

***Decreased Excitability of Prelimbic Pyramidal
Neurons Induced by Extended Cocaine
Self-administration Contributes towards
Compulsive Drug Seeking***

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The role of prelimbic pyramidal neurons in compulsive cocaine seeking

NIDA Mini-Convention
Frontiers in Addiction Research

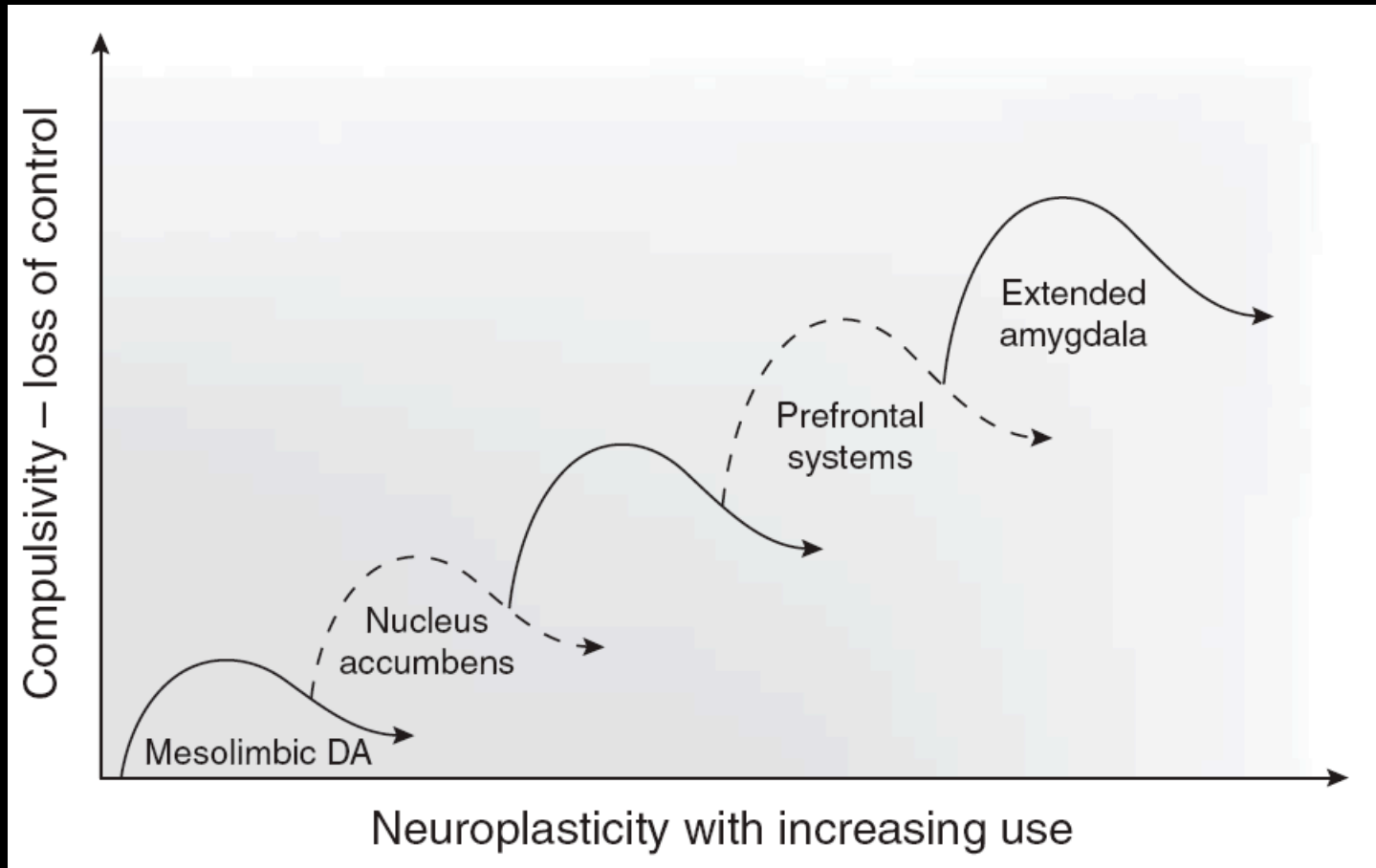
Billy T. Chen
November 11, 2011



Addiction

- Drugs of abuse are thought to usurp normal learning and memory processes.
- Addiction is a series of transition starting from initial use, where drugs have hedonic effects, and evolving into habitual and ultimately compulsive behavior.
- This is hypothesized to result from loss of inhibitory control over drug-seeking behaviors.

Different brain regions are implicated in the development of addiction.

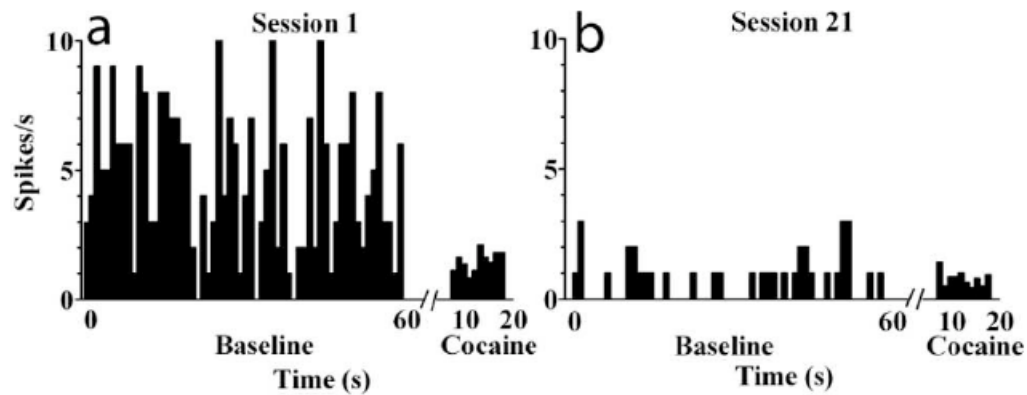


Drug-induced hypofrontality

Human addict



Reduced basal activity in prelimbic cortex (rat)



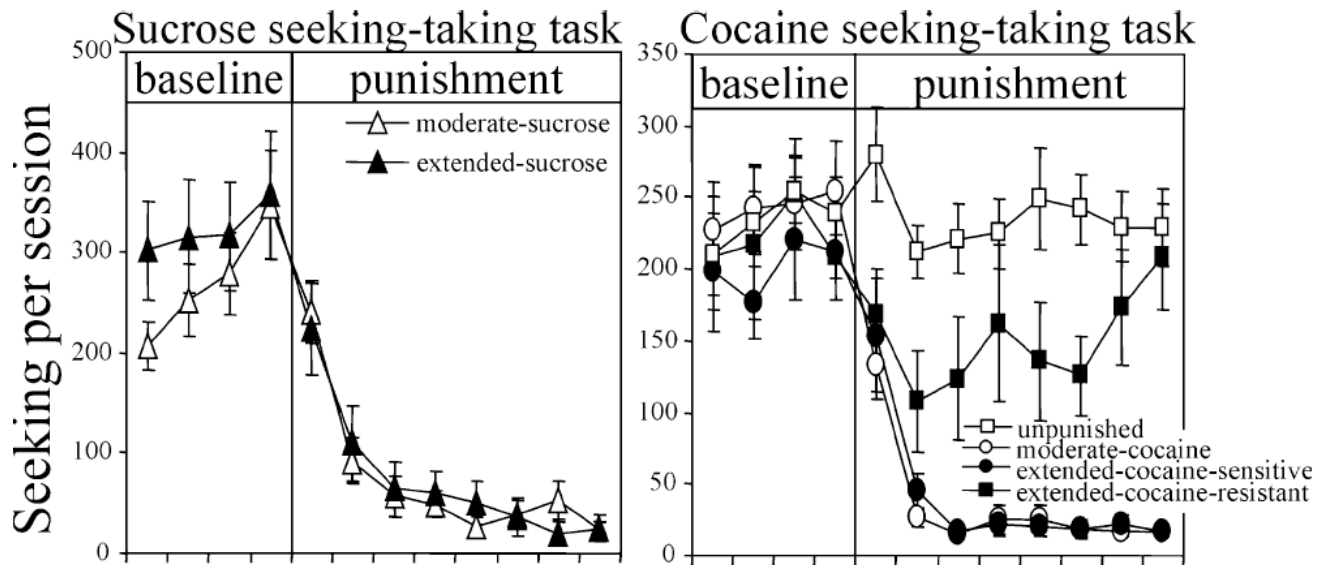
Sun and Rebec 2006

Aims of study

1. Does long-term (compulsive) cocaine self-administration induce hypofrontality in the PFC?
2. How do changes in neuronal activity in the PFC contribute towards compulsive drug use?

