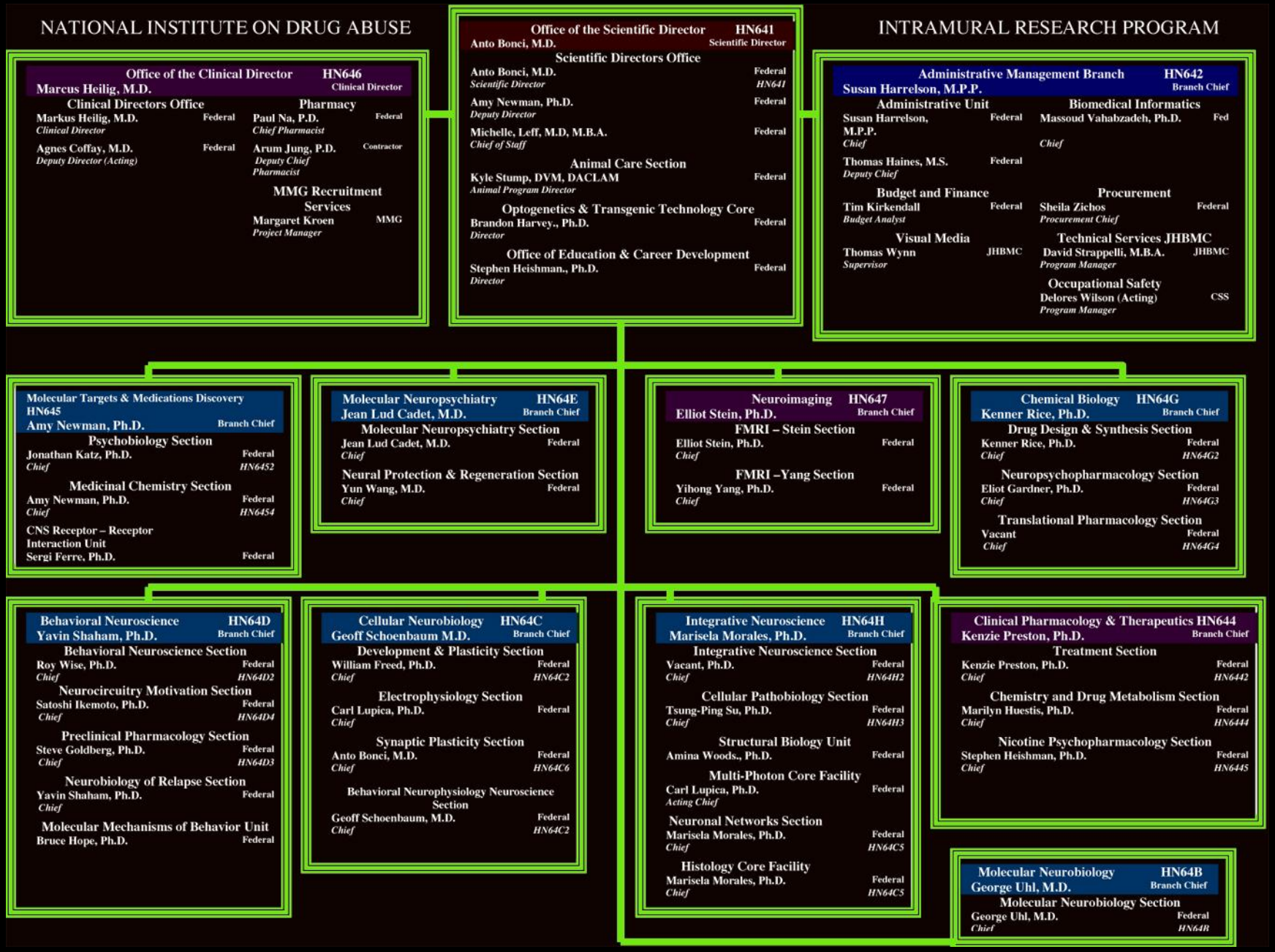
A different kind of imaging: Optogenetics and novel substance abuse treatments

Antonello Bonci, MD

NIDA/NIH

NIDA Intramural Program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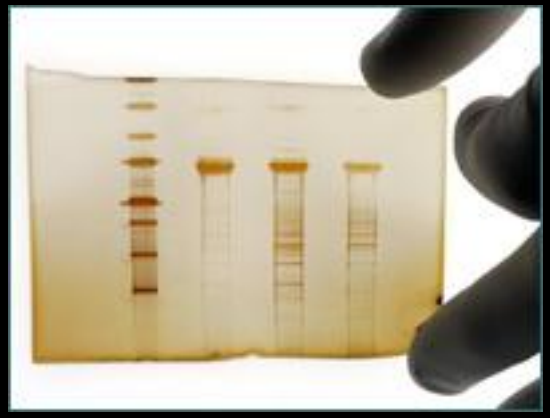
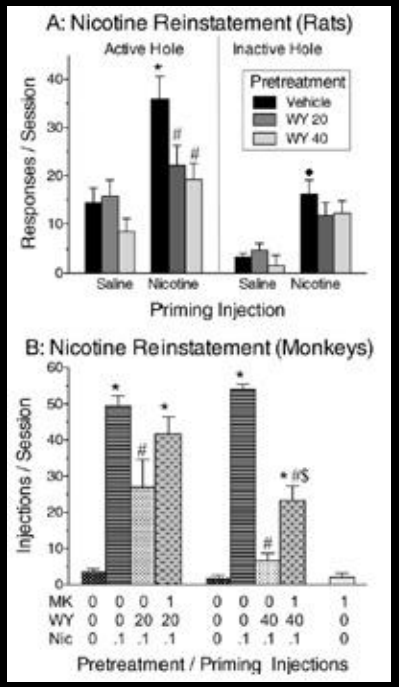
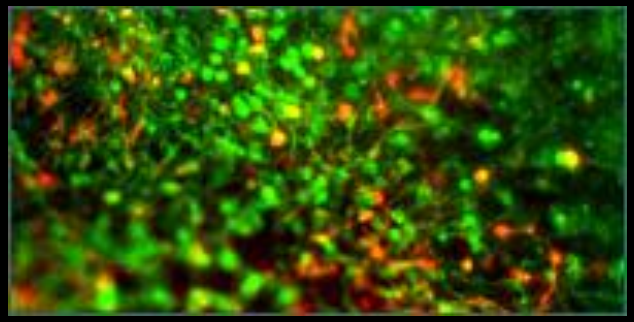
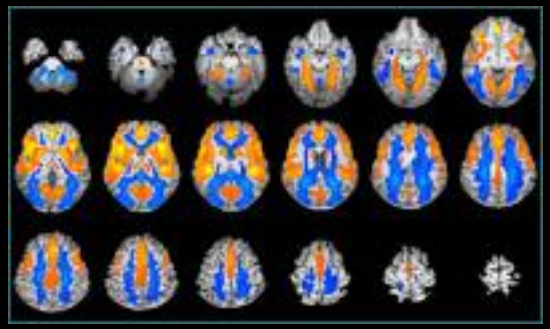
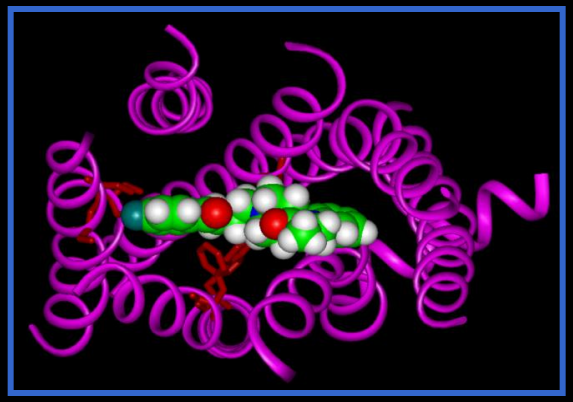








