

The Addicted Synapse: Mechanisms of Structural Plasticity in Nucleus Accumbens

Scott J. Russo

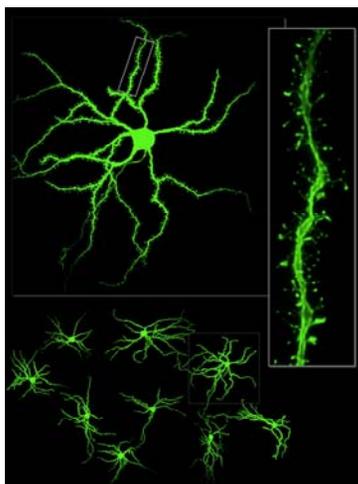
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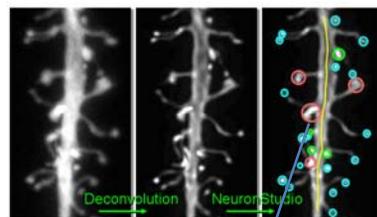
Verona June 8th, 2010

Image from Dani Dumitriu & TheVisualMD

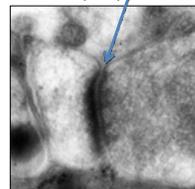
Spines are sites for chemical communication between cells in the brain



Russo et al., 2010



Synapse

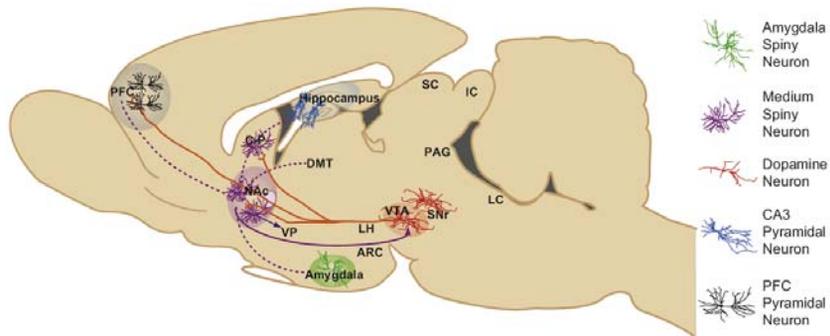
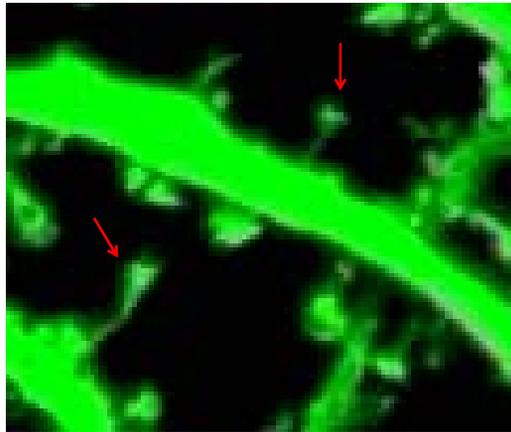


Viewed at 60,000 x normal size

The adult human brain is estimated to contain
from 10^{14} to 5×10^{14} (100-500 trillion) synapses.

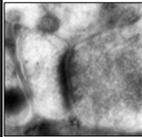
Spines are highly dynamic and change in response to experience

