Motivation

Not all responses can be explained by a simple sensory stimulus-> motor response circuit.

Why do animals spontaneously get up and do something (and then keep doing it)?

Motivational/Reward Pathways provide a mechanism to intiate and maintain behaviors.

Dopamine, Serotonin, and Endogenous Opioid Peptides are the major transmitters of the Reward Pathways.

Motivational Pathologies:
decreased = depression, increased = addiction.

DSM IV Criteria for substance abuse

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

(1) recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

(2) recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)

(3) recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)

(4) continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

B. The symptoms have never met the criteria for Substance Dependence for this class of substance.

Table 1
DSM-IV diagnostic criteria for substance dependence adapted from Mendelson and Mello (1996)

Categories	Symptoms
Tolerance	1. A need for markedly increased amount of the substance to achieve intoxication or desired effects; Markedly diminished effects with continued use of the same amount of the substance
Withdrawal	2. Criteria for withdrawal from the specific substance; The same as (or closed related to) substance taken to relieve or avoid withdrawal symptoms
Binge	3. The substance often taken in larger amounts or over a longer period than was intended
Frequent relapse	4. A persistent desire or unsuccessful efforts to cut down or control substance use
Drug seeking and taking	5. A great deal of time spent in activities necessary to obtain substance, use the substance, or recover from its effects 6. Continued substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
Social activity disruption	7. Important social, occupational, or recreational activities given up or reduced because of substance use

Reward pathways

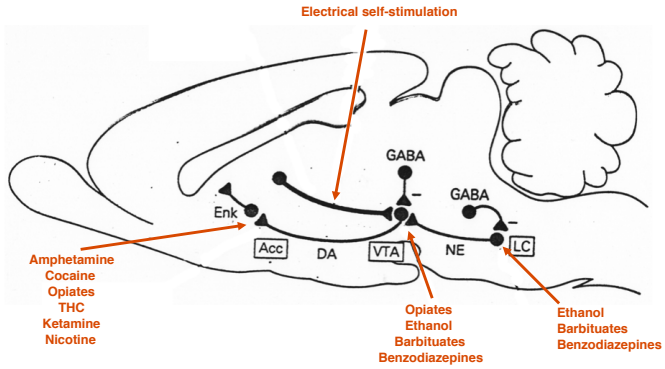
Dopamine and opioid peptides from ventral tegmental area (VTA) to nucleus accumbens (N.Acc.).

–> Exogenous opiates activate opioid receptors (e.g. morphine,heroin)

–> dopamine re-uptake inhibitors (e.g. cocaine, amphetamine)

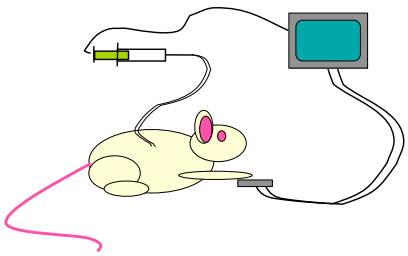
–> increase effective concentration of dopamine at the NAcc synapse.

Reward Pathways



Animal models

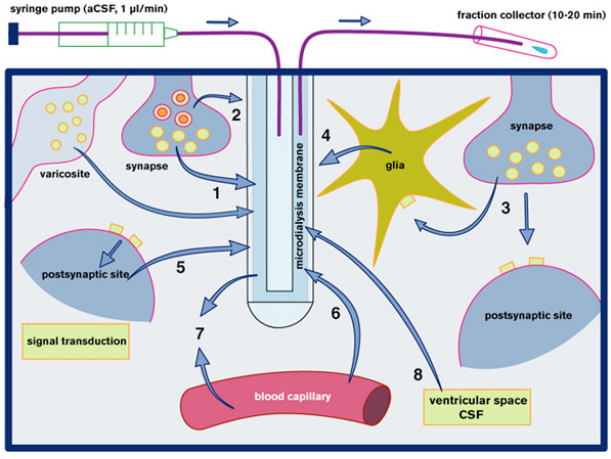
Rats will self-administer drugs of abuse and titrate the dose they get to maintain a steady plasma level (and hence dopamine in the N.Acc.).
This looks like pattern of bar-pressing for brain self-stimulation.



