

Disease Focus

Editor's Note: Disease Focus articles provide brief overviews of a neural disease or syndrome, emphasizing potential links to basic neural mechanisms. They are presented in the hope of helping researchers identify clinical implications of their research. For more information, see http://www.jneurosci.org/misc/ifa_minireviews.dtl.

Drug-Evoked Synaptic Plasticity Causing Addictive Behavior

Christian Lüscher

Departments of Basic and Clinical Neurosciences, University Hospital and University of Geneva, 1211 Geneva, Switzerland

Introduction

The clinical manifestations of drug addiction are the subject of medical literature and fiction alike. In *Novel with Cocaine*, first published almost 80 years ago under a pseudonym and only recently rediscovered, Mark Levi provides a disturbing account of a young Russian man becoming addicted to cocaine. Vadim, the novel's antihero reflects: "Before I came in contact with cocaine I assumed that happiness was an entity, while in fact all human happiness consists of a clever fusion of two elements: the physical feeling of happiness, and the external event providing the psychic impetus for that feeling."

This statement eloquently describes a core element of the addiction process. An initially neutral stimulus becomes attractive when associated with drug consumption, and even after prolonged periods of abstinence this cue may trigger craving and cause the subject to relapse (Stewart et al., 1984; Childress et al., 1988). The risk for relapse remains high after years of abstinence, which constitutes a major challenge for treating drug addiction.

Therefore, many researchers have argued that the secret to understanding addiction lies in the elucidation of the "memory trace" that links the cue to the compulsive drug use. The

implicit underlying hypothesis is that addictive drugs generate an inappropriate learning signal that leads to the encoding of a unique trace, which, when reactivated, has a strong behavioral impact (Redish et al., 2008; Schultz, 2011).

Here we will review emerging evidence that the cellular correlates of the drug memory trace are the various forms of synaptic plasticity, mainly of glutamatergic transmission, in the circuits of the mesolimbic system, which we have previously called "drug-evoked synaptic plasticity" (Lüscher and Malenka, 2011). We will review the literature reporting drug-evoked synaptic plasticity in animal models of addiction and argue for a staged remodeling of the mesolimbic circuitry (Kalivas and O'Brien, 2008) that is eventually responsible for relapse and compulsive drug use.

Animal models

The study of the neurobiological mechanisms underlying addictive behavior requires animal models. While the basis of behavioral pharmacology was laid out using nonhuman primates and rats, more recently genetically modified mice have become extremely useful tools. There is general agreement that no animal model fully reflects the complexity of the human disease. Many behavioral studies, however, reproduce core components of addiction, starting with the self-administration (SA) of the substance (Clark et al., 1961). Depending on the substance involved, SA can be oral (e.g., ethanol or benzodiazepines; Licata and Rowlett, 2008; Vengeliene et al., 2009), intravenous (e.g., cocaine through a jugular catheter in rats or mice; Gerber and Wise, 1989; Jackson

et al., 1998), or even directly into a specific brain region [e.g., morphine into the ventral tegmental area (VTA); Bozarth and Wise, 1981]. While SA is a necessary condition to demonstrate the reinforcing nature of a given substance, it is by no means sufficient (Collins et al., 1984). SA translates well to clinical reports of drug liking; however, used in its most basic form, it does not fully mimic core features of addiction, including loss of control or relapse after periods of extended withdrawal (O'Connor et al., 2011). What are needed for mechanistic investigations of the synaptic drug trace are tests that demonstrate drug-adaptive behavior associated with an external stimulus. Locomotor sensitization, often used as a proxy of incentive saliency, refers to the enhanced locomotor effect of cocaine and other psychostimulants, which can be observed already at the second injection of the drug (Robinson and Berridge, 2001). Locomotor sensitization also has an associative component, as its magnitude depends on the environment (the effect is enhanced in a novel environment; Badiani et al., 1995). Importantly, locomotor sensitization is already observed several days after a single injection (Valjent et al., 2010) and many weeks after repeated injections. A direct measure of the association with the environment can be obtained in the conditioned place preference (CPP) test. In this paradigm, using an apparatus with two distinct compartments, one side is paired with the drug injection, the other with saline. Already after a first session, a preference for the compartment where the drug was received can be measured. Both locomotor sensitization and CPP, however, have the disadvantage that the drug is

Received Aug. 7, 2013; revised Sept. 13, 2013; accepted Sept. 19, 2013.