6 hr loop

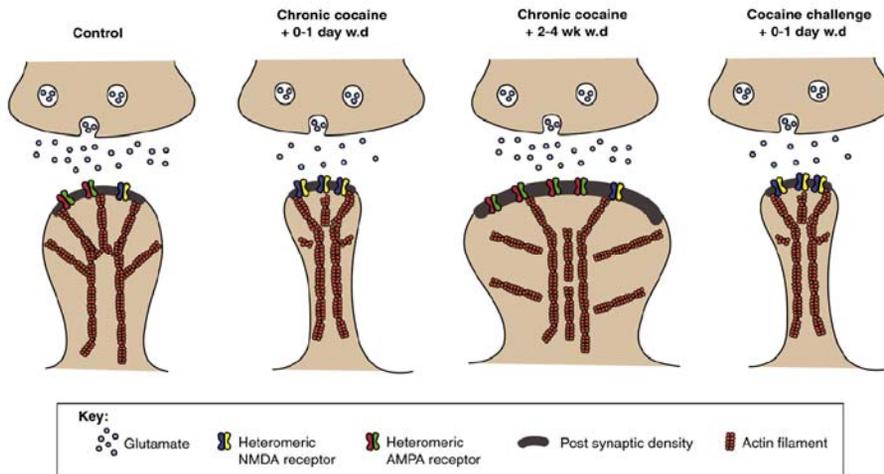


Brain Area - Stimulants	Drug regimen	Structural change	Molecular mediators
NAc medium spiny neuron	EA chronic cocaine (2-4 hr w.d.) EA or SA chronic cocaine (24 hr-months w.d.) EA chronic cocaine 3 week w.d. + challenge dose (24 hr w.d.)	↑ Thin spines ↑ Mushroom spines; dendrite complexity ↑ Thin spines	NFκB, deltaFosB, G9A CDK5, MEF2
VTA dopamine neuron	EA acute cocaine (2-4 hr w.d.)	↑ Spine density	NA
Hippocampus pyramidal neuron	NA	NA	NA
mPFC pyramidal neuron	EA or SA chronic cocaine (24 hr-months w.d.)	↑ Spine density; dendrite complexity	NA
oPFC pyramidal neuron	EA or SA chronic cocaine (24 hr-months w.d.)	↑ Spine density; dendrite complexity	NA

Maze and Russo, 2010



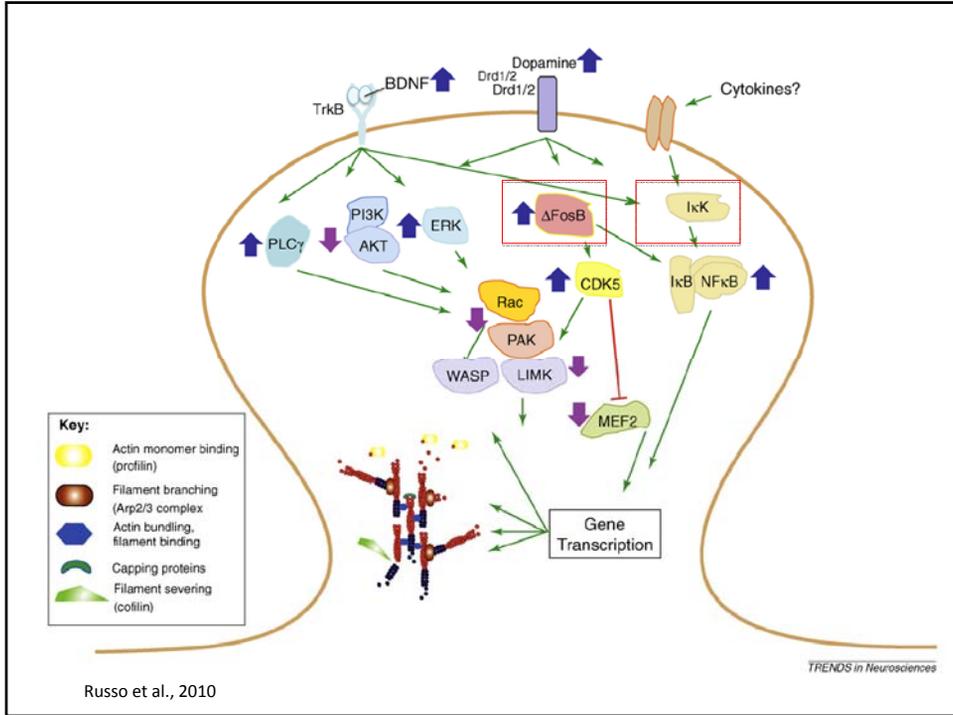
Neurophysiological consequences of drug-induced structural plasticity



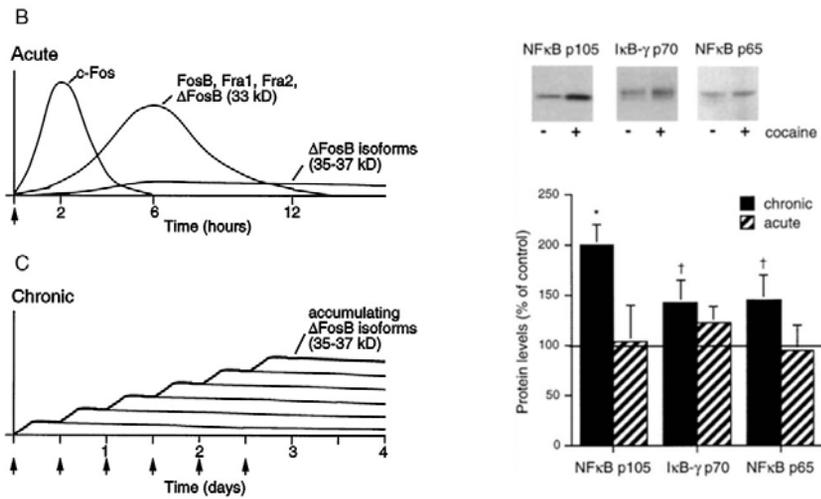
TRENDS in Neurosciences

Russo et al., 2010

How does the environment interact with genes to produce these pathological synapses and how does this control addictive behavior?