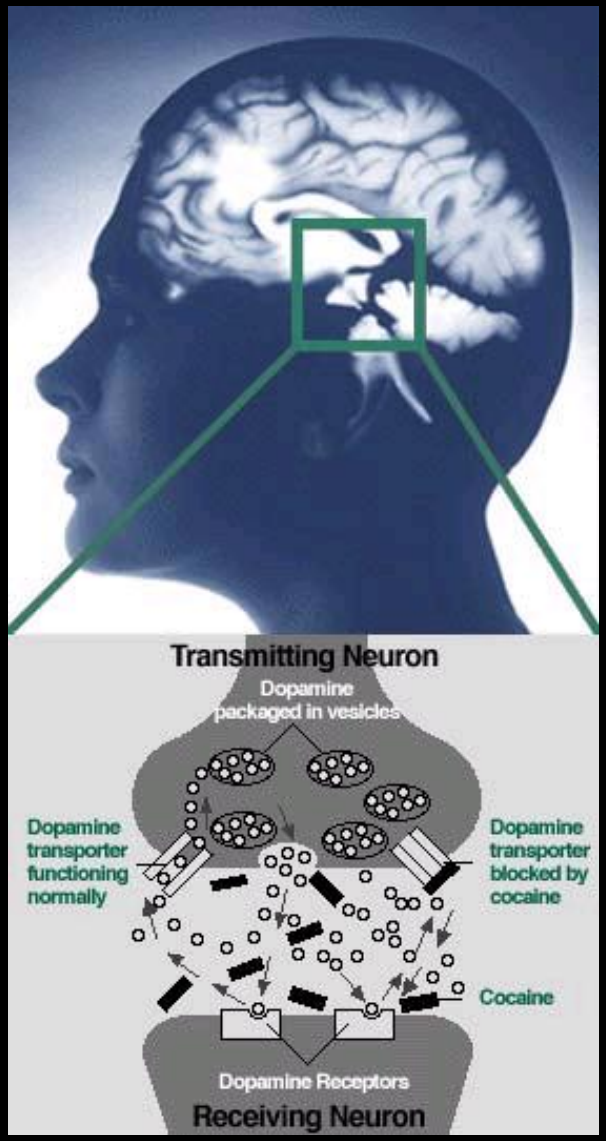


Any addictive behavior depends on changes in electrical activity of specific brain regions

Genetic background

Environmental stimuli

No drugs



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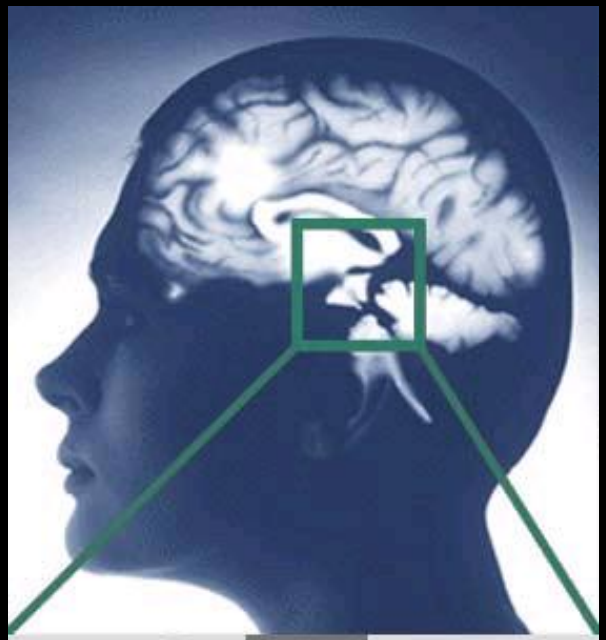

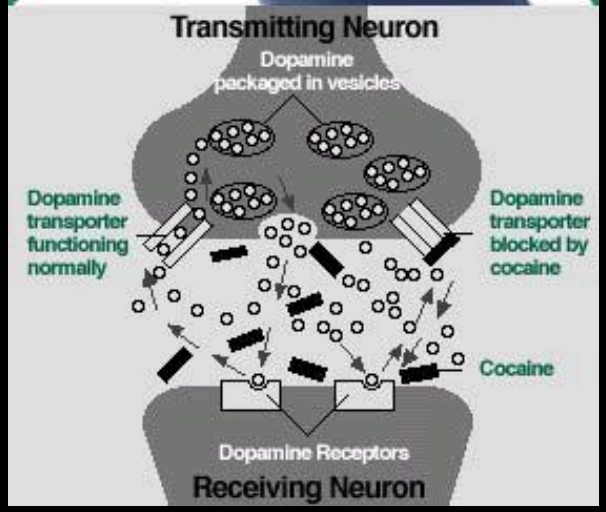

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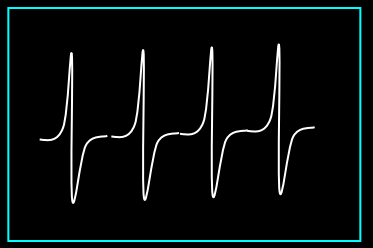
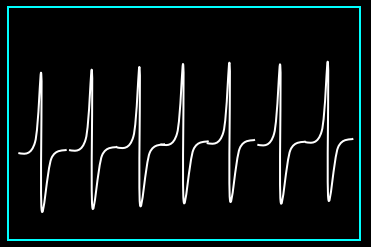


Drugs of abuse → Δ Synapses
Ion channels



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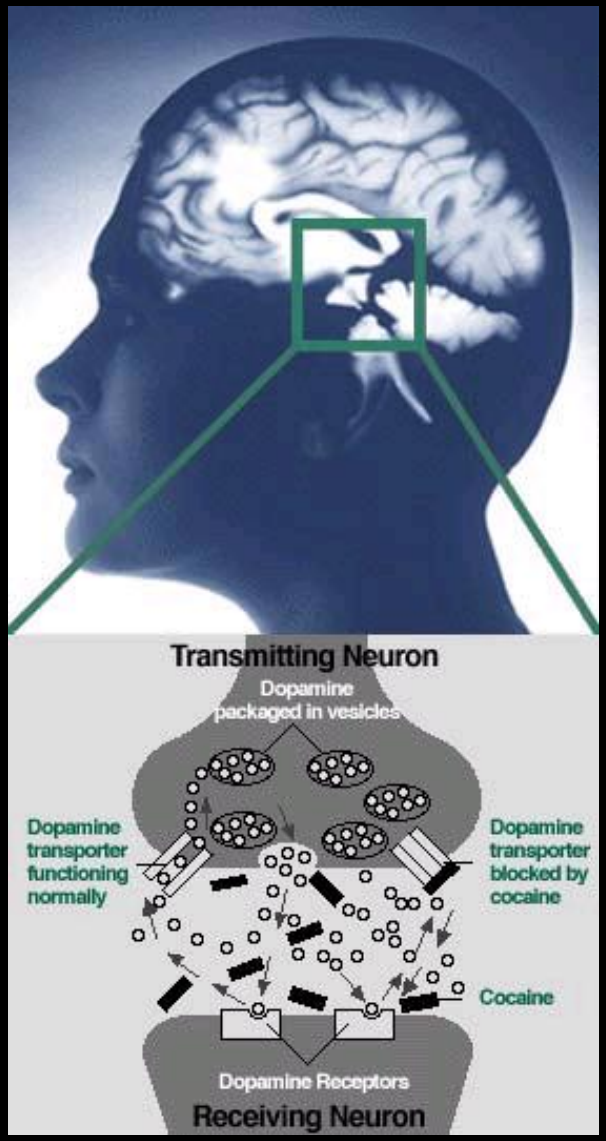