Can we model compulsive drug use in rodents?

Compulsion: Drug use is continued despite incurring negative consequence

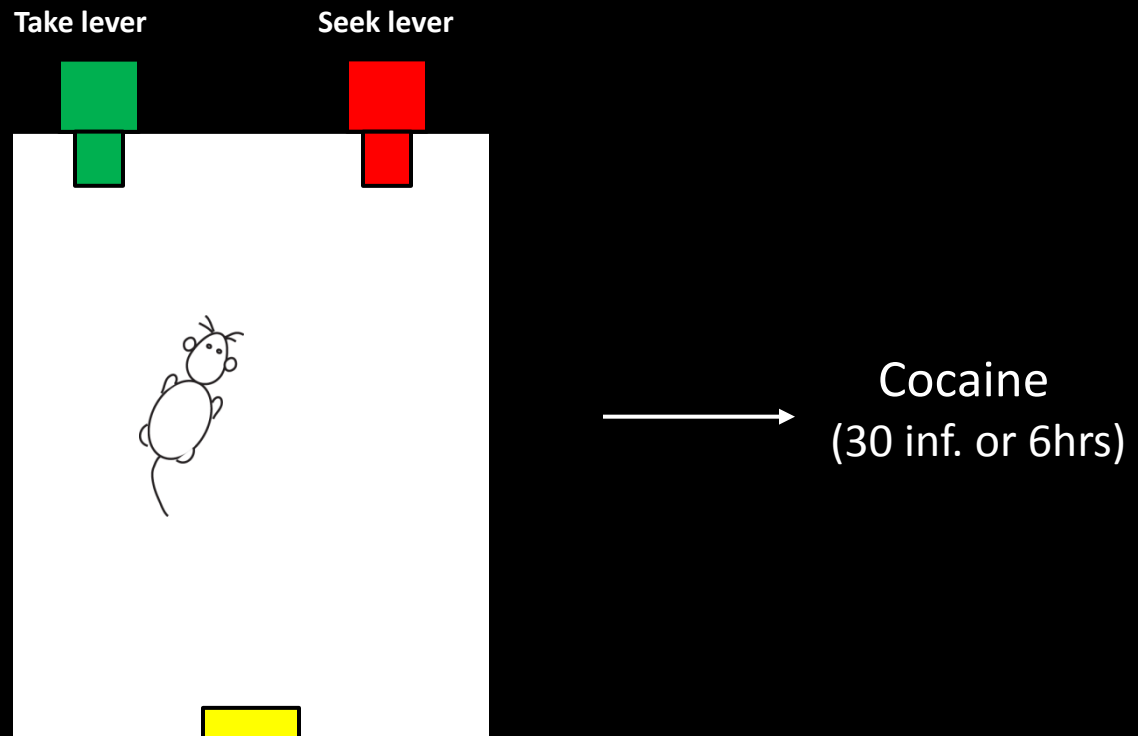


Pelloux et al. 2007, Psychopharm.

Modified self-administration paradigm

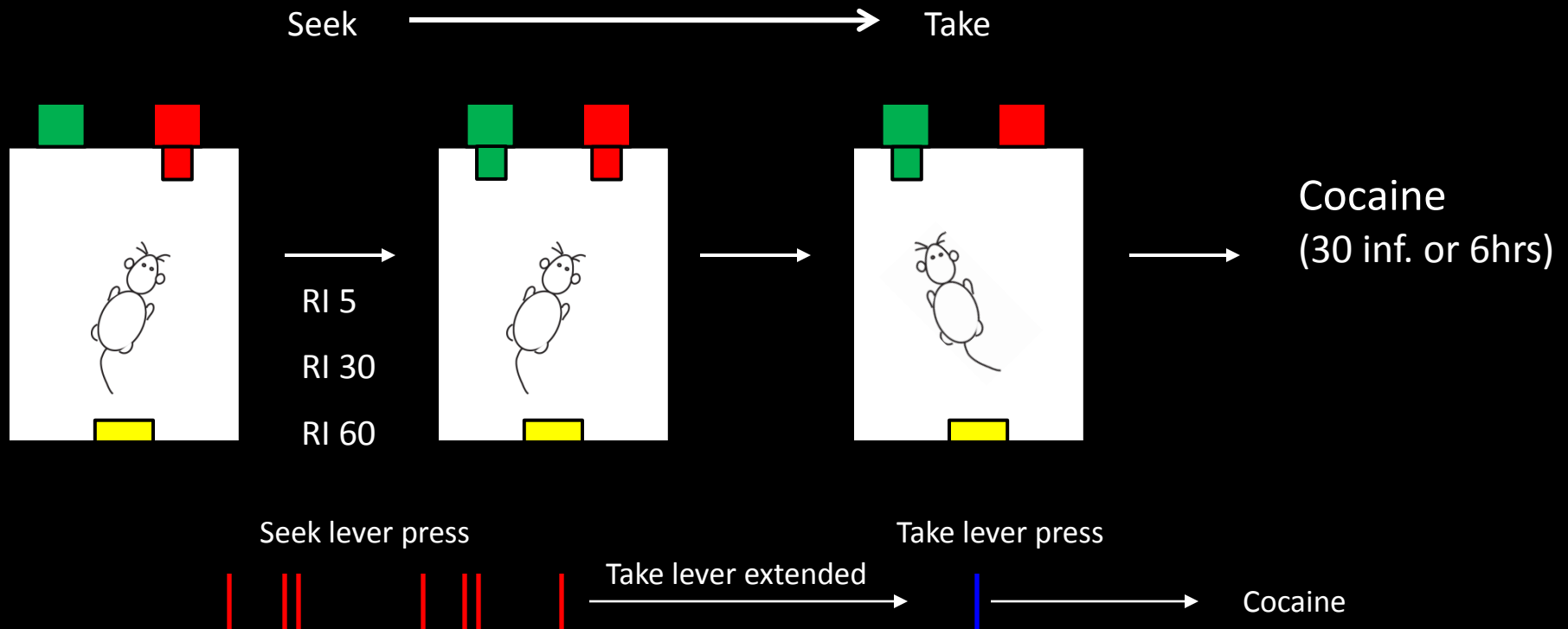
1. Rats are trained to self-administer cocaine on a seek-take chain schedule