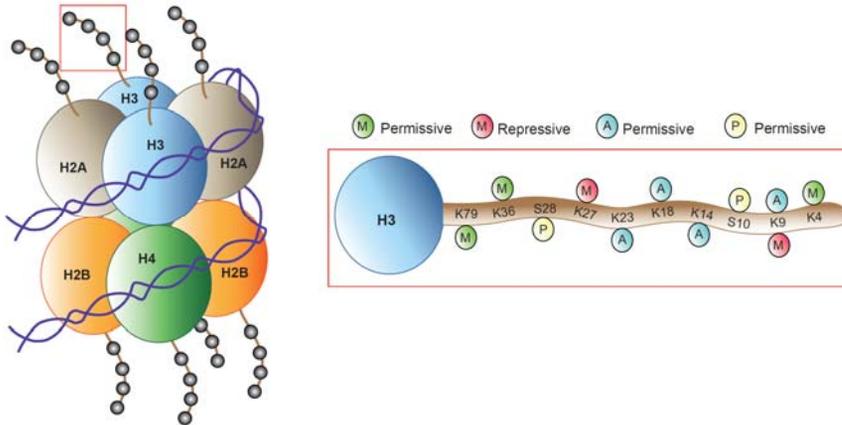


Cocaine leads to Δ FosB accumulation and increased NF κ B expression



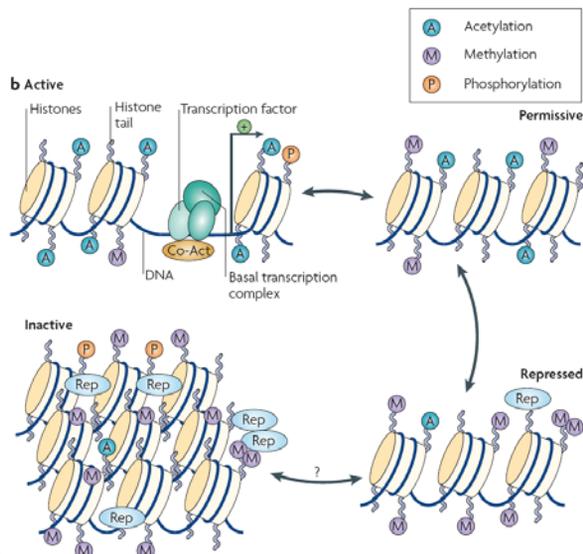
Nestler, 2001

Epigenetic changes are “above the genome”



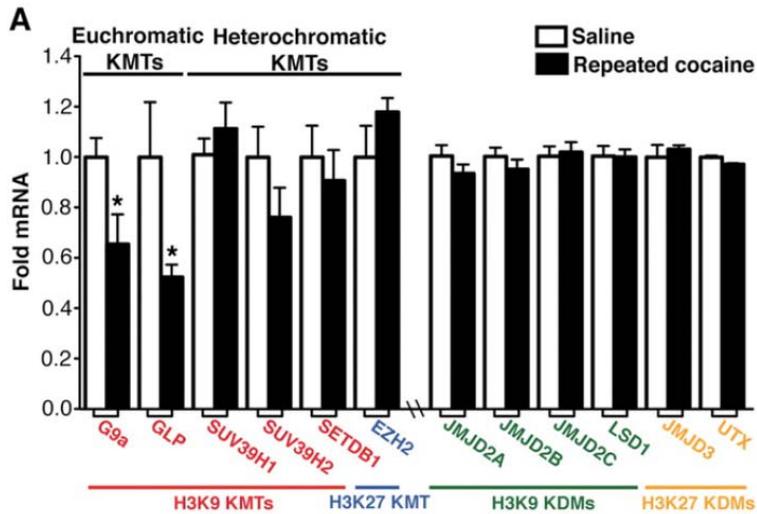
Maze and Russo, 2010

Chemical modifications on genes control the expression of proteins which guide behavior



