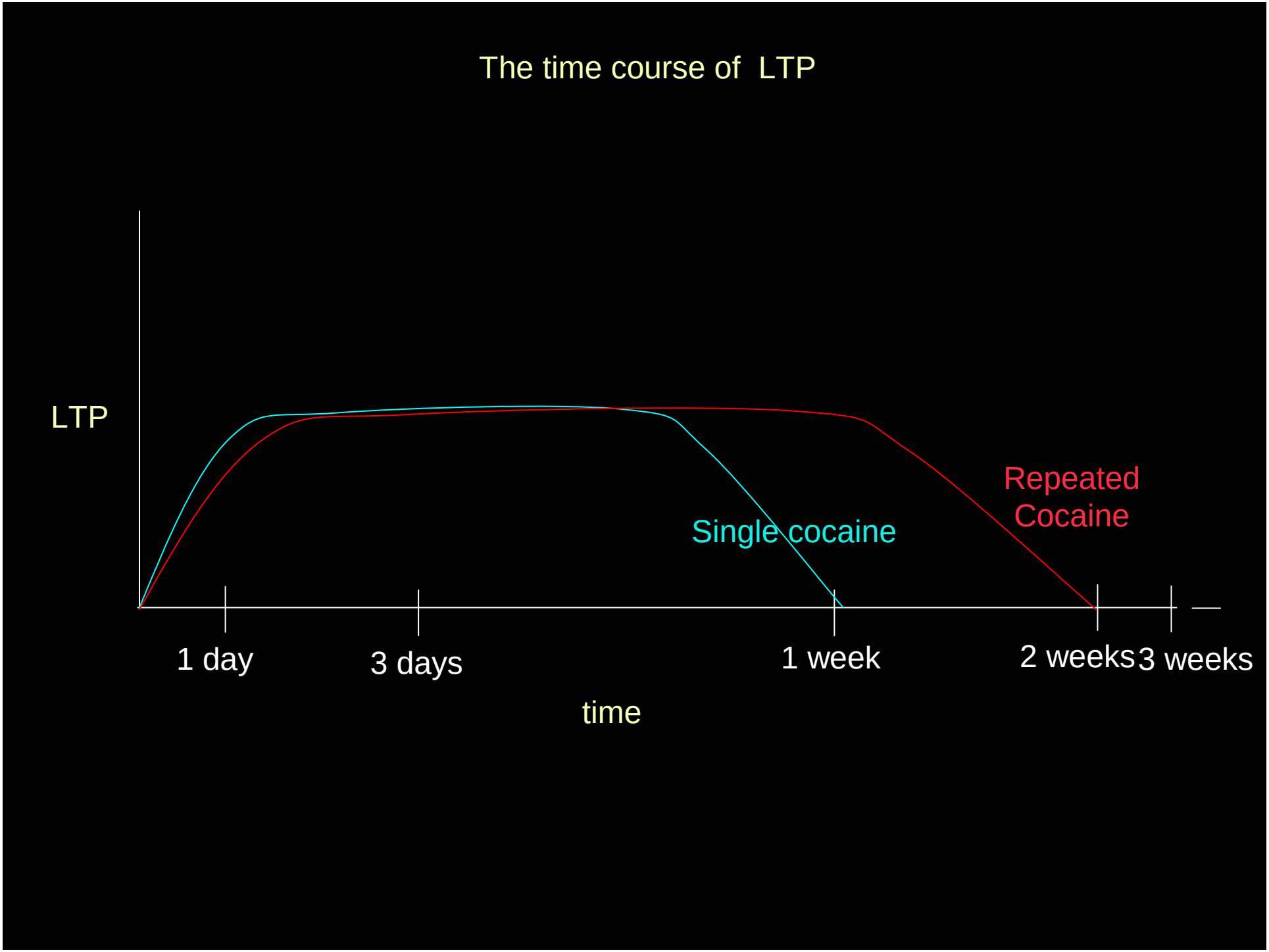
AMPA/NMDA ratio is transiently elevated during reward learning