Genetic background

Environmental stimuli

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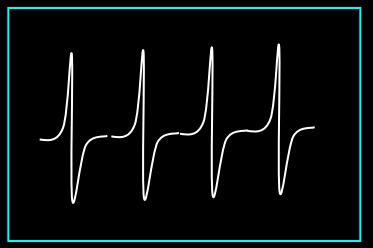

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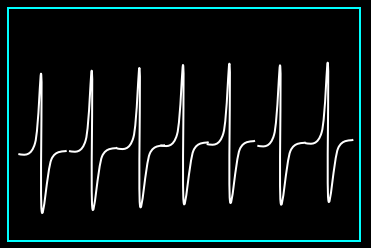
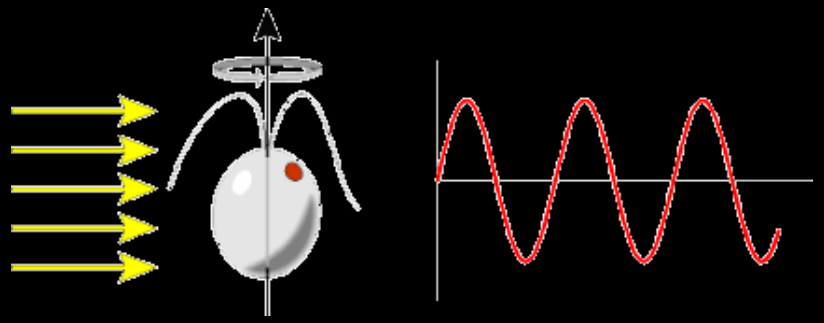


Substance abuse

Light sensitive proteins

Microorganisms

ChannelRhodopsin-2 from *Chlamydomonas reindhardtii* (2005)



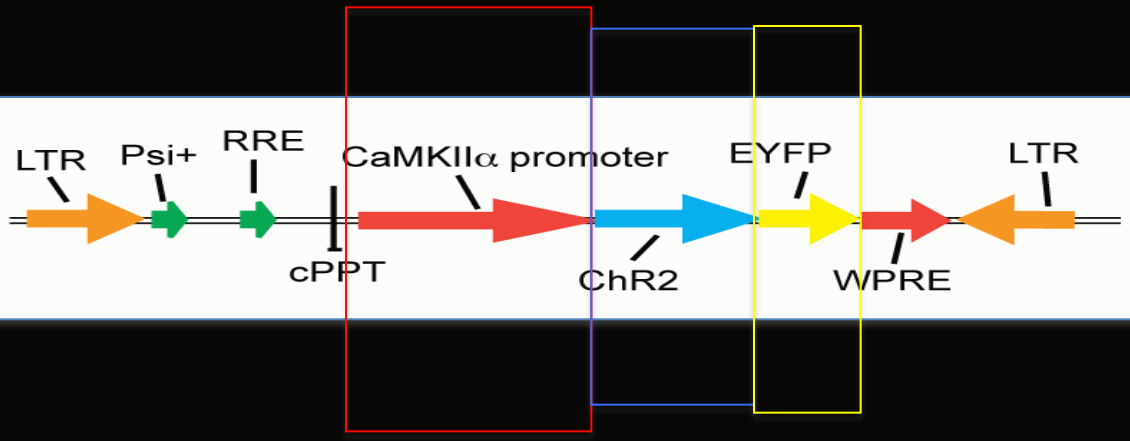
Halorhodopsin from *Natronomonas pharaonis* (2006)

Courtesy of Feng Zhang
And Karl Deisseroth

The channelrhodopsin is packaged into a virus

AAV

AAV-CaMKIIa-ChR2-EYFP:



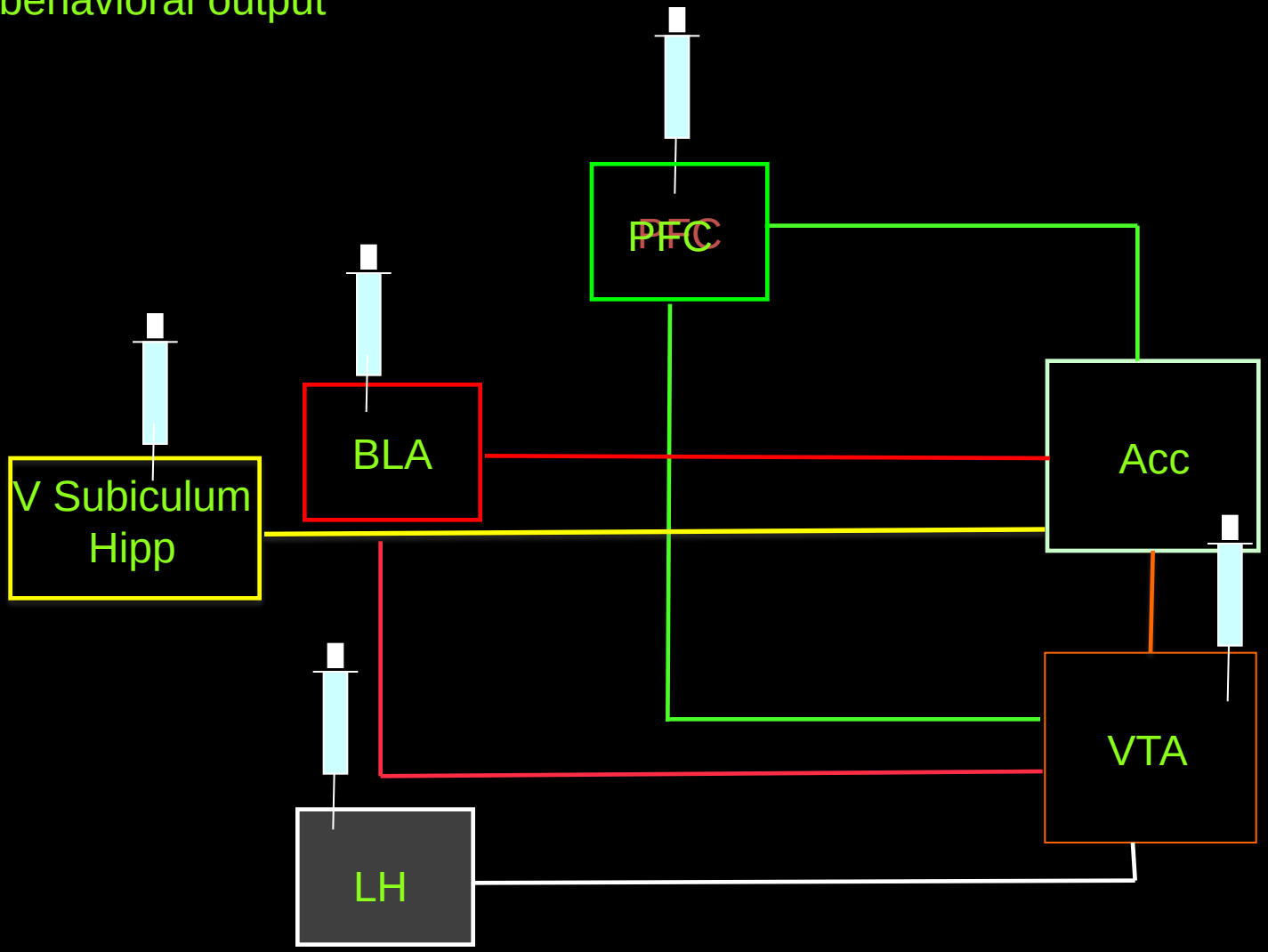
Specificity

visibility

Bidirectional activity

Mapping one pathway at the time, to:

1. determine the role of each pathway in reward-related behaviors and drug exposure
2. determine the relationship between strength of each synaptic inputs and behavioral output



A novel use of optogenetics

1. Does “compulsive” cocaine self-administration induce hypofrontality in the prelimbic portion of the PFC?

1. Can we override PFC hypoactivity (and drug taking) by using optogenetic stimulation of the PFC

What is the best model of compulsive drug use in rodents

- Limitations of extinction-reinstatement model

- Compulsion: Drug use is continued despite incurring into negative consequence - introducing cost (shock) to self-administration paradigm.