http://www.youtube.com/watch?v=de_b7k9kQp0

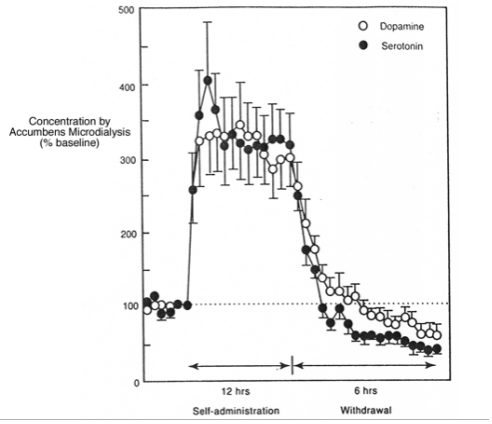
http://www.youtube.com/watch?v=de_b7k9kQp0

Cocaine -> Increase DA & 5HT in n. accumbens

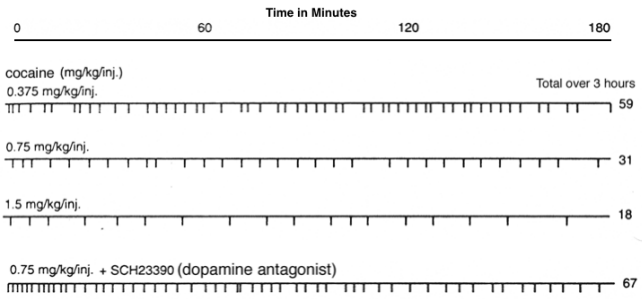


http://www.labautopedia.com/mw/index.php/Microdialysis:_An_introduction

Cocaine -> Increase DA & 5HT in n. accumbens



Bar pressing for cocaine

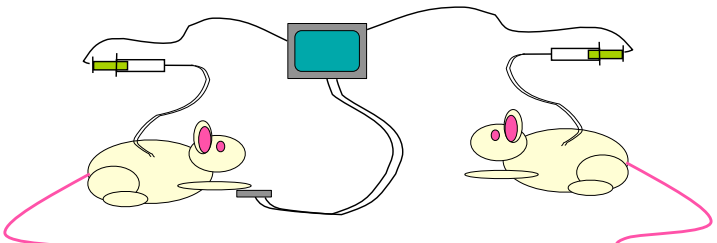


(Control is Yoked animal)

Yoked Control

One rat self-administers the drug

Yoked rat gets same injection of drug at same time as self-administering rat (but can't control injections)



Self-administering
(finds drug rewarding)

Yoked control
(finds drug aversive)

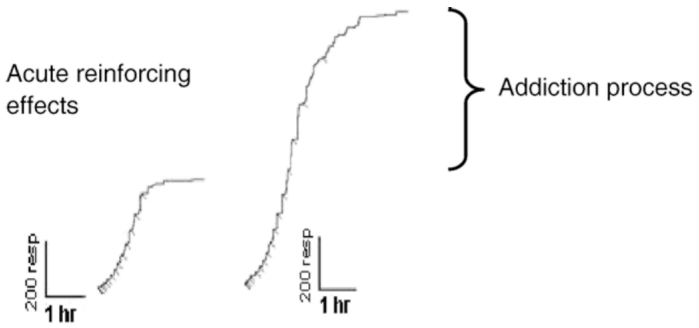


Fig. 1. Cumulative records for a representative rat self-administering cocaine (1.5 mg/kg/inj) on a PR schedule of reinforcement. The record on the left represents the acute reinforcing effects of cocaine. Presumably if the breakpoint were to escalate over time this would reflect an addiction process, as represented in the record on the right. Tick marks on the records indicate a drug infusion in this and subsequent figures.

Issues in the Study of Drug Addiction

Rats will usually not spontaneously administer drugs of abuse, and have to be trained up.

Rats are very good at maintaining steady rate of drug intake ("recreational use").

Very hard to get a rat to "binge" on drugs uncontrollably.

Big effects of context and learned cues.