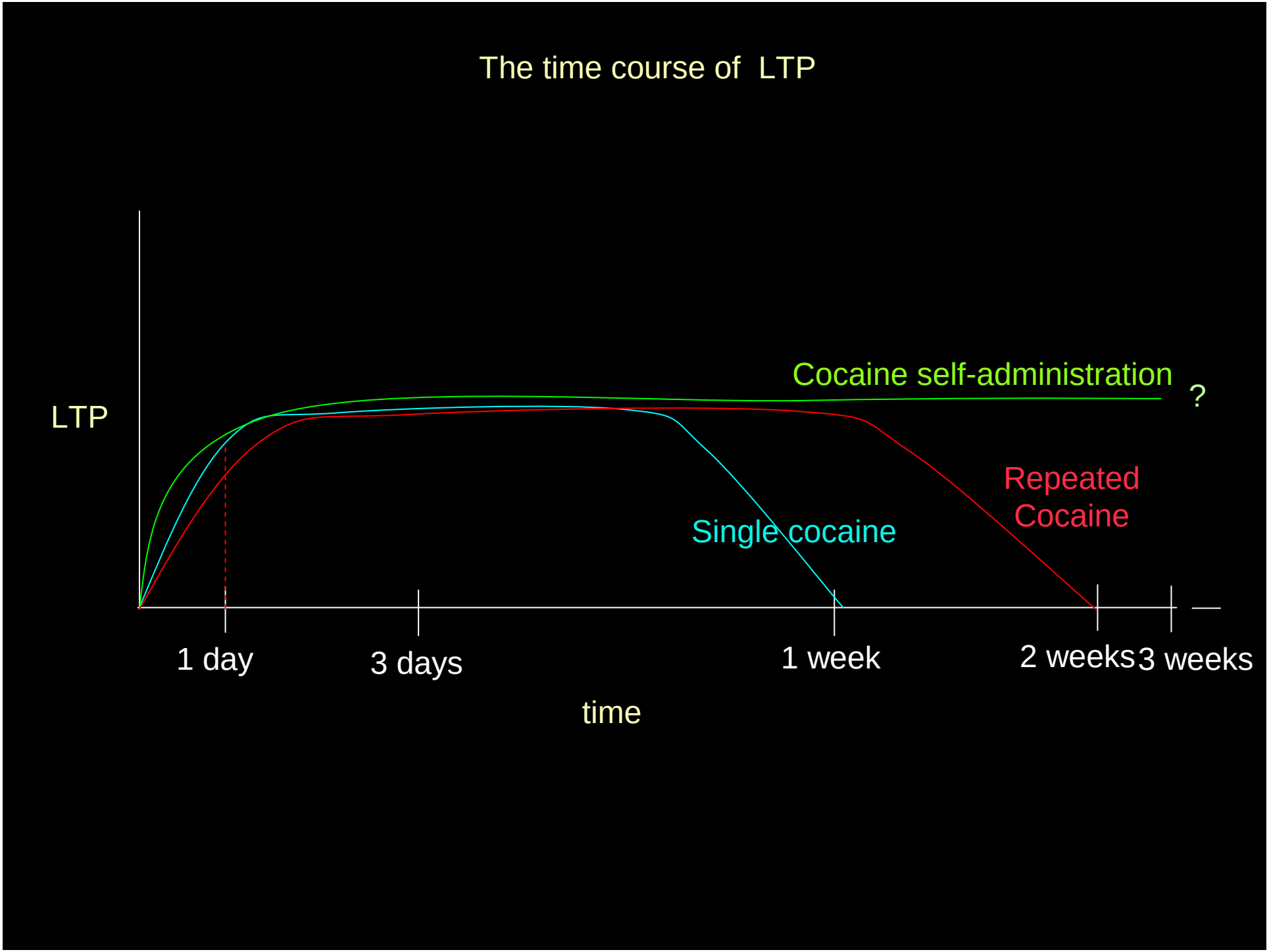


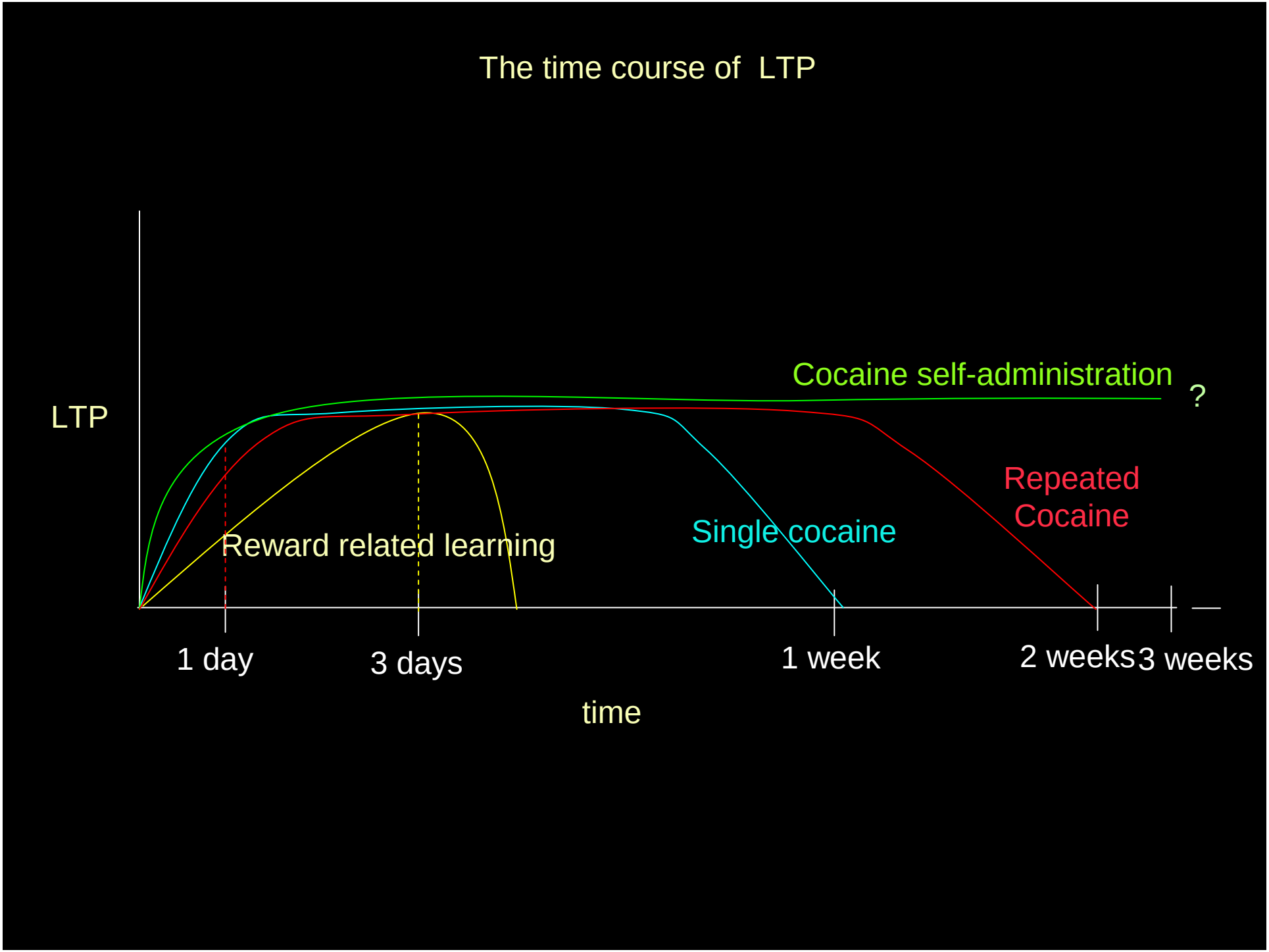


Stuber et al., Science (2008)


The time course of LTP
LTP
Single cocaine
1 day
3 days
1 week
2 weeks
3 weeks
time


The time course of LTP
LTP
Repeated
Cocaine
Single cocaine
1 day
3 days
1 week
2 weeks
3 weeks
time


The time course of LTP
LTP
Cocaine self-administration
?
Repeated
Cocaine
Single cocaine
1 day
3 days
1 week
2 weeks
3 weeks
time


The time course of LTP
LTP
Cocaine self-administration
?
Repeated
Cocaine
Single cocaine
Reward related learning
1 day
3 days
1 week
2 weeks
3 weeks
time

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 a persistent form of cellular memory, lasting at least 3 months

Acknowledgements

Lab Members

Woody Hopf
Emanuela Argilli
Scott Bowers
Billy Chen
June Hahn
Dennis Sparta
Garret Stuber
Kimberly Kempadoo
Sarah Fischbach
Shao-Jun Chang
Ling Wang
Anitra Guillory
Saemi Chao
Steven Lieske

Collaborations

Gallo Center

Selena Bartlett
Howard Fields
Ulrike Heberlein
Patricia Janak
Bob Messing
Dorit Ron
Jennifer Whistler
Ray White
Linda Willbrecht
Viktor Kharazia

UCSF
Pam England
Lou Reichardt
Larry Tecott

Extramural

Karl Deisseroth
Luis deLecea
Peter Kalivas
Rob Malenka
Richard Palmiter
Paul Phillips
Matthjis Verhage

Thanks to NIDA, DoD and State of California