My laboratory is supported by the Swiss National Science Foundation, the National Competence Center "Synapsy," and European Research Council Advanced Grant MeSSI. I thank Meaghan Creed, Kelly Tan, and Eoin O'Connor for many helpful comments on the manuscript. I apologize to all colleagues whose work I was unable to cite due to space limitations.

Correspondence should be addressed to Christian Lüscher, Departments of Basic and Clinical Neurosciences, University Hospital and University of Geneva, 1211 Geneva, Switzerland. E-mail: christian.luscher@unige.ch.

DOI:10.1523/JNEUROSCI.3406-13.2013

Copyright © 2013 the authors 0270-6474/13/3317641-06\$15.00/0

injected by the experimenter, which strongly contrasts with the clinical reality. A more accurate model therefore is cue-induced cocaine seeking (De Wit and Stewart, 1981; Shaham et al., 2003), where lever pressing or nose poking for a drug injection is paired with a cue (light or sound). After acquisition of SA, the simple presentation of the cue will prompt a seeking behavior even though the drug is no longer available. This effect can be observed up to several weeks after the last SA session in rats (Kruzich et al., 2001) and mice (Highfield et al., 2002). One interesting feature is that the seeking behavior becomes stronger over the first few weeks of withdrawal, an observation called “incubation of craving” (Grimm et al., 2001).

Dopamine hypothesis

What is the pharmacological effect defining addictive drugs that is eventually responsible for the adaptive behavior? They all increase mesolimbic dopamine (DA) levels, which mediate their reinforcing effect (Wise, 1987; Di Chiara and Imperato, 1988). While this statement is supported by many experiments, particularly early behavioral pharmacology studies, it has been challenged, most prominently by genetic manipulations. For example, even though cocaine increases mesolimbic DA by inhibiting the DA transporter (DAT); mice lacking the DAT still readily self-administer cocaine (Rocha et al., 1998). Arguably, this observation is incompatible with the DA hypothesis. However, subsequent work during the last decade has demonstrated that in these DAT-lacking mice, abnormally high levels of DA during development induce adaptations in the mesolimbic DA system. Consequently, the results of cocaine self-administration in these mice require reinterpretation. Rather than a complete knockout, a more subtle manipulation consisting of point mutations renders the DAT insensitive to cocaine but induces only minimal effects on DA reuptake (Chen et al., 2006). With the cocaine unable to bind this mutated DAT, these knock-in mice no longer self-administered cocaine. This observation supports the hypothesis that DA increases are necessary for the reinforcing effects of cocaine. As a side note, a similar knock-in approach has identified the GABA_A receptor subtype containing the $\alpha 1$ subunit in VTA GABA neurons as the initial target responsible for the addictive properties of benzodiazepines (Tan et al., 2010). Amplification of GABA_A receptors in VTA GABA neurons leads to the disinhibition of DA neurons, a cellular mechanism shared with opioids, γ -hydroxybutyrate, and can-