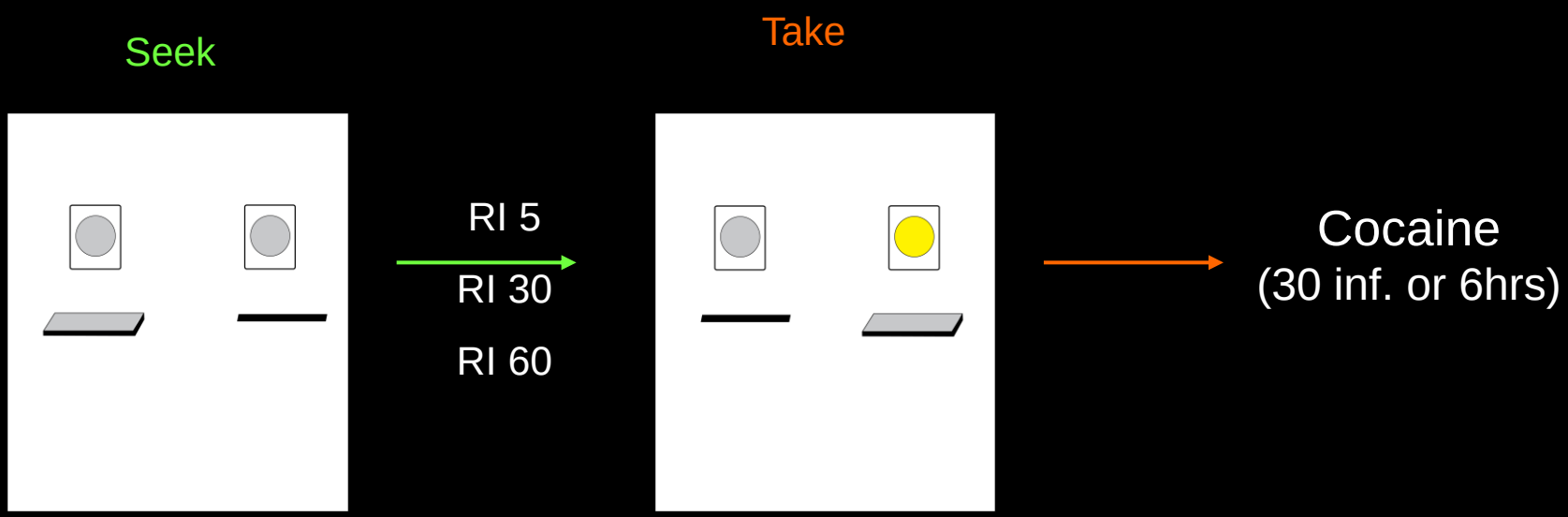
After Deroche-Gamonet et al., Science (2004)

Vanderschuren et al., Science (2004)

Modified self-administration paradigm

1. Rats are trained to self-administer cocaine on a seek-take chain schedule (about 2 months) *with progressively longer Random Intervals.*

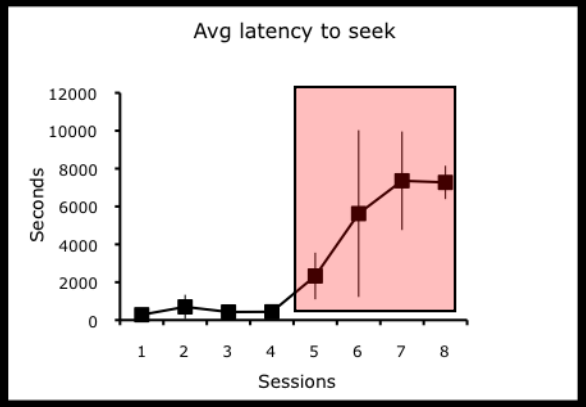
2. At the very end of training, rats receive 4 sessions of non-contingent foot shock in 30% of trials