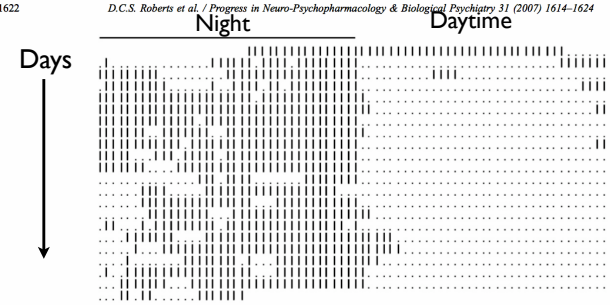
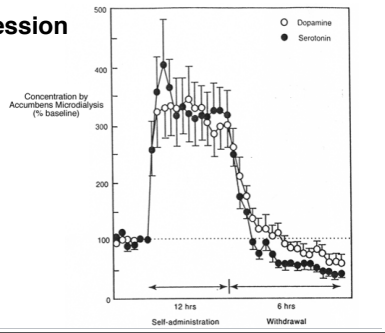


Fig. 8. Circadian pattern of cocaine self-administration (1.5 mg/kg/inj) appears when access is limited to 3 discrete trials per hour. Each row represents one 24 h period. Injections are denoted by an upward line. A dot denotes a trial in which the rat declined to self-administer. Cocaine was provided for 21 consecutive days. The horizontal line at the top indicates the dark phase of the cycle.

Drug Addiction
= short-circuit of Food Reward

Cocaine
–> increases DA and 5HT levels in Accumbens
–> rebound decrease of dopamine and serotonin release
–> withdrawal and depression
–> relapse.



Tolerance:

decreased number of receptors, decreased postsynaptic second messengers, or increase in target transporters.

So takes more drug to boost the system

Withdrawal:

Response to endogenous neurotransmitter is also reduced.

so when drug is not onboard neurotransmitter levels are too low in the synapse

Nasty side-effects, because receptors for drugs are not just in reward pathways

Drugs of Abuse

1. Rats and Monkeys will self-administer the drug

2. The drug increases electrical self stimulation of the reward pathways

3. The drug increases dopamine release in the reward pathways

Verified drugs of abuse:

Cocaine, amphetamine (dopamine receptors/transporters)

Morphine, heroin, other opiates (opiod peptide receptors)

Nicotine (nicotinic acetylcholine receptors)

MDMA (ecstasy; serotonin transporters)

Ethanol, barbituates, benzodiazepines (GABA Cl- channel receptors)

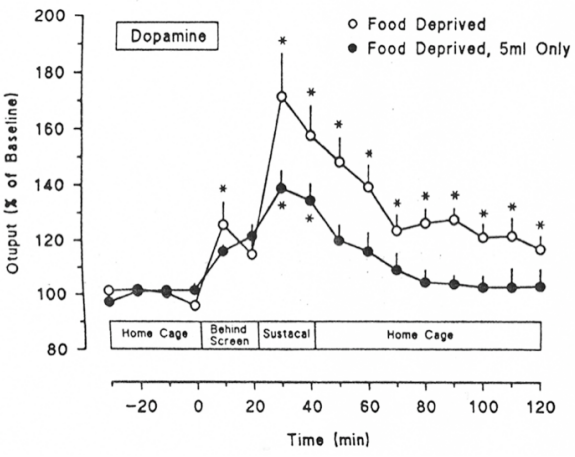
Not so easy to get self administration:
THC (marijuana) (cannabinoid receptors)

Drug Addiction
= short-circuit of Food Reward

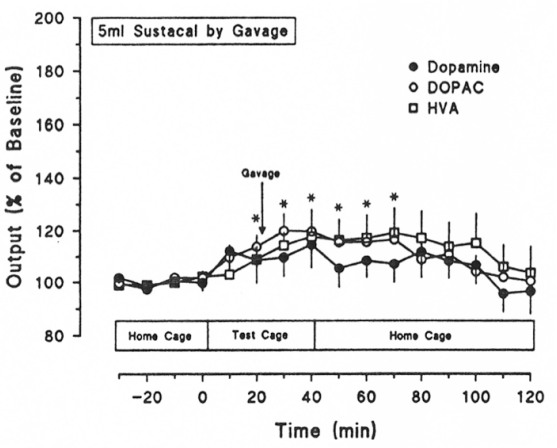
Cocaine
–> increases DA and 5HT levels in Accumbens
–> rebound decrease of dopamine and serotonin release
–> withdrawal and depression
–> relapse.