Seek – Take chain schedule



Modified self-administration paradigm

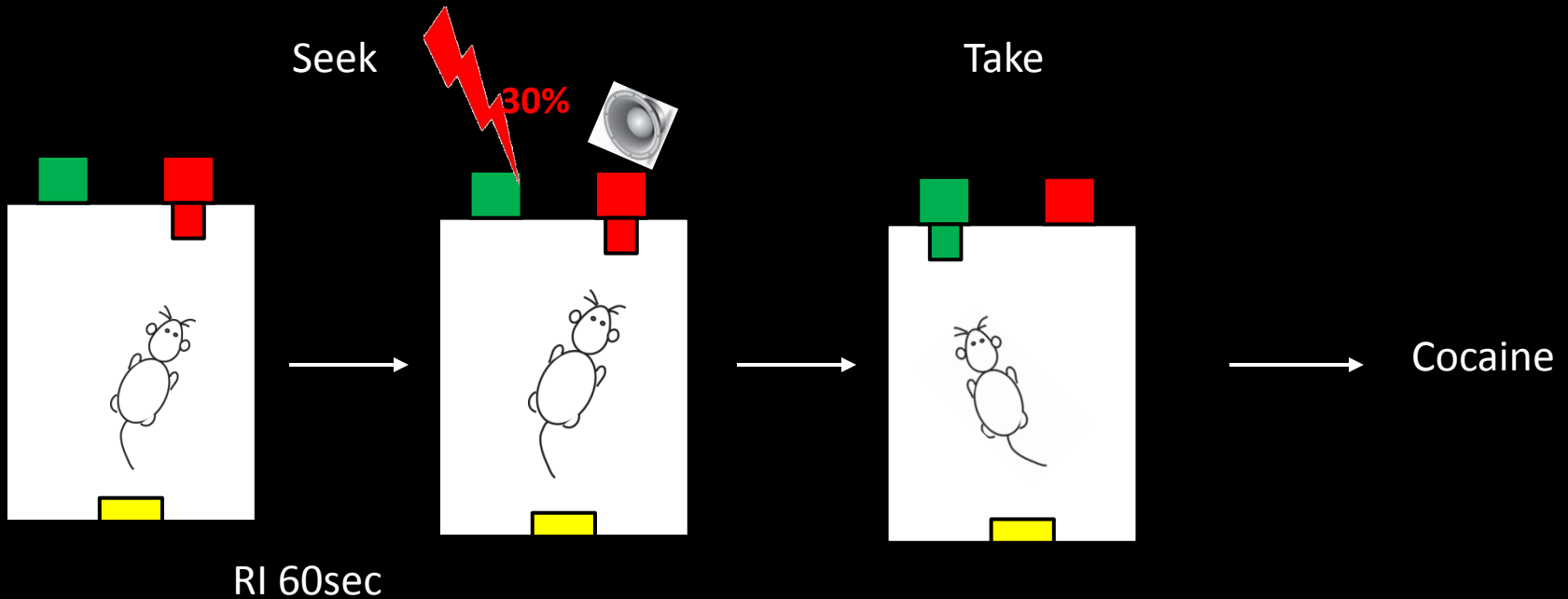
2. Rats are trained to self-administer cocaine on a seeking-taking chain schedule *with progressively longer Random Interval schedule*.



Behavior paradigm (cont.)

2 months

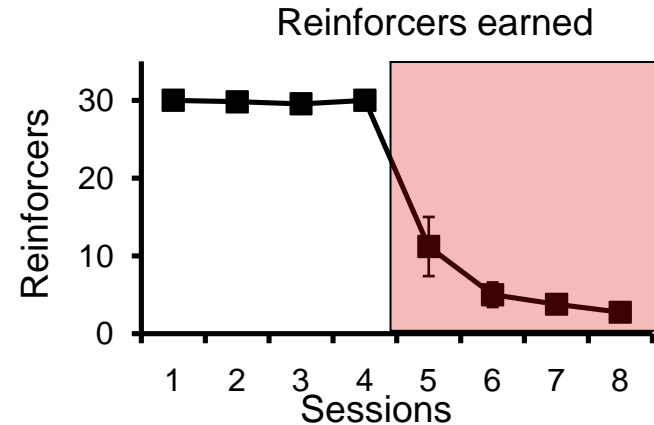
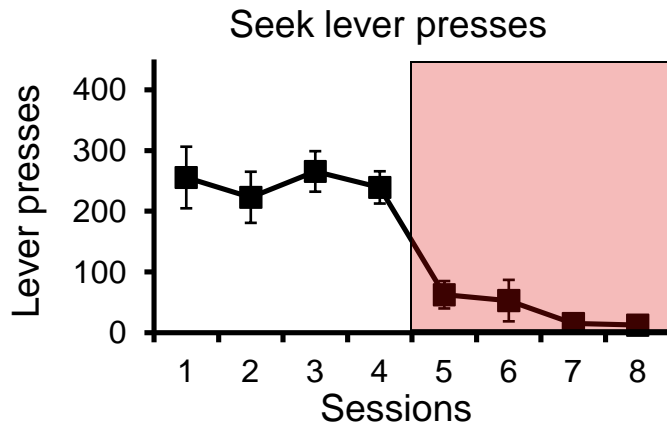
Seek-take task	Extended (80 inf) With seek-take interspersed	Seek-take baseline	ChR2	Punishment (Shock)	ChR2
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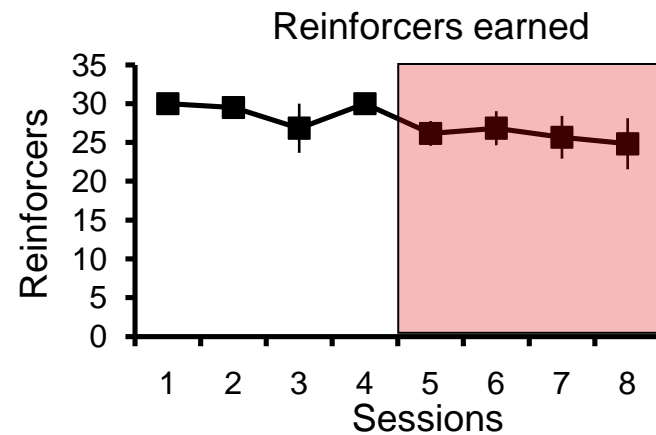
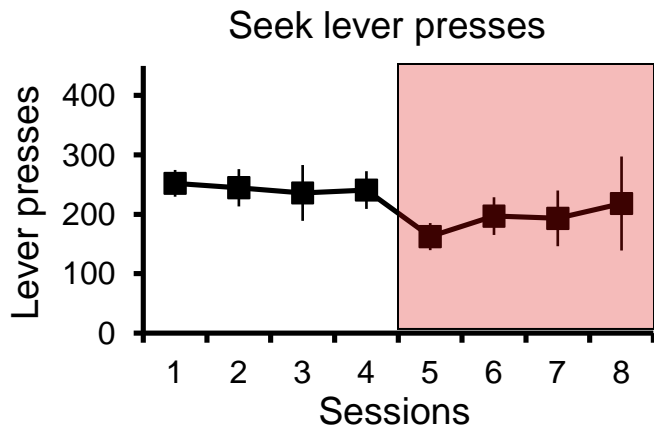
Cocaine seek-take Addicted rat

Non-compulsive and compulsive groups

Punishment sensitive

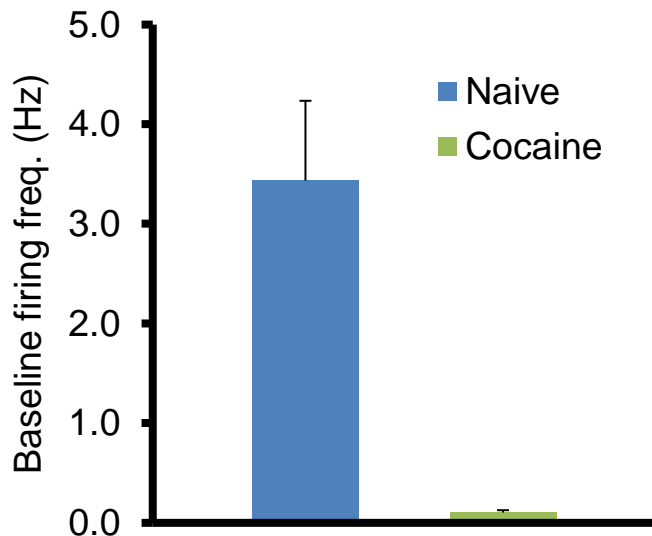
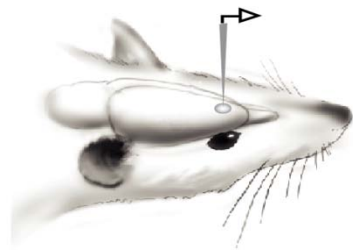