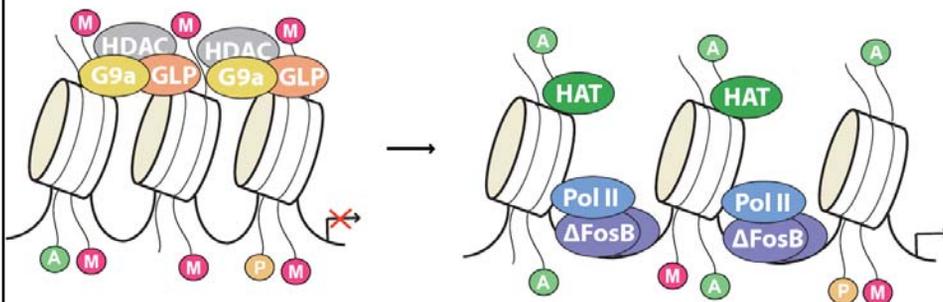
Tsankova et al., 2007

Cocaine decreases the histone methylating enzymes G9a and GLP



Maze et al., 2010

Transcriptional mechanisms of structural plasticity

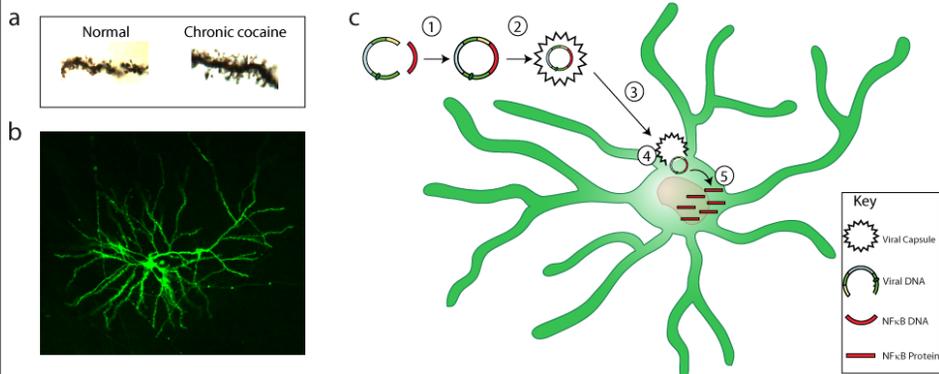


- + NFκB, MEF2, CDK5 gene
- G9A gene
- + Structure genes

Maze and Russo, 2010

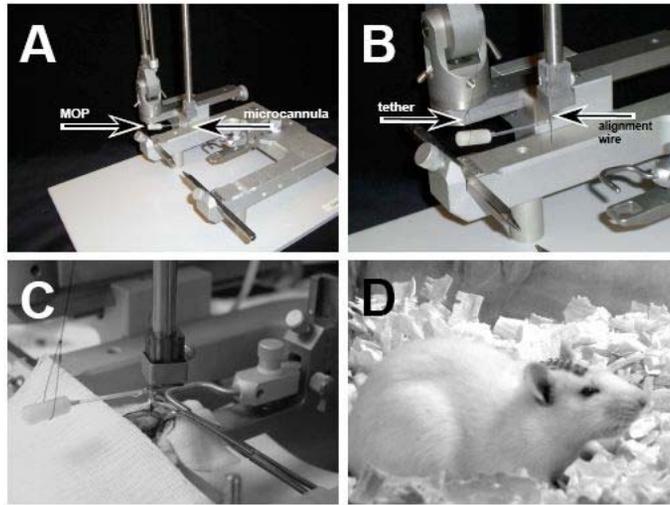
How do we study the functional consequences on addiction-related synapse plasticity and behavior?

What is gene therapy?

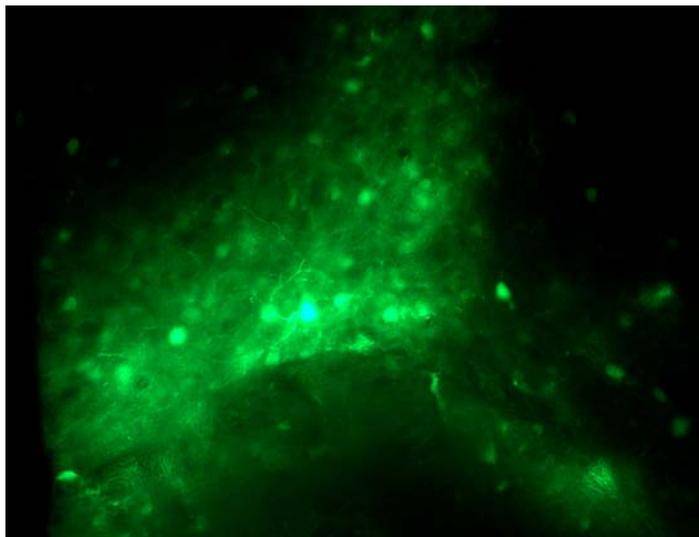


Gene therapy has with success in treating neurological disorders and may one day be useful in treating addiction.