Food or other natural pleasure
–> much smaller increase in DA in Accumbens

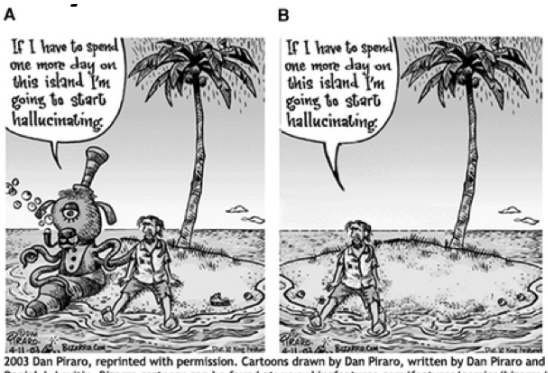
Eating increases Dopamine in N. Acc.



Dopamine increase requires taste



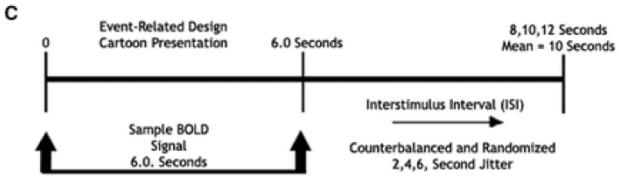
Jokes increase activity in Reward Pathways



2003 Dan Piraro, reprinted with permission. Cartoons drawn by Dan Piraro, written by Dan Piraro and Daniel J. Levitin. Bizarro cartoons can be found at: www.kingfeatures.com/features/comics/bizarro/about.htm

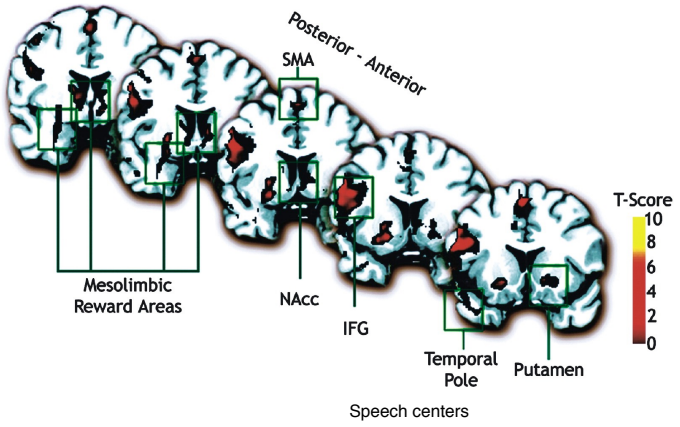
Figure 1 .Example of a Funny Cartoon and the Same Cartoon with Funny Cues Omitted

Stimulus Presentation

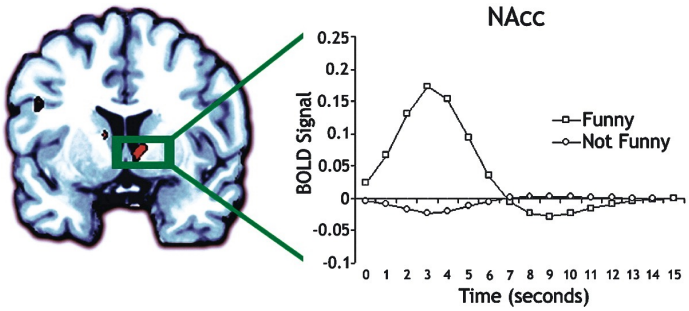


Stimuli were presented in an event-related fMRI paradigm, with each cartoon being presented in random order for 6000 ms. A jittered interstimulus interval (ISI) was used, varying randomly between 2000, 4000, and 6000 ms and counterbalanced, a priori, across funny and nonfunny events. Analysis was limited to the blood-oxygenation level-dependent (BOLD) signal acquired during stimulus presentation (Figure 1C) . Data were collected in one 15 min and 4 s session consisting of 84 events using a TR of 2000 ms

Funny - Non Funny Brain Activation



Time Series of Accumbens Activation



Molecular Mechanisms

Acquisition of addiction requires multiple trials/ chronic exposure.