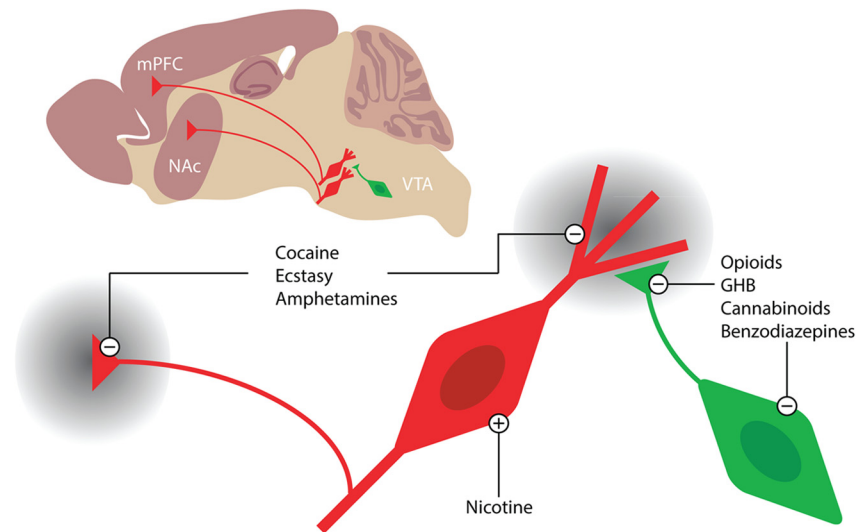


Figure 1. The mesocorticolimbic dopamine system as an initial target of addictive drugs. The VTA, at the origin of the mesocorticolimbic system, is composed of dopamine projection neurons that are under inhibitory control of GABA interneurons (sometimes described as an independent nucleus at the tail of the VTA, the rostromedial tegmentum). The main targets are the NAc and the mPFC. Addictive drugs cause an increase in mesocorticolimbic dopamine through three distinct cellular mechanisms: direct activation of dopamine neurons (e.g., nicotine); indirect disinhibition of dopamine neurons [opioids, gamma-hydroxybutyric acid (GHB), cannabinoids, and benzodiazepines]; as well as interference with dopamine reuptake (cocaine, ecstasy, and amphetamines). Note that the latter group also increases dopamine in the VTA itself, owing to the perturbation of the reuptake of dendritically released dopamine (modified from Lüscher and Malenka, 2011, with permission).

nabinoids [Fig. 1 (modified from Lüscher and Ungless, 2006)]. By contrast, nicotine can directly stimulate DA neurons, and psychostimulants exert their effect by interfering with DA reuptake, as discussed above. The DA hypothesis, therefore, is still relevant and has received even more direct support from optogenetic manipulations of VTA DA neurons, which confirmed that their activation is sufficient to support self-administration and conditioned place preference (Tsai et al., 2009; Adamantidis et al., 2011; Lammel et al., 2012). Whether DA neuron activity is also sufficient to drive long-lasting adaptive behavior remains to be explored.

Drug-evoked synaptic plasticity

While the requirement for increased DA may explain the acute reinforcing effects of addictive drugs, it does not provide an explanation for craving and relapse. After all, these key features of addiction manifest long after the drugs have been cleared from the brain. Given the established modulatory role of DA on glutamatergic and GABAergic transmission, the synaptic trace of addictive drugs may actually be expressed at these synapses and not necessarily involve a change in DA modulation. The experimental demonstration of such a trace was achieved over a decade ago using a clever *ex vivo* approach. Briefly, slices of the VTA were prepared 1 d following a single injection of cocaine and glutamatergic

transmission at AMPA receptor (AMPA) and NMDA receptor (NMDAR) was recorded in VTA DA neurons. Since the number of synapses stimulated in this preparation is beyond the control of the experimenter, the ratio of AMPA- and NMDAR-mediated synaptic currents was calculated and found to be increased after the cocaine treatment (Ungless et al., 2001).

Subsequent investigations revealed that this early drug trace can be observed with all addictive drugs tested to date, including ethanol, morphine, and nicotine, but also amphetamines and benzodiazepines (Saal et al., 2003; Das et al., 2008; Heikkinen et al., 2009). The plasticity was also observed after a 2-h-long optogenetic stimulation of the VTA DA neurons, mimicking the increased firing typically observed with a single dose of morphine or nicotine (Brown et al., 2010). This increased AMPA/NMDA ratio is due to an enhanced AMPA transmission in conjunction of a decreased NMDA transmission. The molecular expression mechanism therefore involves a redistribution of both AMPARs and NMDARs. While the absolute number of AMPARs remains unchanged (Mameli et al., 2007), the GluA2-containing receptors at baseline are exchanged for GluA2-lacking receptors (Bellone and Lüscher, 2006; Argilli et al., 2008).