Punishment-resistant



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

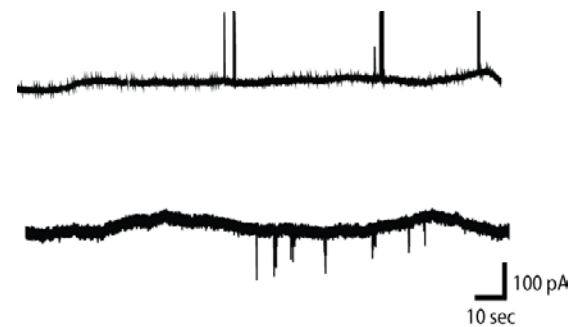
In vivo whole-cell recording in anesthetized rat, targeting prelimbic region



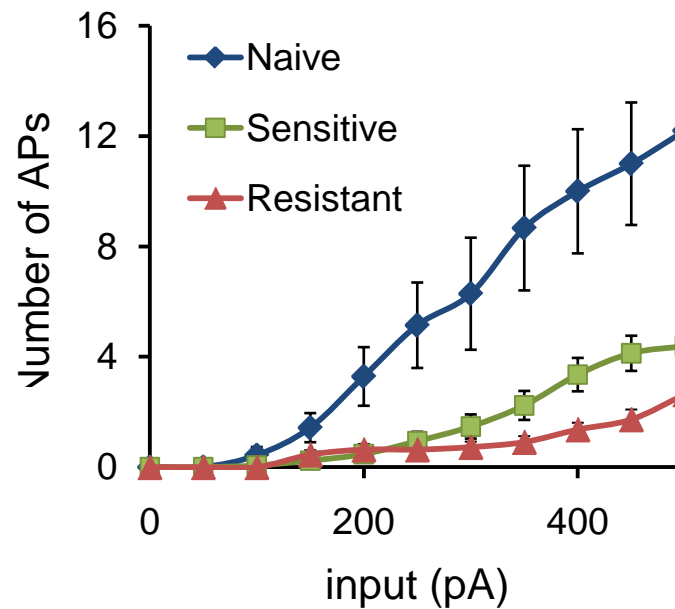
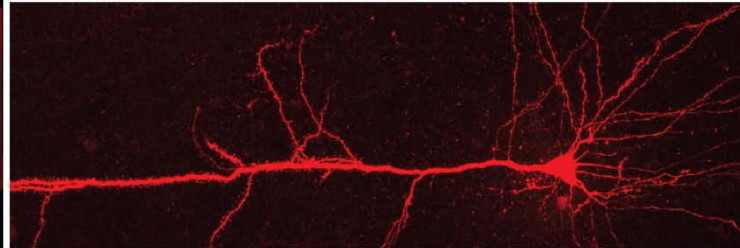
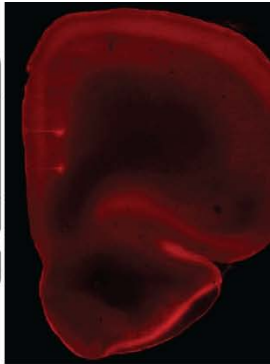
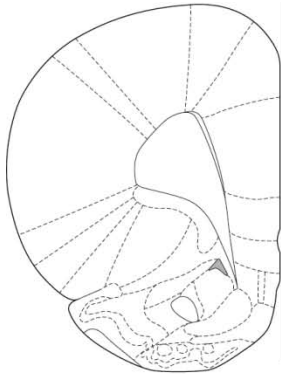
Naive



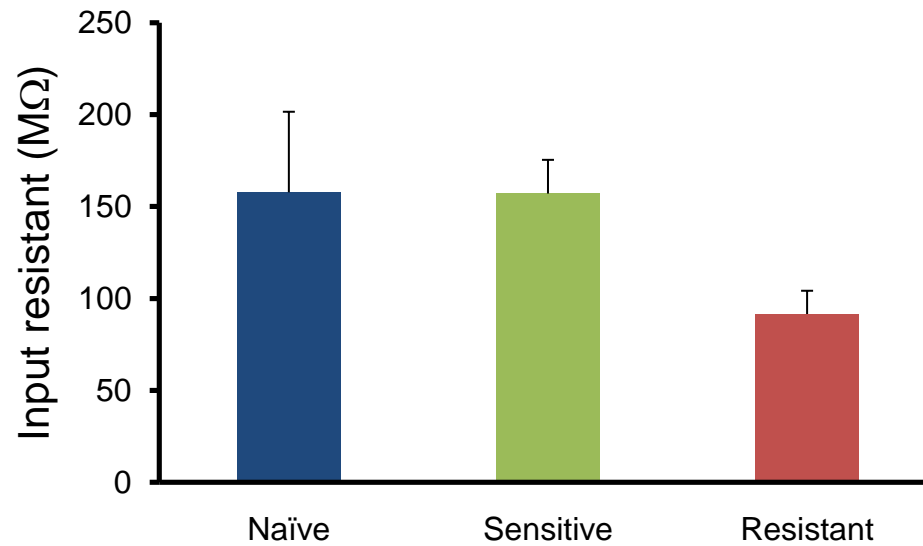
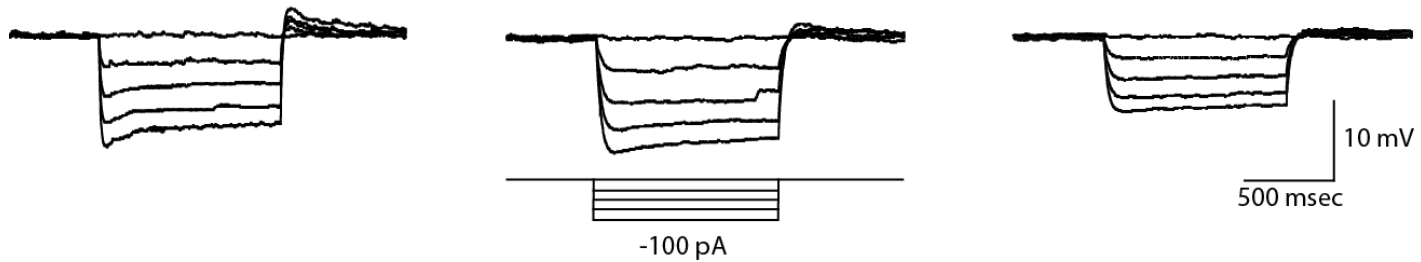
Cocaine