Thought to be mediated by chronic changes in reward pathway (VTA to N.Acc.) in receptor number, second messengers, and transcription factors induced by repeated drug use.

Leads to:

Craving -- to reverse withdrawal

Tolerance -- requiring higher doses

Synaptic Changes in Addiction

Increased spines and synapses in N. Accumbens neurons that respond to cocaine and recieve dopamine input

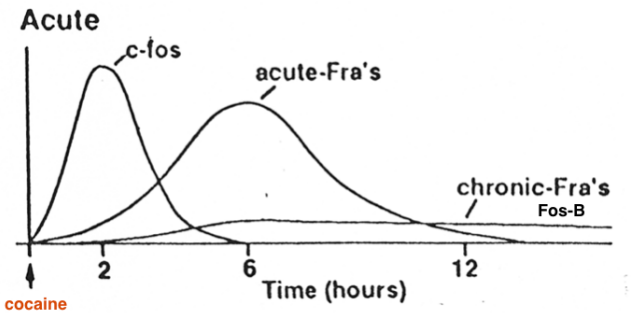
Synaptic changes mediated by increases in transcription factors like delta Fos B

Transgenic increase in ΔFosB leads to synaptic changes similar to cocaine, increases sensitivity to cocaine

ΔFosB knockdown reduces natural rewards (maternal behavior, wheel running)

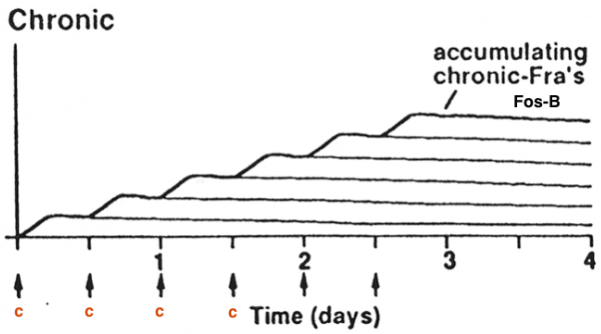
Gene expression after Cocaine

(single injection causes transient expression of transcription factors)

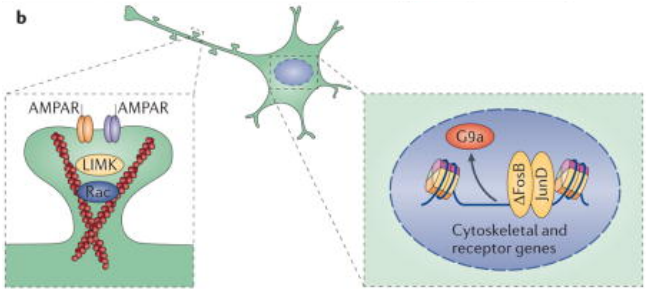


Gene expression after repeated Cocaine

(build up of transcription factors -> change in neural circuitry)



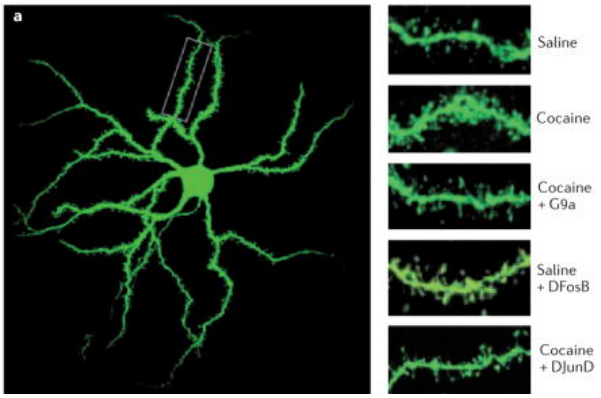
Although the molecular underpinnings of these structural changes remain incompletely understood, several factors that control gene transcription and chromatin regulation have been implicated (as depicted in the example dendrites on the right).



A key goal is to now identify how these epigenetic factors control cytoskeletal and [illegible] cytoskeleton-altering genes to regulate spine morphology and consequently changes in neuronal circuitry and addiction-related behaviors.