At the same time, GluN3A-containing NMDARs appear in exchange for GluN2A

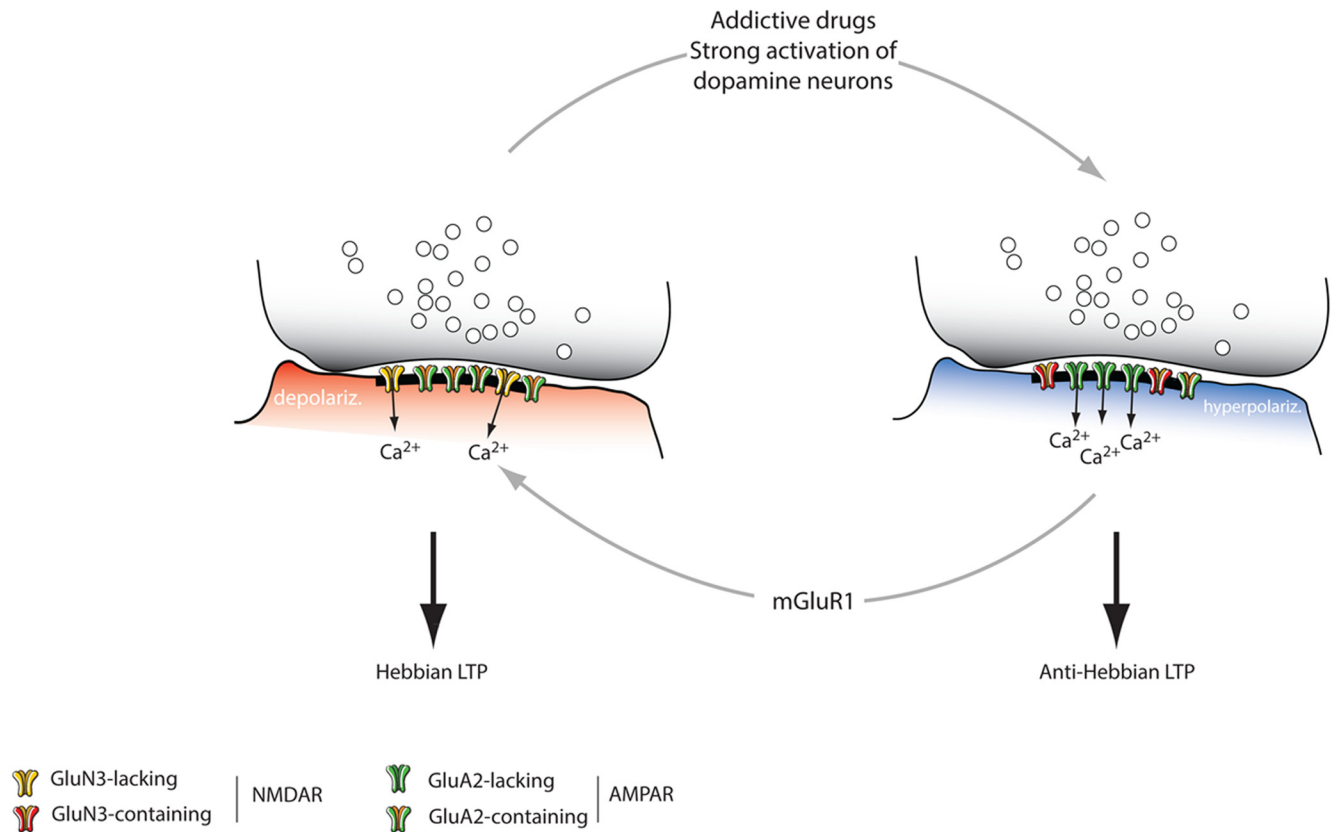


Figure 2. Drug-evoked synaptic plasticity in dopamine neurons of the ventral tegmental area. Addictive drugs or strong stimulation of dopamine neurons causes a synaptic plasticity on the excitatory afferents. This plasticity is expressed by the dual exchange of AMPA and NMDA receptors: GluA2-lacking AMPA receptors and GluN3A-containing NMDA receptors are inserted. As a consequence calcium enters the postsynaptic cell more readily when the membrane is hyperpolarized, which inverts the rules for activity-dependent synaptic plasticity. At baseline, LTP is induced when glutamate is released onto depolarized dopamine neurons (Hebbian LTP that is NMDAR dependent), while after cocaine exposure LTP can be observed when glutamate transmission coincides with a hyperpolarization (anti-Hebbian LTP that is AMPAR dependent). Normal transmission is restored by the activation of mGluR1. Together, addictive drugs evoked a permissive metaplasticity at excitatory afferents onto VTA dopamine neurons, which gate subsequent adaptations downstream (see text).

containing NMDARs, again leaving the total number of NMDARs unchanged (Yuan et al., 2013). After a single injection, this plasticity persists for ~1 week, after which transmission is normalized. This normalization requires the presence of metabotropic glutamate receptor 1 (mGluR1) receptors, which are located perisynaptically and are most efficiently activated with a short burst of activity. mGluR1 activation engages mammalian target of rapamycin-dependent local protein synthesis (Mameli et al., 2007). Interestingly, mGluR1-driven reinsertion of GluA2-containing AMPARs has also been observed at synapses in multiple brain areas (Clem and Huganir, 2010; McCutcheon et al., 2011), suggesting a conserved mechanism for neurons to eliminate GluA2-lacking AMPARs from the synapse.