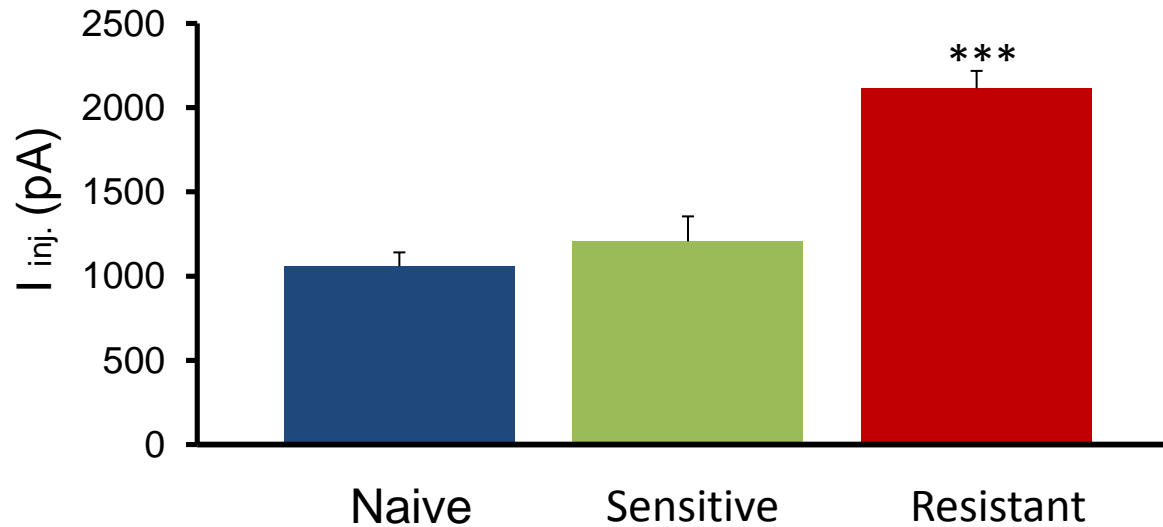
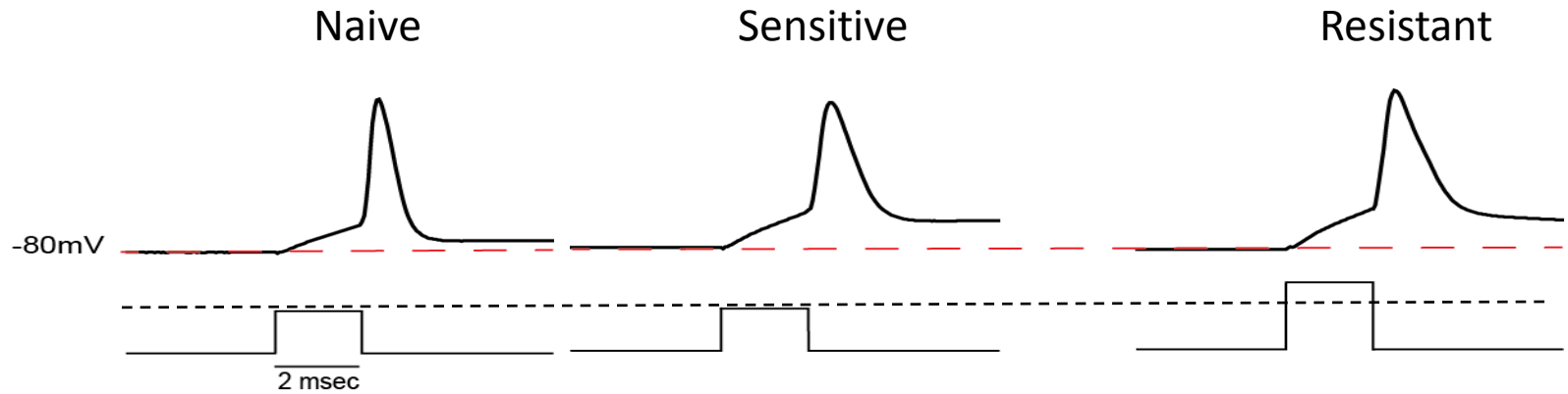
Long-access to cocaine decreases excitability of deep-layer cortical neurons



Resistant rats have lower Input resistant

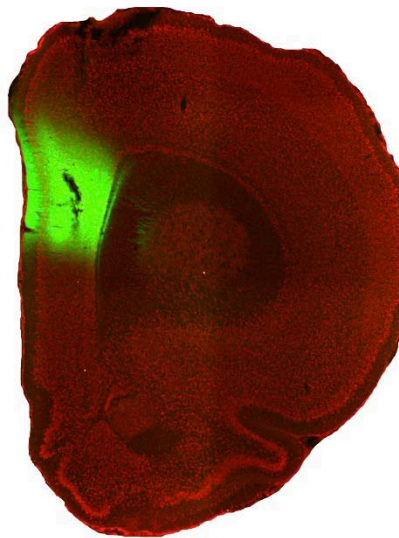


More current is needed to evoke action potential in mPFC neurons from Resistant rats.