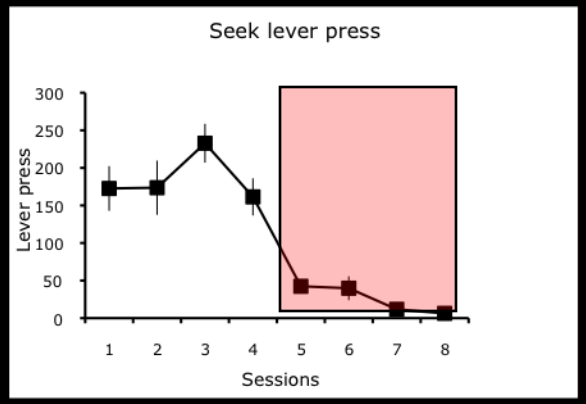


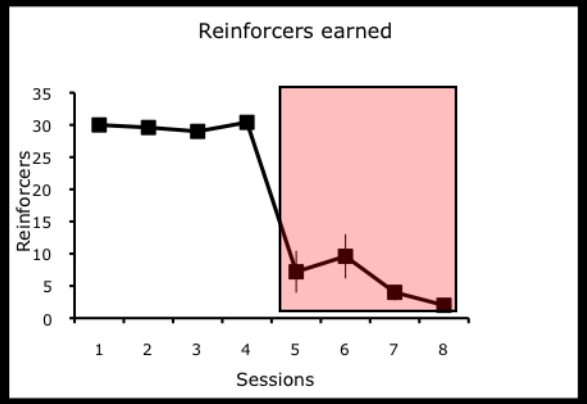
Chen et al., (Nature) under revision

1. Rats are divided into non-compulsive and compulsive groups

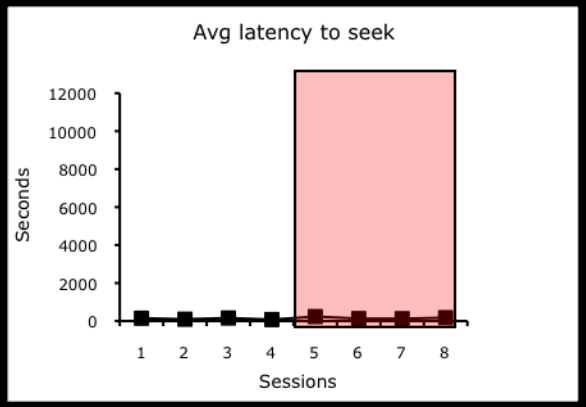
shock sensitive

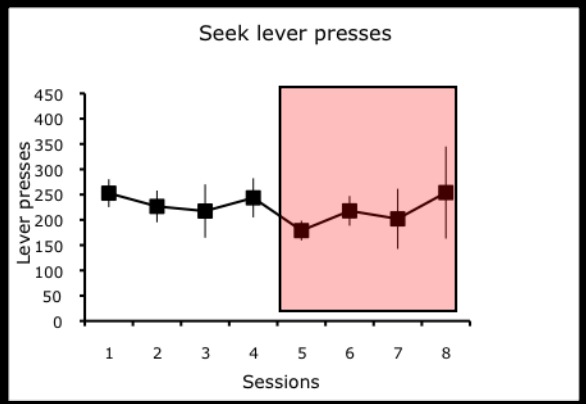


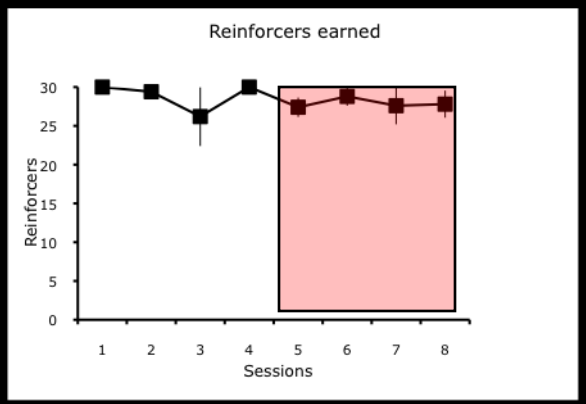




Shock-resistant



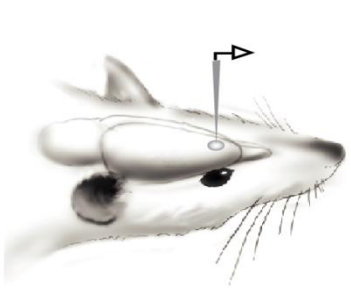


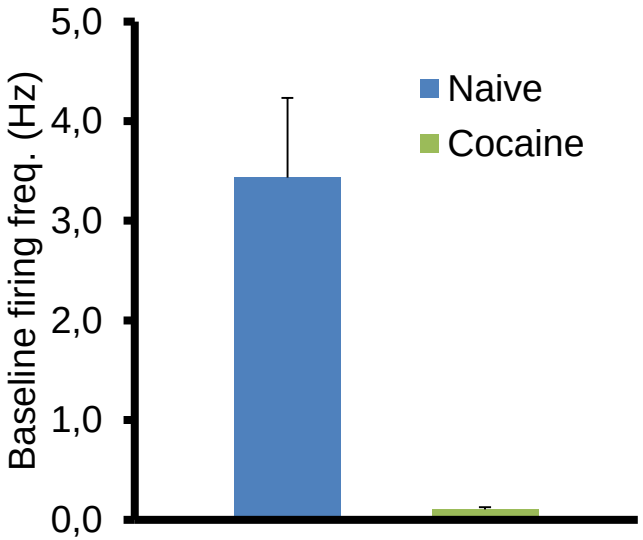


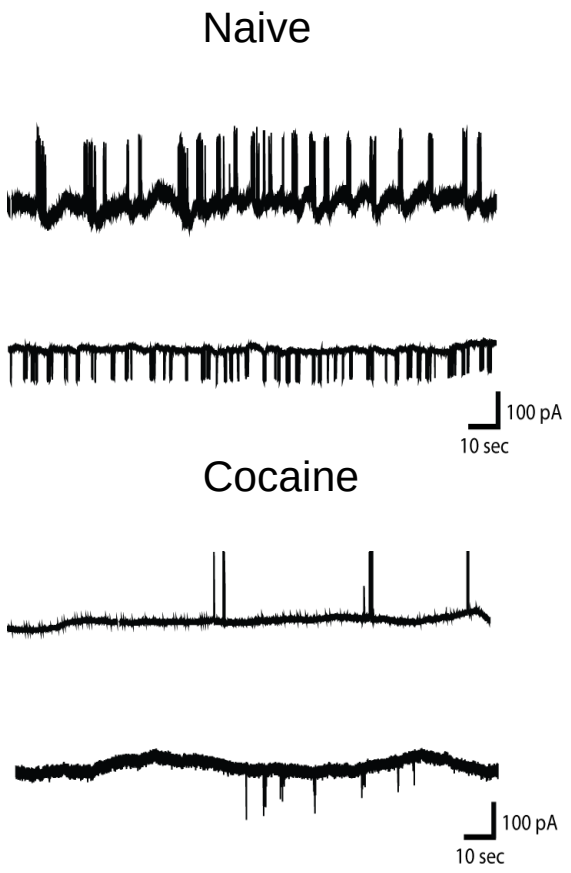
Chen et al., (Nature) under revision

Hypofrontality in prelimbic neurons after long-access cocaine self-administration

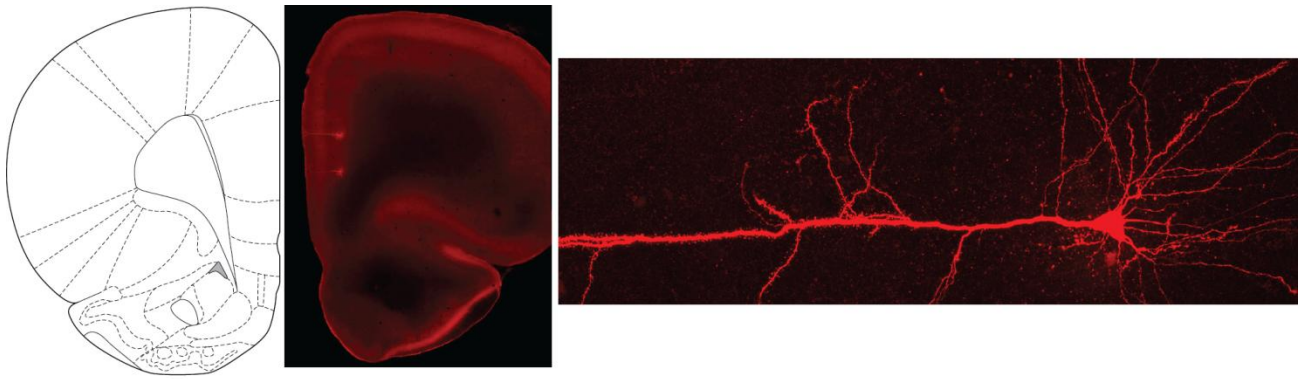
In vivo whole-cell recording in anesthetized rat, targeting prelimbic region

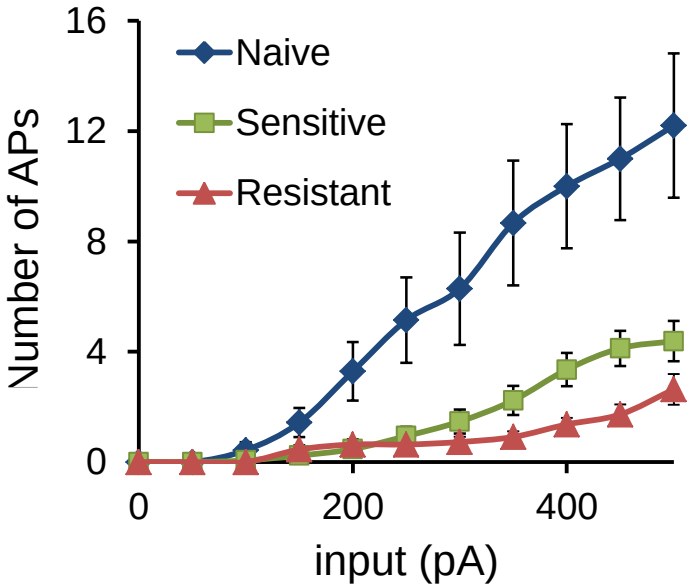






Long-access to cocaine decreases excitability of deep-layer cortical neurons





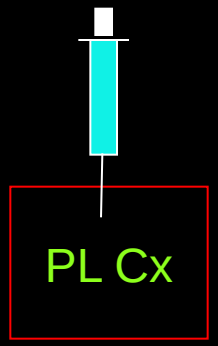
Chen et al., (Nature) under revision

Hypothesis:

Optogenetic activation of the prelimbic area could reduce compulsive cocaine seeking