The case for a permissive metaplasticity
The complexity of the expression mechanisms of drug-evoked synaptic plasticity in the VTA indicates that the effect of addictive drugs on the mesolimbic circuit is not a straightforward potentiation of

transmission, but suggests a shift of synaptic calcium signaling from NMDARs to AMPARs (Creed and Lüscher, 2013). In naive mice, glutamatergic transmission can cause synaptic entry of calcium, provided the DA cell is depolarized, which relieves the NMDARs from the magnesium block. In contrast, after cocaine treatment, GluN3A-containing NMDARs have a very low permeability for divalent cations and are inefficient conductors of calcium. In contrast, the GluA2-lacking AMPARs readily conduct calcium. In fact, owing to the inward rectification, the greater the hyperpolarization, the more calcium enters the cell. In other words, in naive animals, the postsynaptic neurons must be depolarized to engage calcium signaling, whereas after cocaine administration, hyperpolarization is required. As a consequence, the rules for activity-dependent potentiation of synaptic transmission are inverted (Mameli et al., 2011). This can be experimentally demonstrated by using a spike timing-dependent potentiation (STDP) protocol, where the postsynaptic neuron receives either a depolarizing

or a hyperpolarizing current injection (Fig. 2). In slices from cocaine-treated animals, depolarizing STDP was no longer able to potentiate transmission; however, the potentiation could be rescued by switching to a hyperpolarizing STDP. Together, these findings strongly suggest a permissive role for this early form of drug-evoked synaptic plasticity. In this sense, the AMPA and NMDA receptor alterations induced by drug exposure can be considered a metaplasticity, enabling specific forms of subsequent activity-dependent synaptic plasticity.

Causal role of drug-evoked synaptic plasticity in behavior

Establishing a causal relationship between drug-evoked synaptic plasticity and drug-adaptive behavior has been challenging, in part because of the temporal discrepancy between these two phenomena. A single injection already leaves a synaptic trace (discussed above) that lasts for ~1 week but may not drive many behavioral adaptations. Interestingly, a recent study using retrograde tracing techniques has provided

information that the VTA DA neurons that project to the nucleus accumbens (NAc) are particularly prone to undergo drug-evoked synaptic plasticity (Lammel et al., 2012). These early forms of drug-evoked plasticity are merely building blocks of circuit remodeling, which, after repetitive exposure, eventually lead to behavioral alterations. In line with this interpretation, in mice where NMDA receptors were selectively abolished in DA neurons (DAT-Cre ERT2 \times GluN1flox; Zweifel et al., 2008), the behavioral repercussions of drug exposure are observed only after a delay and following several injections. Specifically, reinstatement of drug seeking was reduced, which involves an extended circuitry including the NAc (Engblom et al., 2008).

Further evidence for a stepwise remodeling of mesolimbic circuitry comes from experiments suggesting a hierarchical organization of drug-evoked synaptic plasticity between the VTA and the NAc. Quick and efficient reversal of cocaine-evoked plasticity in the VTA by local or systemic application of a positive allosteric modulator of the mGluR1 prevented some drug-evoked synaptic adaptations in the NAc (Mameli et al., 2009). Lesion experiments and pharmacological manipulations implicate connections to and from the NAc in the integration of rewarding drug effects and contextual environmental cues (Sesack and Grace, 2010). The crucial plasticity that presumably mediates this integration occurs at the excitatory afferents onto medium spiny neurons (MSNs), which represent 95% of neurons in the NAc and are an interface between limbic and motor functions (Mogenson et al., 1980). There are two populations of MSNs that are divided into two equal-sized classes depending on the type of dopamine receptors (either D₁R or D₂R) they express and their projection sites (Gong et al., 2007). Both D₁R MSNs and D₂R MSNs receive excitatory afferents from the medial prefrontal cortex (mPFC), the ventral hippocampus (vHippo), and the basolateral amygdala (BLA; Papp et al., 2012). Previous studies have attributed the emotional valence to the BLA input (Cador et al., 1989), which, when selectively stimulated, is reinforcing (Stuber et al., 2011). The activation of the mPFC-to-NAc projection has been implicated in the initiation of action and the actual seeking behavior, and there is evidence linking the hypoactivity of cortical projection neurons to compulsive cocaine consumption (Chen et al., 2013). Finally, the afferents from the vHippo would code for the context (Sesack and Grace, 2010). Regardless of the origin, syn-