How do we deliver it to brain?



Expression of a fluorescent protein in brain



Studying addiction in laboratory animals

- Locomotor sensitization.



- Conditioned place preference.

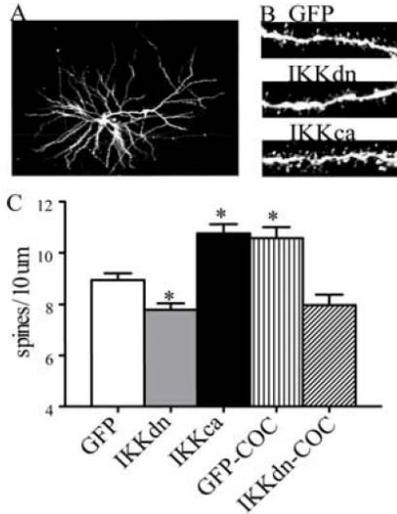


- Self-administration



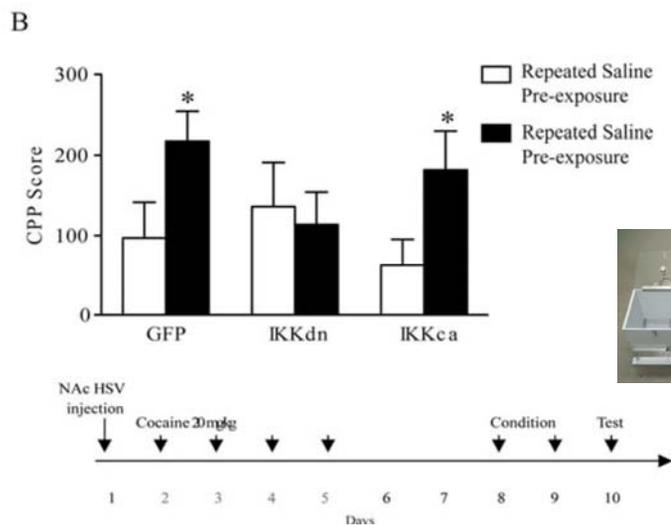
Can we target molecules in nerve cells to control drug addiction-related synapse plasticity and behavior?

Gene therapy to block NFκB reverses cocaine-induced synapse plasticity



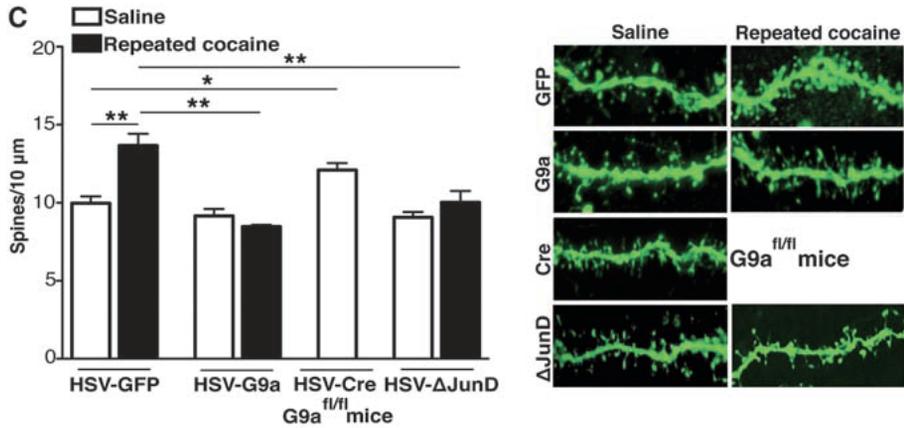
Russo et al., 2009

Gene therapy to inhibit NFκB decrease hypersensitivity to cocaine.