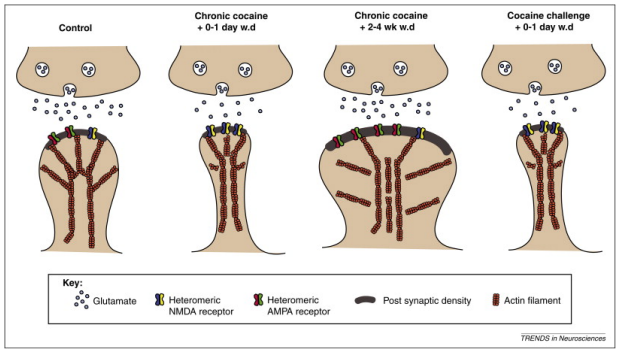
Nat Rev Neurosci. 2011 Oct 12; 12(11): 623–637.

nearly all drugs of abuse alter the structural connectivity of neurons in the reward circuitry, an effect most evident in changes in the number, shape, and size of dendritic spines on MSNs (medium spiny neurons, as depicted on the left) in the nucleus accumbens (NAc)



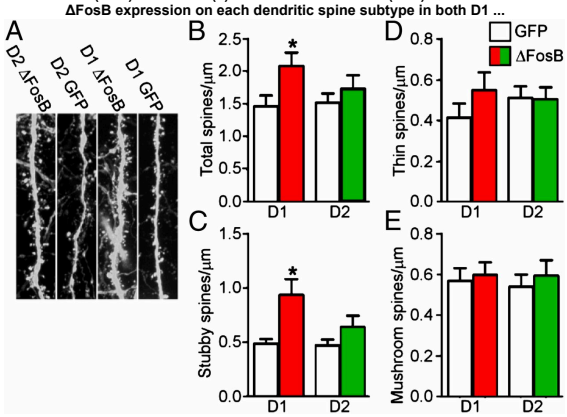
It is also likely that structural plasticity of the NAc plays a role in volition and decision-making, as self-administered drugs generally cause larger changes in spine density than the same doses administered by experimenters

Nat Rev Neurosci. 2011 Oct 12; 12(11): 623–637.



Model of addiction-related synaptic and structural plasticity in nucleus accumbens (NAc). Chronic exposure to cocaine results in a time-dependent and transient reorganization of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartic acid (NMDA) glutamate receptors at NAc medium spiny neuron (MSN) synapses, as well as structural changes in the spine head of NAc MSNs that correlate with distinct forms of synaptic plasticity. For example, chronic cocaine induces surface expression of NMDA receptors, silent synapse formation and long-term depression (LTD) at early withdrawal time points. During more prolonged withdrawal (wd), these synaptic changes reverse with the result being increased expression of surface AMPA receptors, a consolidation of the synapse into a mushroom-shaped spine and long-term potentiation (LTP). These effects rapidly revert back again upon exposure to a challenge dose of cocaine leading to restructuring of the spine into thin spines and a depression of synaptic strength. Reproduced from ref 82: Russo SJ, Dietz DM, Dumitriu D, Morrison JH, Malenka RC, Nestler EJ. The addicted synapse: mechanisms of synaptic and structural plasticity in nucleus accumbens. Trends Neurosci. 2010;33:267-276. Copyright © Elsevier 2010

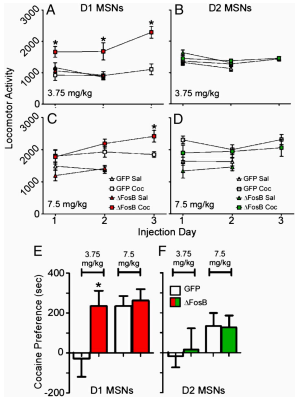
ΔFosB expression increases immature spines in D1 but not D2 NAc MSNs. (A) Sample pictures of spines from control (GFP) and ΔFosB(+) D1 and D2 NAc MSNs. (B–E) Quantification of effects of ΔFosB expression on each dendritic spine subtype in both D1 ...