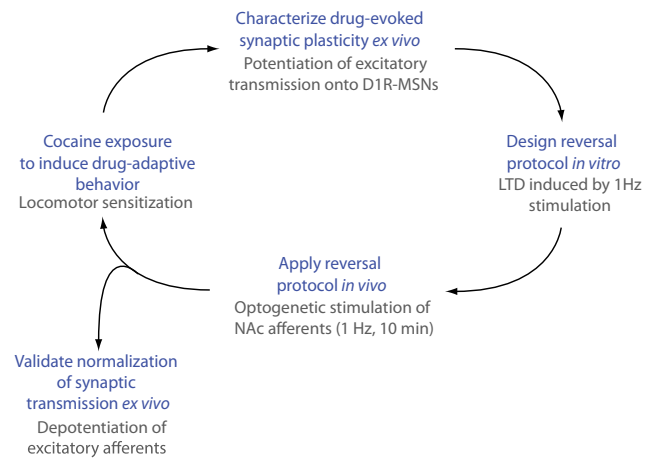


Figure 3. Experimental blueprint to establish causal relationship between drug-evoked synaptic plasticity and drug-adaptive behavior. In gray example experiments are from a proof-of-principle study (Pascoli et al., 2011). For further explanation see text.

aptic plasticity at glutamatergic transmission onto MSNs has been correlated with cue-induced relapse to cocaine seeking (Conrad et al., 2008). Given the proposed functions of these specific inputs, cocaine may evoke distinct forms of plasticity at excitatory synapses onto MSNs, which would contribute to specific components of adaptive behavior. What will be needed to address this hypothesis is the selective manipulations at identified synapses (Fig. 3). With the advance of cell type-specific optogenetic control of neuronal activity, such experiments are now possible. The blueprint for this approach consists of exposing the animal to the drug, such that a drug-adaptive behavior can be observed (e.g., repetitive injections of cocaine to cause locomotor sensitization), and characterizing drug-evoked synaptic plasticity *ex vivo* (e.g., potentiation of mPFC afferents onto D₁R MSNs). Since most forms of plasticity can be reversed by an appropriate stimulation protocol, the next step consists of finding a protocol that can normalize transmission *in vitro* (e.g., 1 Hz NMDAR-dependent depotentialization). This protocol can then be applied *in vivo* after transfecting the appropriate upstream neurons and activating the afferent axons by terminal illumination (e.g., injection of optogenetic effector channelrhodopsin-2 into the mPFC shining light into the NAc) to test the effect of depotentialization on drug-adaptive behavior (e.g., erasure of sensitization). A proof of principle study (Pascoli et al., 2011) has shown that this approach is feasible. Another example using this approach links incubation of craving to the potentiation of excitatory transmission from the amygdala to the NAc (Lee et al., 2013). Yet further experiments must be performed to understand the role of drug-evoked synaptic plasticity at iden-

tified synapses in other behavior (e.g., cue-induced cocaine seeking modeling relapse).

The challenge of individual vulnerability

One of the striking features of addiction is only poorly understood: the individual vulnerability. At equal levels of drug consumption, some people readily lose control, while others maintain a controlled recreational use for many years. Just think of alcohol, a drug that is legal in many countries that the overwhelming majority of people can enjoy recreationally during an entire adult lifetime without ever losing control. This is also well documented for nicotine and cannabis, and even holds true for “harder” drugs such as amphetamines and cocaine, the latter leading to addiction in ~20% of regular users over a span of >10 years (Wagner and Anthony, 2002). While several genetic variations have been associated with drug use (Goldman et al., 2005), a causal relationship remains to be established. Moreover, most studies described above focus on generic mechanisms that underlie the behavioral changes, and little is known about the neurobiology underlying individual vulnerability. One requirement is certain; individual vulnerability can be observed only after prolonged drug exposure. This requirement is not met in most animals models presented above, which is why behavioral pharmacology screens show very little variability. However, pioneering work using SA for several months in rats have demonstrated that animal-to-animal variability can also be observed in rodents (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). In a subsequent study, it has been argued that

high impulsivity predicts the development of addiction-like behavior in rats (Belin and Everitt, 2008).