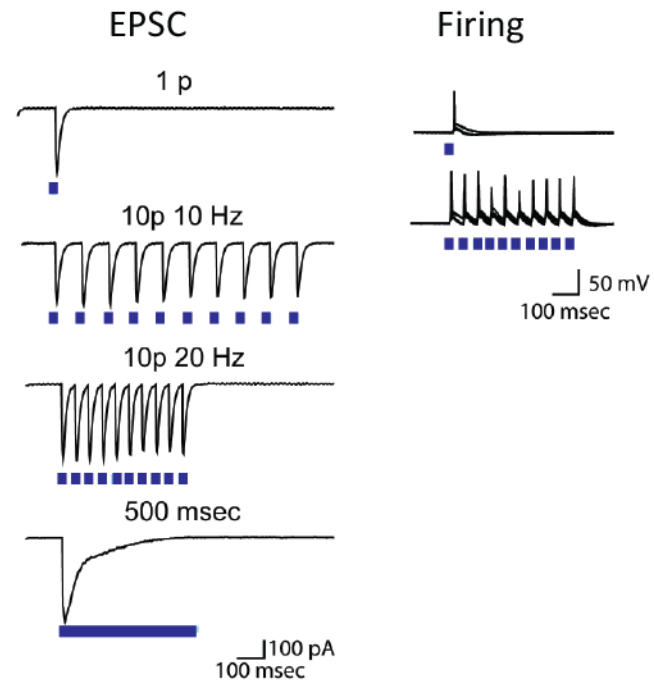


Augmenting activity in the prelimbic area

Channelrhodopsin-expressing mPFC neurons exhibit robust photo-excitation

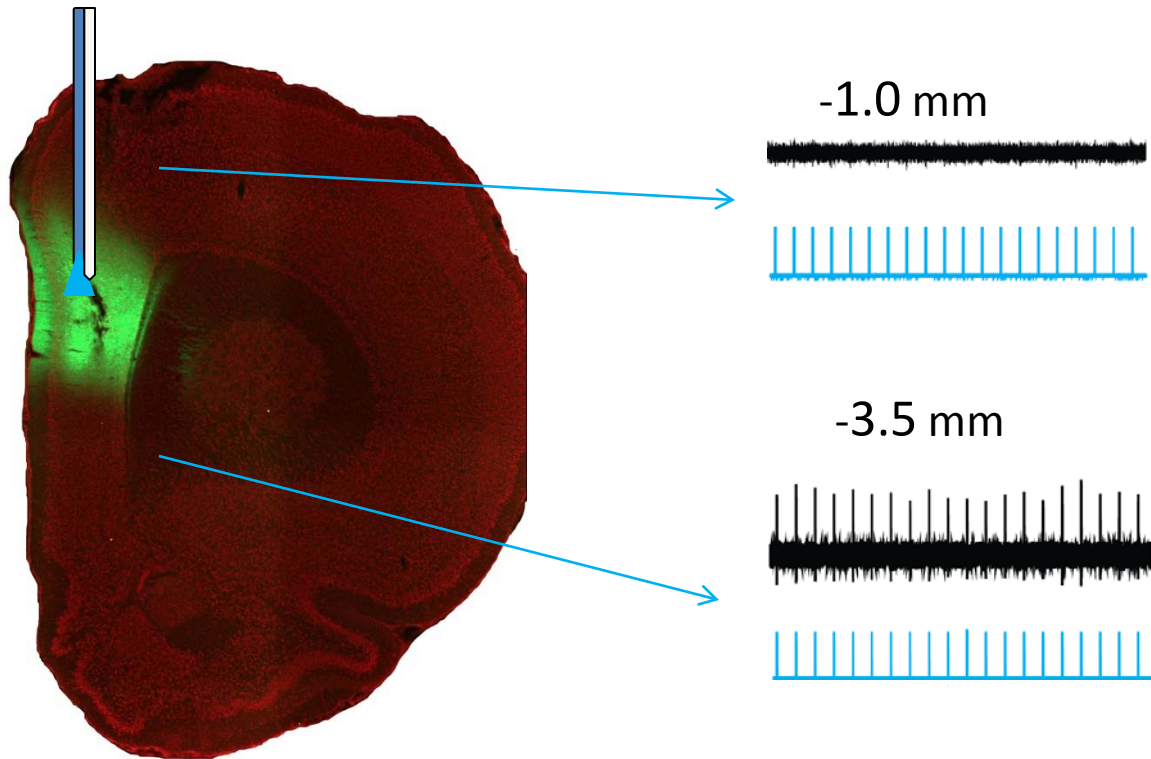


Ex vivo

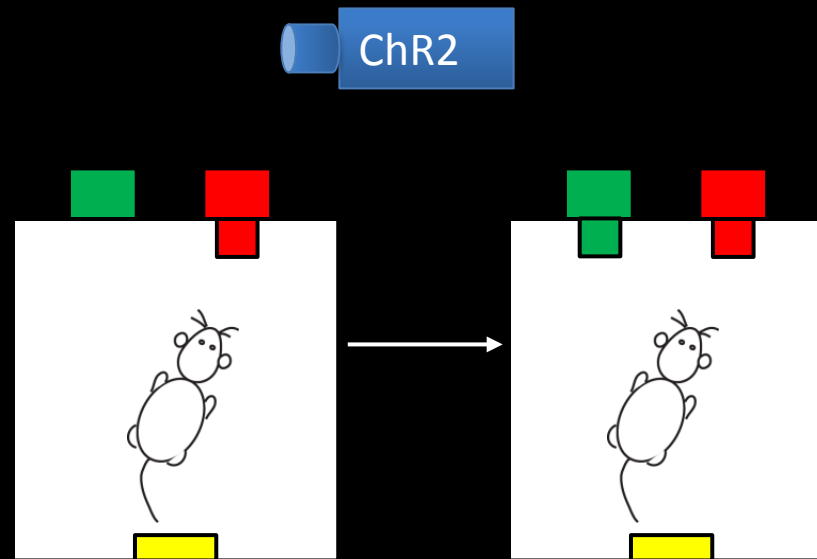


In vivo photo-stimulation

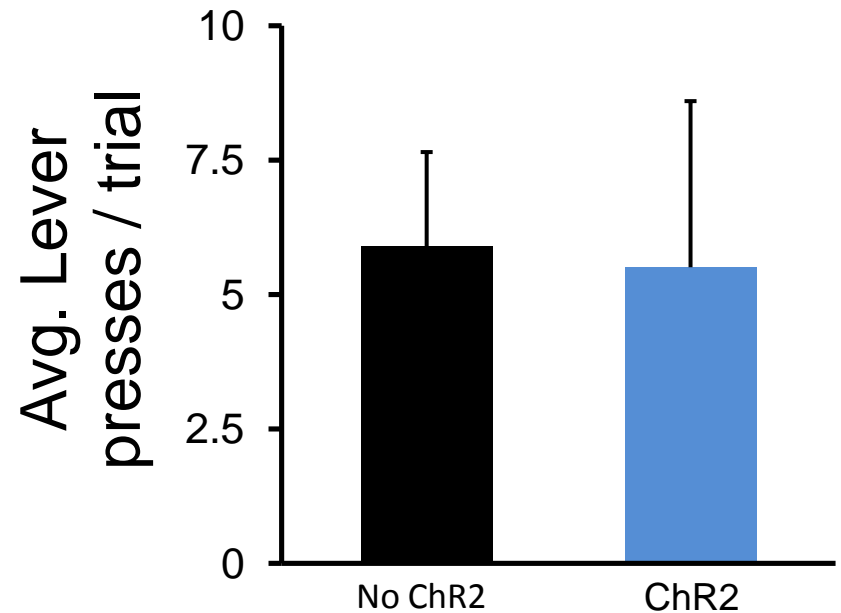
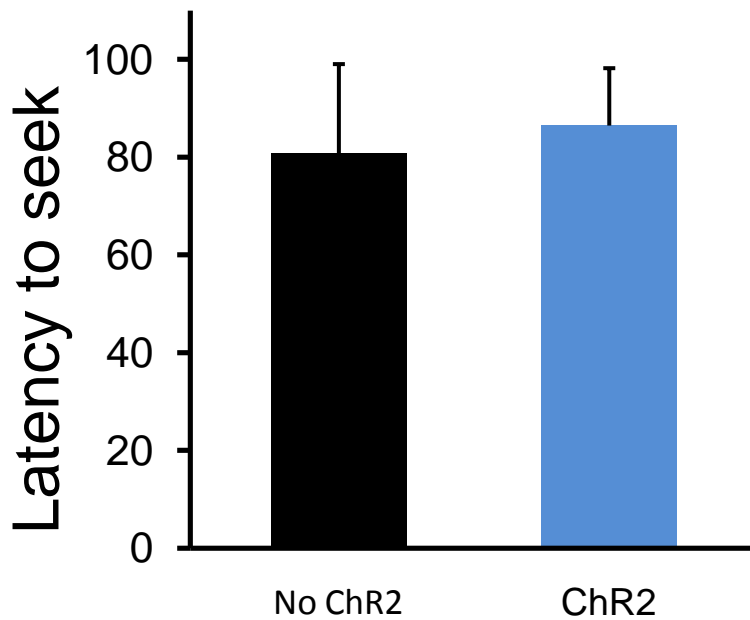
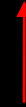
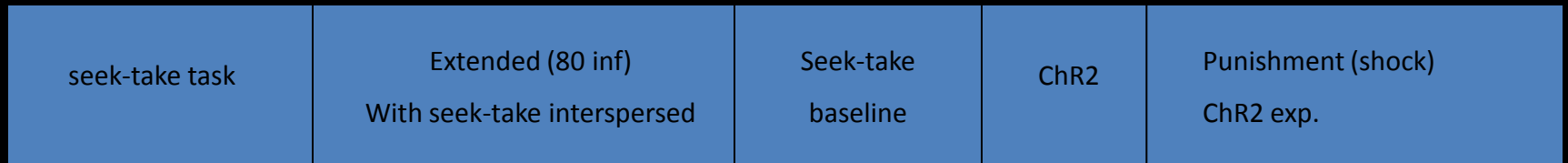
Optrode recording



1 Hz stimulation during Seek chain



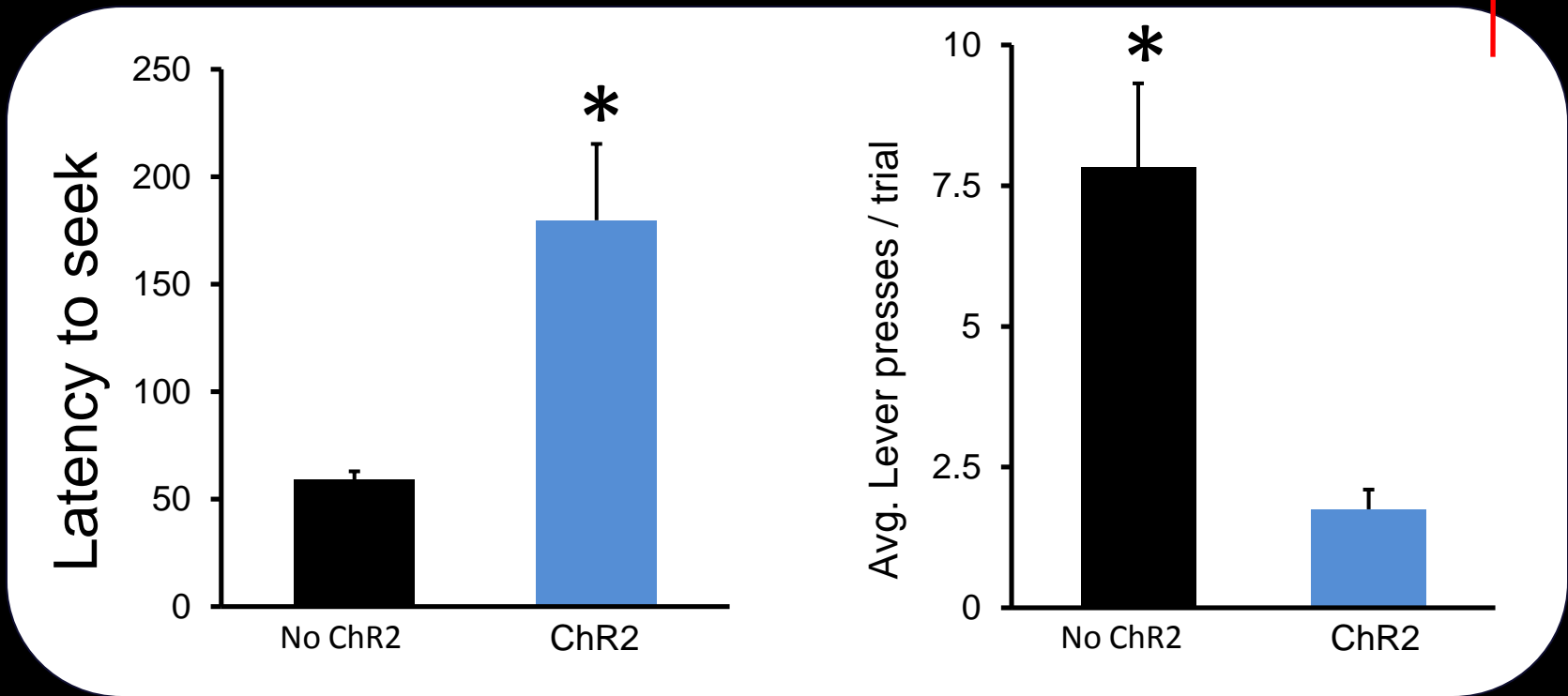
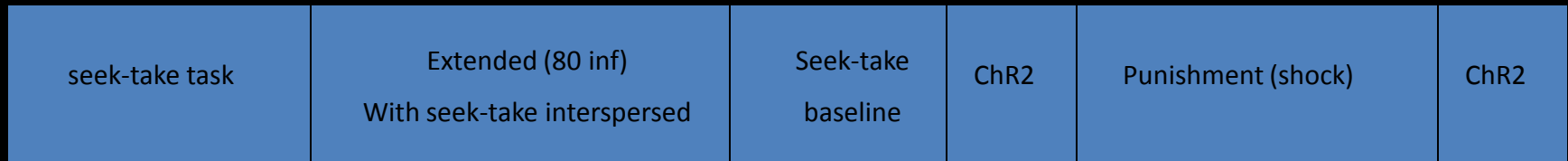
Activation of prelimbic neurons *prior* to punishment has no effect on the rat's drug-seeking behavior