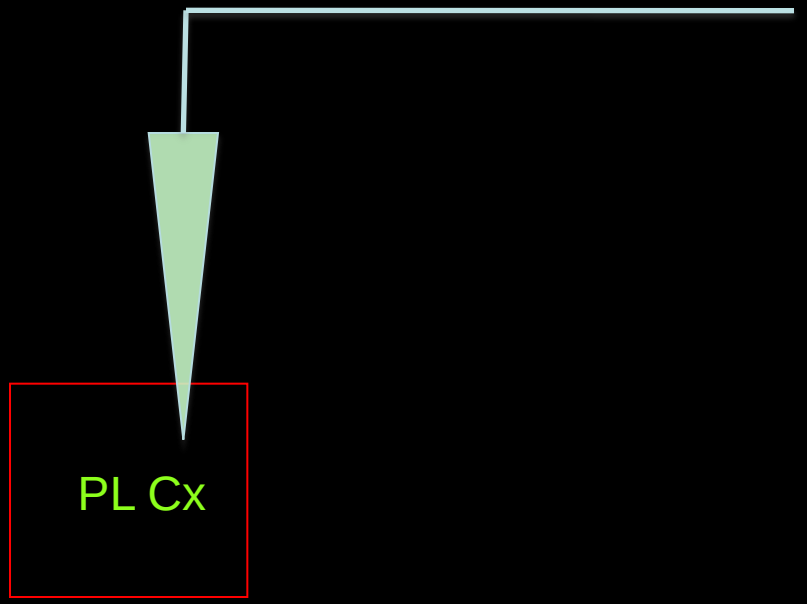
ChR2 method

1. Inject the AAV containing the CaMKIIα Promoter (before training)



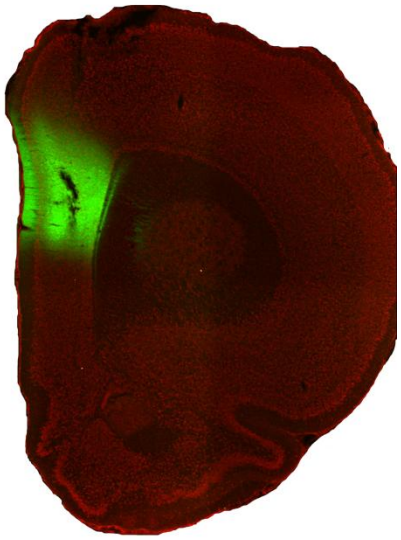
2. Be patient

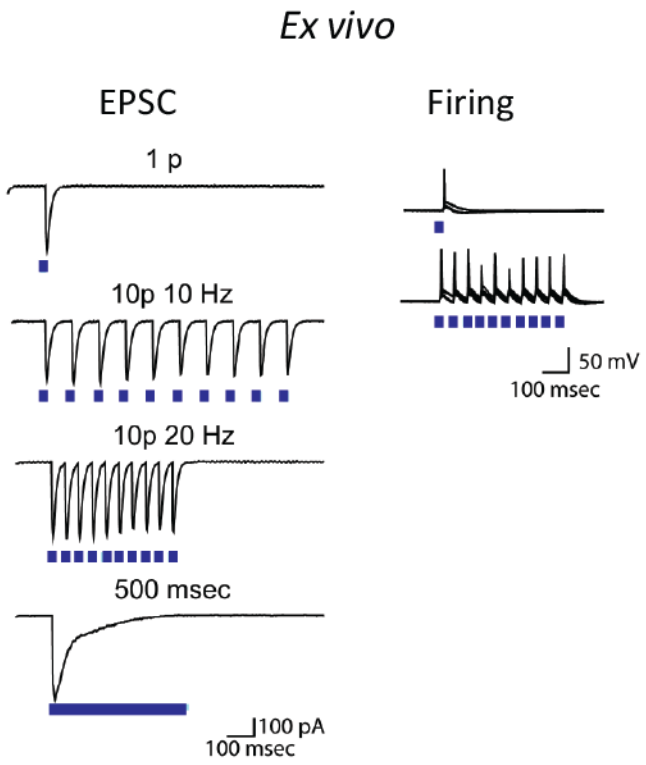
3. Record or perform *in vivo* expp



Chen et al., (Nature) under revision

Channelrhodopsin-expressing mPFC neurons exhibit robust photo-excitation



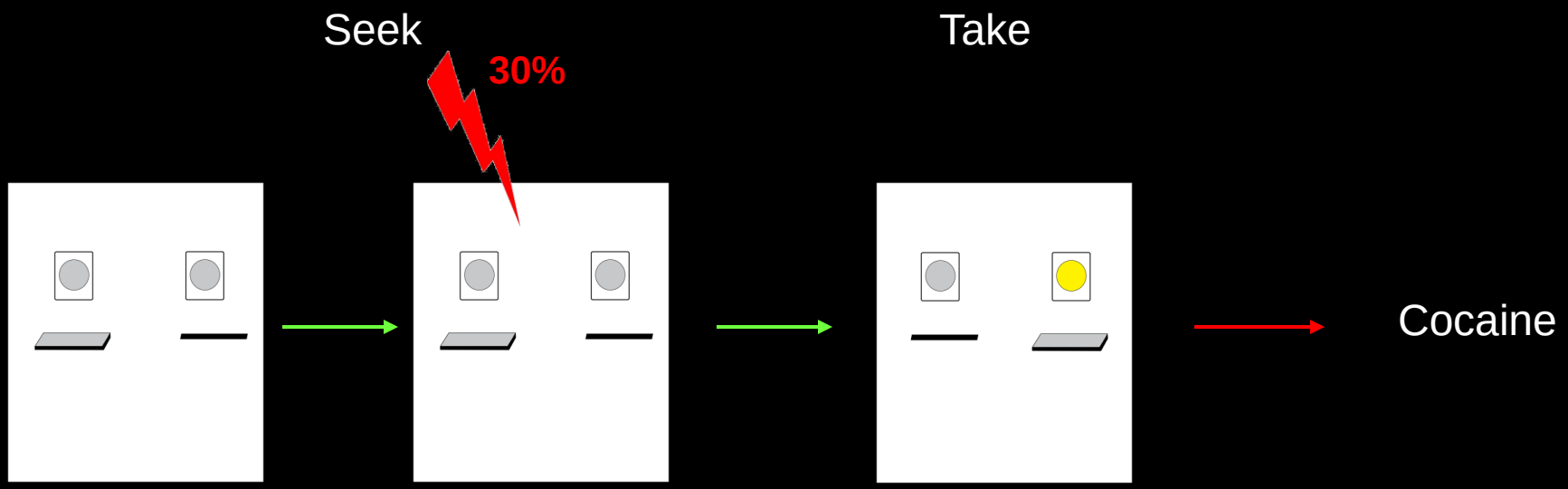


Chen et al., (Nature) under revision

An Optogenetic approach to this question

- 4 days of “shock” training

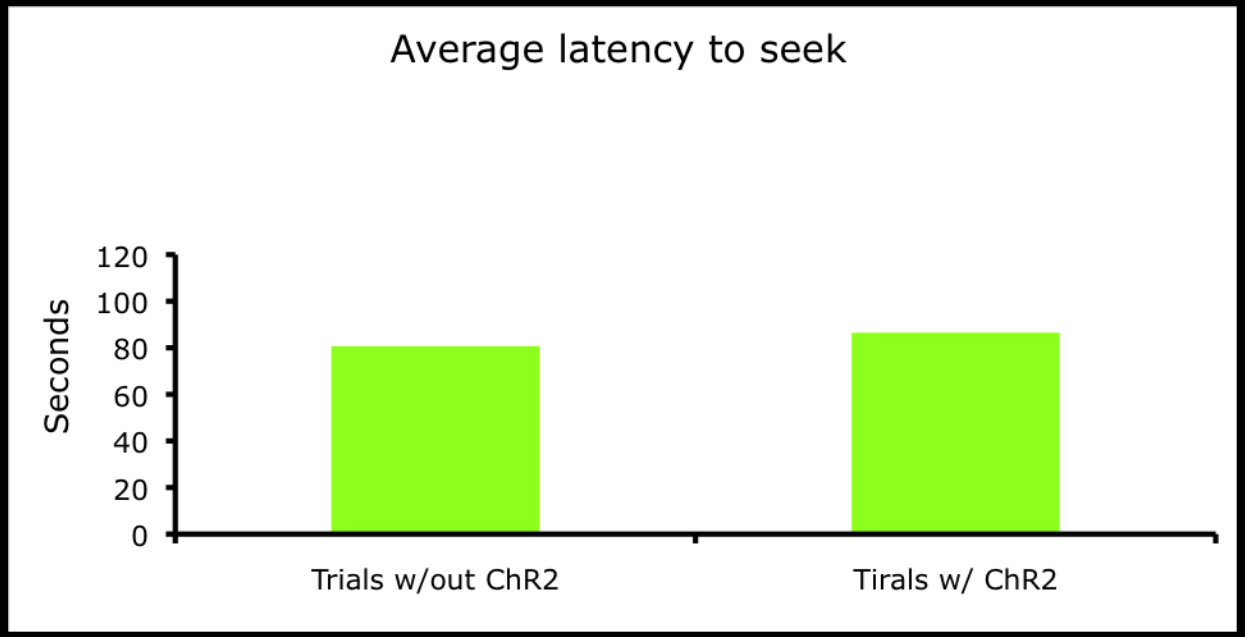
- On day 5, ChR stimulationin the PLCx (@1 Hz) throughout the seek period