Brad A. Grueter et al. PNAS 2013;110:5:1923-1928

PNAS

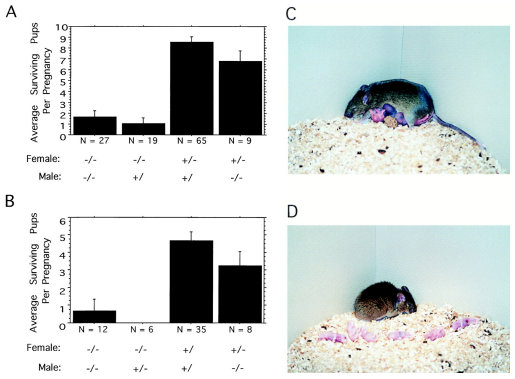
Expression of ΔFosB in D1 but not D2 NAc MSNs promotes behavioral responses to cocaine.



Brad A. Grueter et al. PNAS 2013;110:5:1923-1928

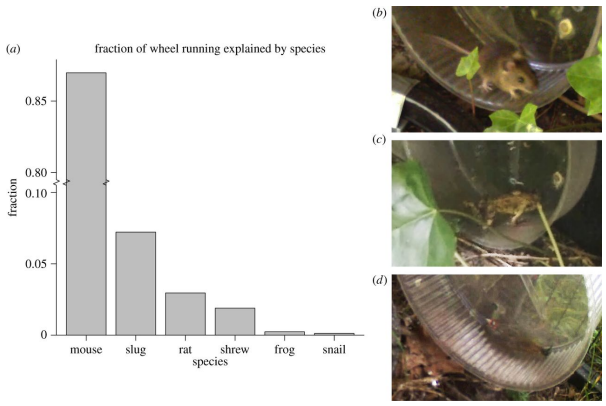
PNAS

A Defect in Nurturing in Mice Lacking the Immediate Early Gene *fosB*



Brown, Cell 86 (1996) 297

Various animals use the running wheels, though mice are by far the most common.

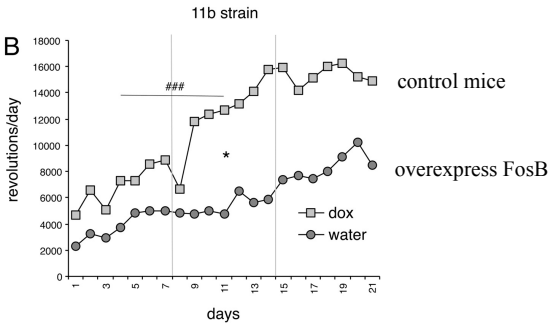


Johanna H. Meijer, and Yuri Robbers Proc. R. Soc. B 2014;281:20140210

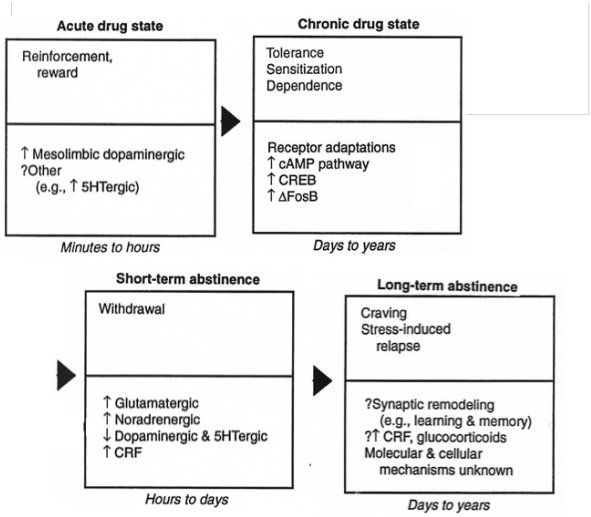
PROCEEDINGS OF THE ROYAL SOCIETY B

https://www.youtube.com/watch?v=TbB1FJB6Y0s

ΔFosB overexpression decreases wheel running behavior



Martin Werme et al. J. Neurosci. 2002;22:8133-8138



Addictions and Comorbidity

Cocaine, Amphetamine

Heroin, Opiates

Alcohol, Nicotine, other drugs…
Localize receptors in limbic system
behavioral and neural homologies with "standard" addictive drugs.

Comorbidity of depression, addiction, and other psychiatric disorders.