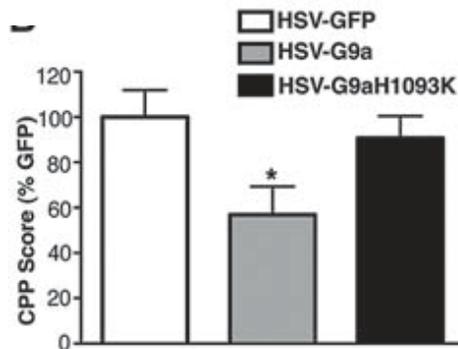
Russo et al., 2009

Gene therapy to replace G9a reverses cocaine-induced synapse plasticity.



Maze et al., 2010

Gene therapy to replace G9a in addicted animals decreases hypersensitivity to cocaine

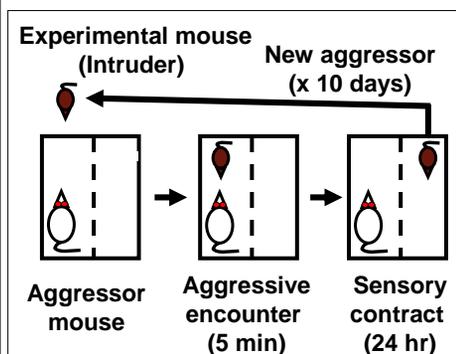


Maze et al., 2010

Why are humans most susceptible to addiction when they are stressed?

Social Defeat Stress Model

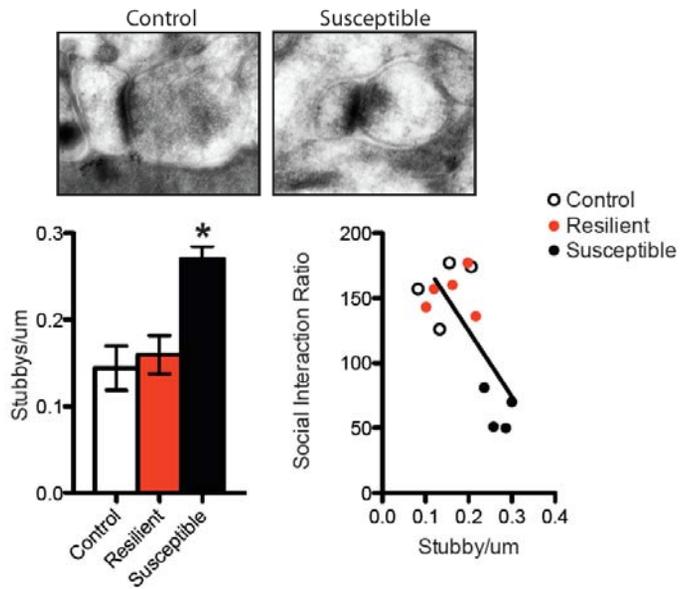
Chronic social defeat causes:



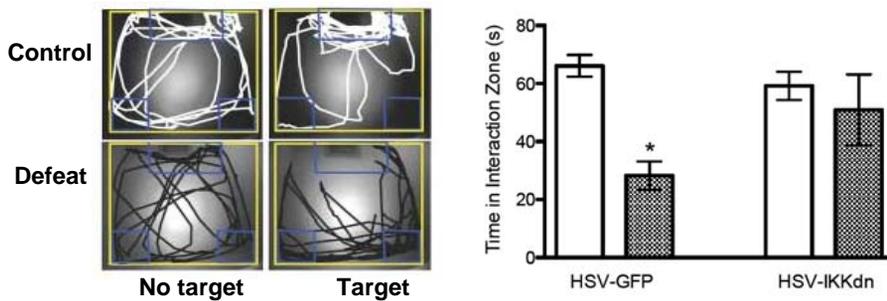
- Anhedonia-like symptoms (decreased interest in sucrose and sex)
- Anxiety-like symptoms
- Hyperactivity of HPA axis
- Disrupted circadian rhythms
- Metabolic syndrome
- Profound social avoidance
- Increases addictive behavior

Berton et al., 2006
Krishnan et al., 2007

Social Defeat Stress and drugs causes similar changes in the synapse.



Gene therapy to inhibit NFκB can reverse social avoidance in mice



Can this also reduce stress-related relapse, a huge problem in drug addiction treatment?

Should the goal of psychiatric treatment be to reverse maladaptive plasticity?

- Pharmacological interventions for addiction (target glutamate or other important signaling pathways).
- Behavioral Therapy (motivational interviewing, CBT, etc.).
- Invasive surgical techniques (viral-mediated gene transfer).

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