Chen et al., (Nature) under revision

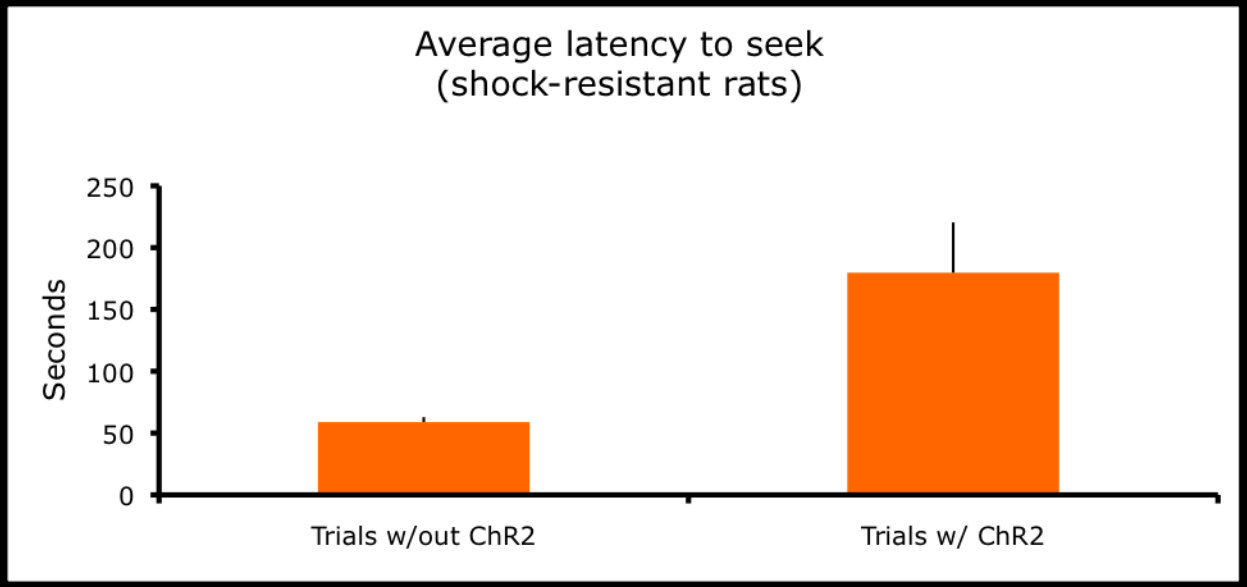
ChR-driven activation of prelimbic cortex decreases cocaine-seeking behavior

First series of controls:
Activation of prelimbic neurons *prior* to punishment has no effect on the rat's seeking behavior



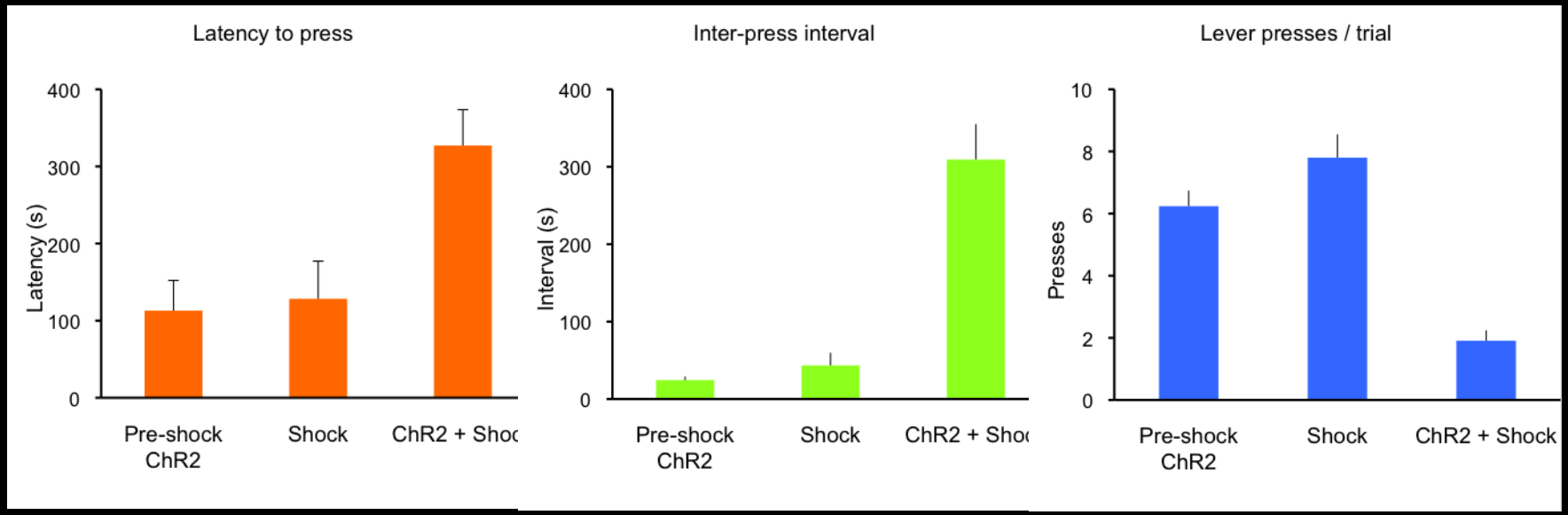
Chen et al., (Nature) under revision

After the rats learned that they might be shocked, ChR activation reduces cocaine taking significantly



Chen et al., (Nature) under revision

Prelimbic photostimulation decreases compulsive cocaine seeking only *after* Shock sessions