Emerging ideas for rational addiction treatments

A more comprehensive understanding of the precise nature of circuit remodeling caused by addictive drugs resulting from specific forms of drug-evoked synaptic plasticity may help us to design novel rational treatments for the human disease. Such treatments may be pharmacological in nature or use neuromodulatory approaches such as deep brain stimulation or transcranial magnetic stimulation (TMS). The former may target specific types of receptors known to appear only after drug exposure, such as the GluA2-lacking AMPARs or the GluN3-containing NMDARs, but these types of pharmacological interventions are really only in their infancy. It may also be possible to exploit and enhance the physiological mechanism of reversing drug-evoked synaptic plasticity. One area of focus may be on the mGluR1 receptors, which can reverse the redistribution of AMPARs and NMDARs.

Perhaps a more selective intervention would be to target specific areas of the reward circuitry, such as the NAc, with deep brain stimulation. However, novel protocols would have to be developed, as current high-frequency stimulation (>100 Hz) is unlikely to affect plasticity. TMS may have the appeal of being noninvasive. If we succeed in determining the cortical afferents undergoing drug-evoked synaptic plasticity to develop efficient reversal protocols, TMS may emerge as a promising treatment option.

Ultimately, the understanding of drug-induced plasticity at specific synapses must be furthered to develop a therapy that reverses plasticity and associated drug-induced adaptive behavior. The goal is to provide a cure for addiction and to prove Aaron Sorkin wrong when he recounted in a 2012 interview with the *W* magazine: "... the hardest thing I do every day is not take cocaine. You don't get cured of addiction—you're just in remission."

References

Adamantidis AR, Tsai HC, Boutrel B, Zhang F, Stuber GD, Budygin EA, Touriño C, Bonci A, Deisseroth K, de Lecea L (2011) Optogenetic interrogation of dopaminergic modulation of the multiple phases of reward-seeking behavior. *J Neurosci* 31:10829–10835. [CrossRef Medline](#)

Argilli E, Sibley DR, Malenka RC, England PM, Bonci A (2008) Mechanism and time course of cocaine-induced long-term potentiation in

the ventral tegmental area. *J Neurosci* 28:9092–9100. [CrossRef Medline](#)

Badiani A, Anagnostaras SG, Robinson TE (1995) The development of sensitization to the psychomotor stimulant effects of amphetamine is enhanced in a novel environment. *Psychopharmacology (Berl)* 117:443–452. [CrossRef Medline](#)

Belin D, Everitt BJ (2008) Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. *Neuron* 57:432–441. [CrossRef Medline](#)

Bellone C, Lüscher C (2006) Cocaine triggered AMPA receptor redistribution is reversed in vivo by mGluR-dependent long-term depression. *Nat Neurosci* 9:636–641. [CrossRef Medline](#)

Bozarth MA, Wise RA (1981) Intracranial self-administration of morphine into the ventral tegmental area in rats. *Life Sci* 28:551–555. [CrossRef Medline](#)

Brown MT, Bellone C, Mameli M, Labouèbe G, Bocklisch C, Balland B, Dahan L, Luján R, Deisseroth K, Lüscher C (2010) Drug-driven AMPA receptor redistribution mimicked by selective dopamine neuron stimulation. *PLoS One* 5:e15870. [CrossRef Medline](#)

Cador M, Robbins TW, Everitt BJ (1989) Involvement of the amygdala in stimulus-reward associations: interaction with the ventral striatum. *Neuroscience* 30:77–86. [Medline](#)

Chen BT, Yau HJ, Hatch C, Kusumoto-Yoshida I, Cho SL, Hopf FW, Bonci A (2013) Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking. *Nature* 496:359–362. [CrossRef Medline](#)

Chen R, Tilley MR, Wei H, Zhou F, Zhou FM, Ching S, Quan N, Stephens RL, Hill ER, Nottoli T, Han DD, Gu HH (2006) Abolished cocaine reward in mice with a cocaine-insensitive dopamine transporter. *Proc Natl Acad Sci U S A* 103:9333–9338. [CrossRef Medline](#)

Childress AR, McLellan AT, Ehrman R, O'Brien CP (1988) Classically conditioned responses in opioid and cocaine dependence: a role in relapse. *NIDA Res Monogr* 84:25–43. [Medline](#)

Clark R, Schuster CR, Brady JV (1961) Instrumental conditioning of jugular self-infusion in the rhesus monkey. *Science* 133:1829–1830. [CrossRef Medline](#)