Photostimulation of mPFC decreases compulsive cocaine seeking



What happens after the rats learned that they might be shocked?



Conclusion

- Rats with a history of long-term cocaine use exhibit hypofrontality in the prelimbic region of the PFC.

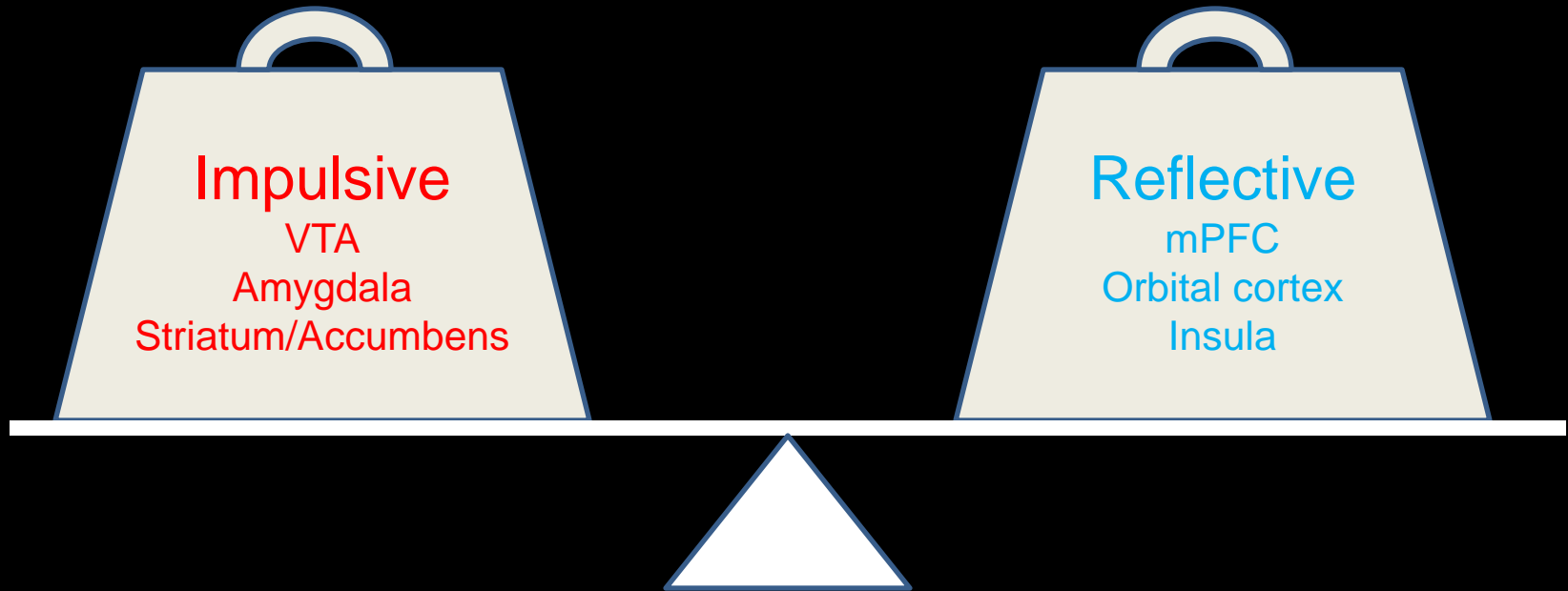
Conclusion

- *Rats with a history of long-term cocaine use exhibit hypofrontality in the prelimbic region of the PFC.*
- Introducing negative consequence (cost) reveals the role of mPFC in mediating inhibitory control over unwanted behaviors.

Conclusion

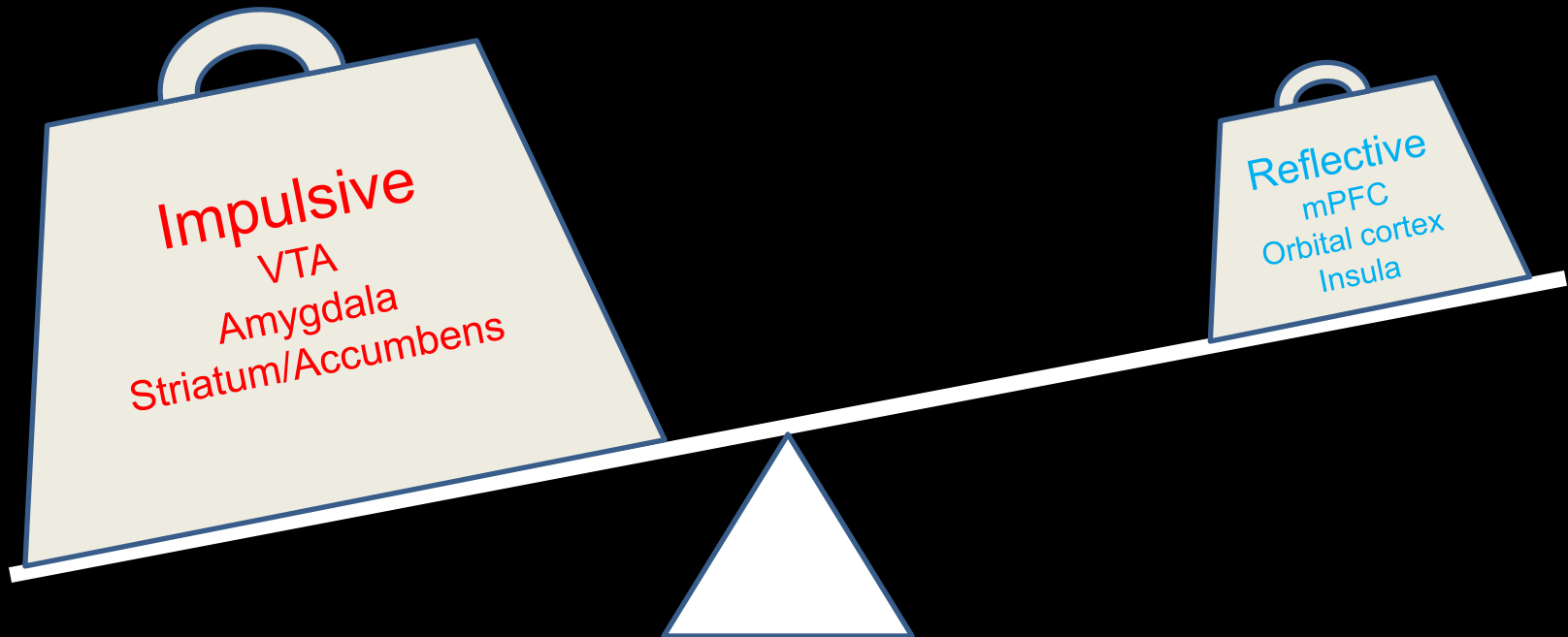
- *Rats with a history of long-term cocaine use exhibit hypofrontality in the prelimbic region of the PFC.*
- *Introducing negative consequence (cost) reveals the role of mPFC in mediating inhibitory control over unwanted behaviors.*
- Photo-stimulation of prelimbic region decreases compulsive cocaine-seeking behavior.