Chen et al., (Nature) under revision

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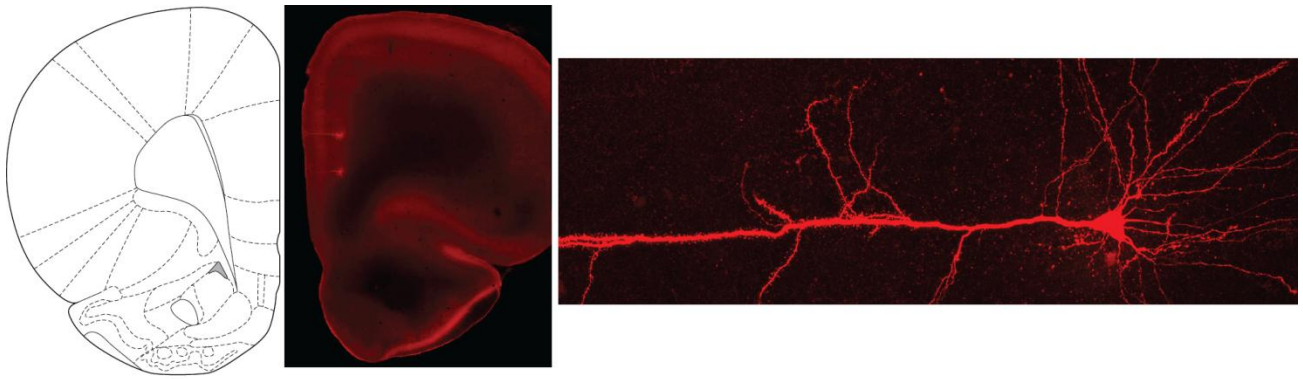
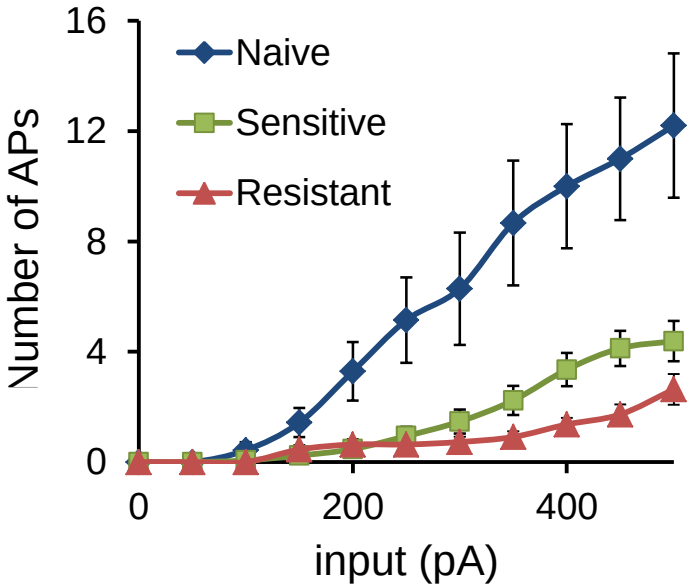
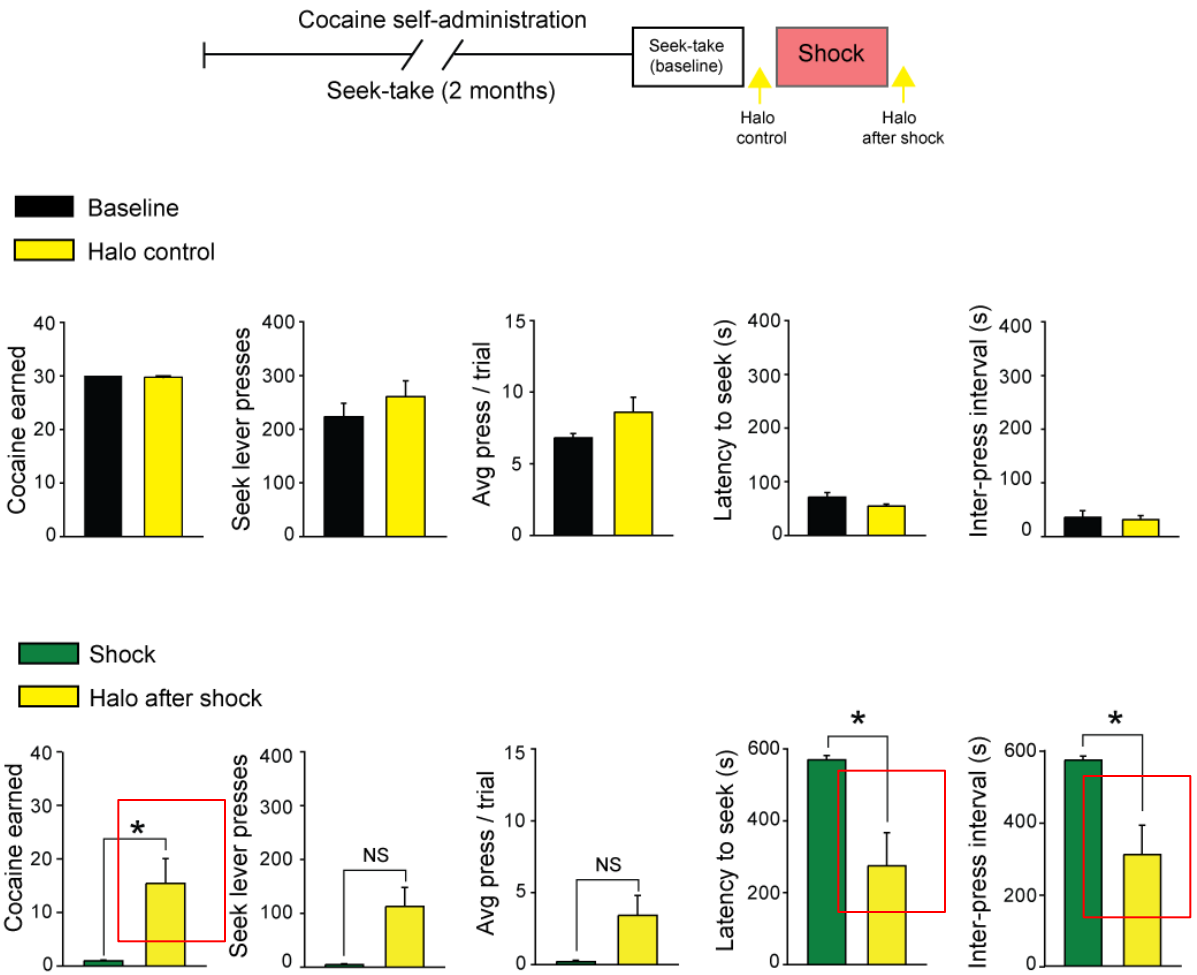




Chen et al., (Nature) under revision

Shock-sensitive rats increase cocaine seeking and become like the shock-resistant



An opportunity for a TMS study

Summary and conclusions

- ~30% of rats will self-administer cocaine despite negative consequences (SR rats).
- Neurons in the prelimbic region of the PFC are significantly less active following prolonged cocaine self-administration, with shock resistant rats having the least active.
- Activation of prelimbic neurons with channelrhodopsin decreases cocaine seeking and taking behavior in SR rats,
- Inhibition of prelimbic neurons in shock sensitive rats increases cocaine seeking after shock sessions, turning the SS rats into SR rats
- Therapeutic potentials by stabilizing and increasing prelimbic cortex function (TMS, etc.)

Acknowledgements

Lab Members

Past

Mark Ungless (ICL)
Stephanie Borgland (UBC)
Garret Stuber (UNC)
Scott Bowers (VCU)
Billy Chen
Kay Tye (MIT)
Manu Argilli
Bjorn Schilstrom (KI)

Current

Jon Britt
Lindsay De Biase
Nick Edwards
Beate Fingers
Said Kourrich
Ikue Kusumoto
Nathan Marchant
Ross McDevitt
Marco Pignatelli
Hau-Jie Yau
Stephanie Goddard
Steph Chung

Collaborations

Extramural

Rob Malenka
Karl Deisseroth
Feng Zhang
Howard Fields
Fred Ambroggi
Luis deLecea

Intramural

Jean Lud Cadet
Sergi Ferre
Brandon Harvey
Bruce Hope
Satoshi Ikemoto
Marisela Morales
Geoff Schoenbaum
Yavin Shaham
Roy Wise
Faiza Benaliouad

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