Addiction: loss of willpower to resist drugs



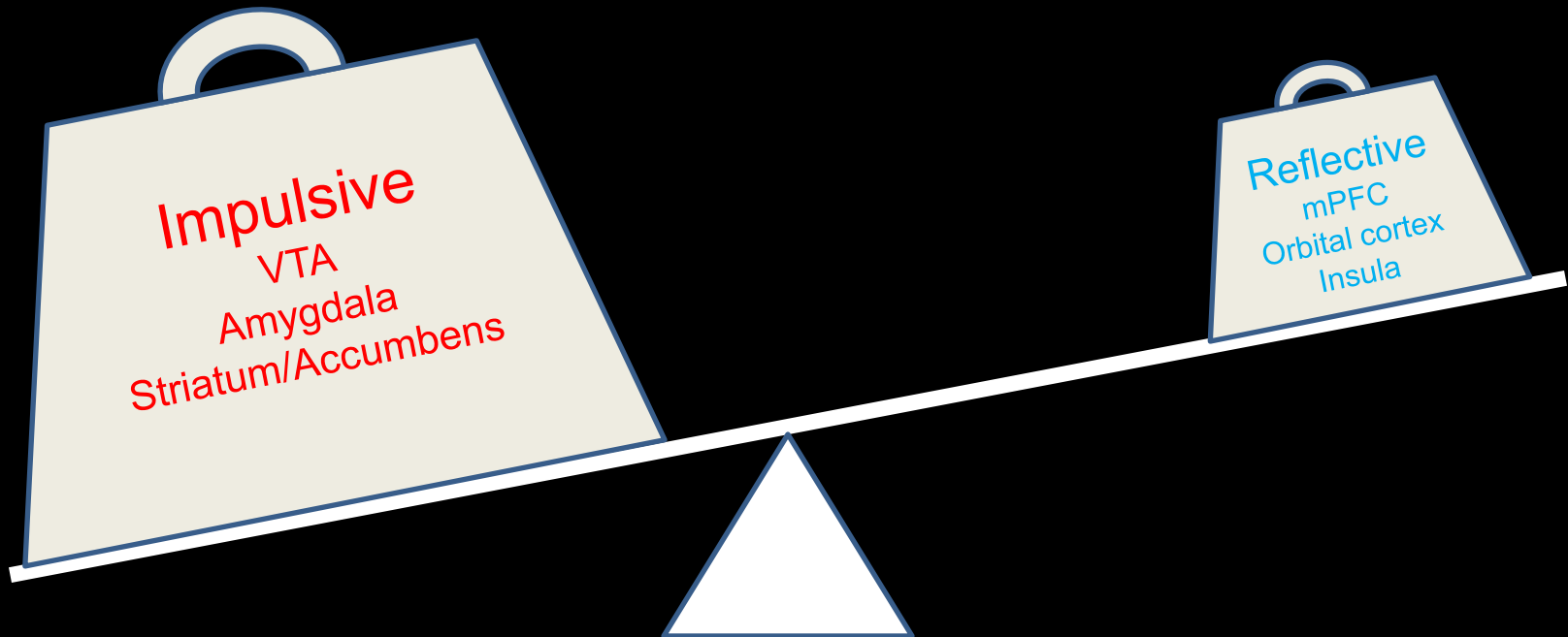
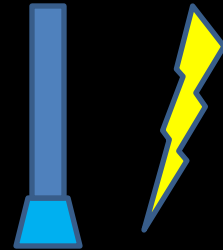
Addiction: loss of willpower to resist drugs

Prolong drug use

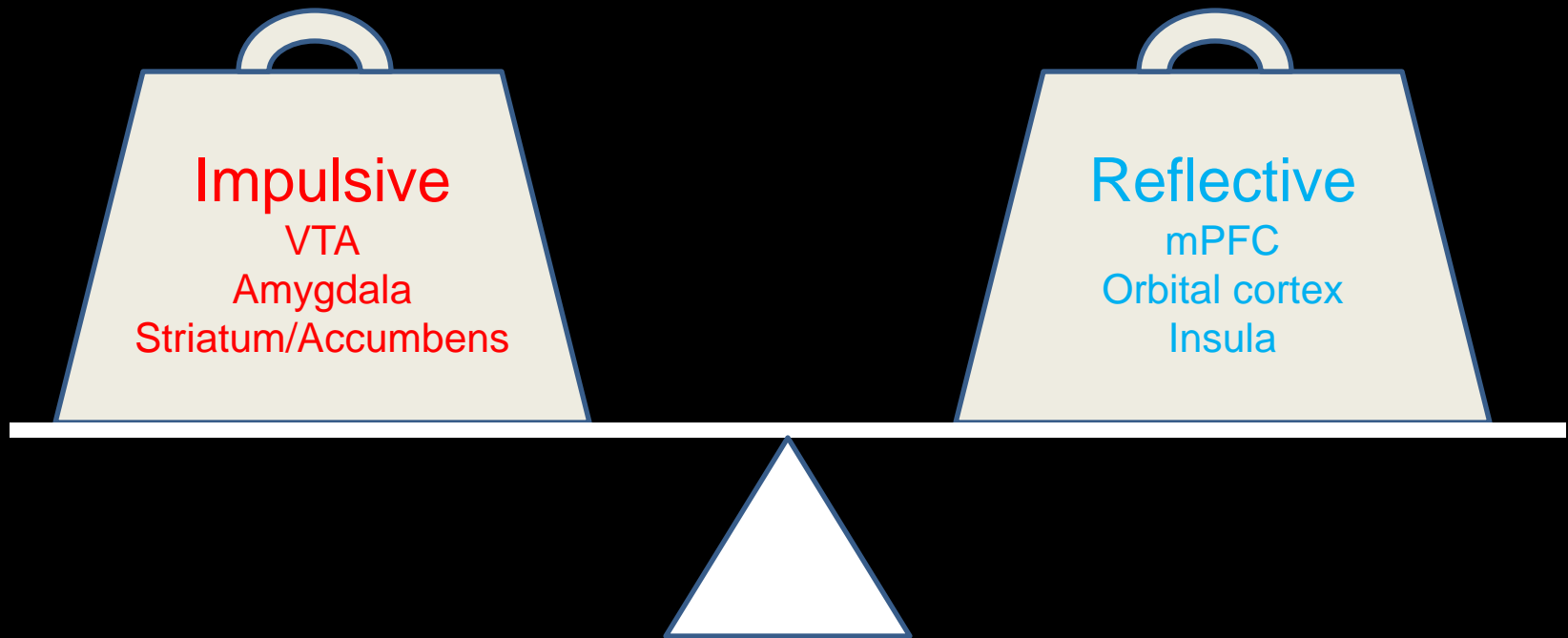


Addiction: loss of willpower to resist drugs

Therapeutic approach



Addiction: loss of willpower to resist drugs



Acknowledgements

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