Clem RL, Huganir RL (2010) Calcium-permeable AMPA receptor dynamics mediate fear memory erasure. *Science* 330:1108–1112. [CrossRef Medline](#)

Collins RJ, Weeks JR, Cooper MM, Good PI, Russell RR (1984) Prediction of abuse liability of drugs using IV self-administration by rats. *Psychopharmacology (Berl)* 82:6–13. [Medline](#)

Conrad KL, Tseng KY, Uejima JL, Reimers JM, Heng LJ, Shaham Y, Marinelli M, Wolf ME (2008) Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. *Nature* 454:118–121. [CrossRef Medline](#)

Creed MC, Lüscher C (2013) Drug-evoked synaptic plasticity: beyond metaplasticity. *Curr Opin Neurobiol* 23:553–558. [CrossRef Medline](#)

Das P, Lilly SM, Zerda R, Gunning WT 3rd, Alvarez FJ, Tietz EI (2008) Increased AMPA receptor GluR1 subunit incorporation in rat hippocampal CA1 synapses during benzodi-

azepine withdrawal. *J Comp Neurol* 511:832–846. [CrossRef Medline](#)

Deroche-Gamonet V, Belin D, Piazza PV (2004) Evidence for addiction-like behavior in the rat. *Science* 305:1014–1017. [CrossRef Medline](#)

De Wit H, Stewart J (1981) Reinstatement of cocaine-reinforced responding in the rat. *Psychopharmacology (Berl)* 75:134–143. [CrossRef Medline](#)

Di Chiara G, Imperato A (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci U S A* 85:5274–5278. [CrossRef Medline](#)

Engblom D, Bilbao A, Sanchis-Segura C, Dahan L, Perreau-Lenz S, Balland B, Parkitna JR, Luján R, Halbout B, Mameli M, Parlato R, Sprengel R, Lüscher C, Schütz G, Spanagel R (2008) Glutamate receptors on dopamine neurons control the persistence of cocaine seeking. *Neuron* 59:497–508. [CrossRef Medline](#)

Gerber GJ, Wise RA (1989) Pharmacological regulation of intravenous cocaine and heroin self-administration in rats: a variable dose paradigm. *Pharmacol Biochem Behav* 32:527–531. [CrossRef Medline](#)

Goldman D, Oroszi G, Ducci F (2005) The genetics of addictions: uncovering the genes. *Nat Rev Genet* 6:521–532. [CrossRef Medline](#)

Gong S, Doughty M, Harbaugh CR, Cummins A, Hatten ME, Heintz N, Gerfen CR (2007) Targeting Cre recombinase to specific neuron populations with bacterial artificial chromosome constructs. *J Neurosci* 27:9817–9823. [CrossRef Medline](#)

Grimm JW, Hope BT, Wise RA, Shaham Y (2001) Neuroadaptation. Incubation of cocaine craving after withdrawal. *Nature* 412:141–142. [CrossRef Medline](#)

Heikkinen AE, Möykkynen TP, Korpi ER (2009) Long-lasting modulation of glutamatergic transmission in VTA dopamine neurons after a single dose of benzodiazepine agonists. *Neuropsychopharmacology* 34:290–298. [CrossRef Medline](#)

Highfield DA, Mead AN, Grimm JW, Rocha BA, Shaham Y (2002) Reinstatement of cocaine seeking in 129X1/SvJ mice: effects of cocaine priming, cocaine cues and food deprivation. *Psychopharmacology (Berl)* 161:417–424. [CrossRef](#)

Jackson A, Mead AN, Rocha BA, Stephens DN (1998) AMPA receptors and motivation for drug: effect of the selective antagonist NBQX on behavioural sensitization and on self-administration in mice. *Behav Pharmacol* 9:457–467. [CrossRef Medline](#)

Kalivas PW, O'Brien C (2008) Drug addiction as a pathology of staged neuroplasticity. *Neuropsychopharmacology* 33:166–180. [CrossRef Medline](#)

Kruzich PJ, Congleton KM, See RE (2001) Conditioned reinstatement of drug-seeking behavior with a discrete compound stimulus classically conditioned with intravenous cocaine. *Behav Neurosci* 115:1086–1092. [CrossRef Medline](#)

Lammel S, Lim BK, Ran C, Huang KW, Betley MJ, Tye KM, Deisseroth K, Malenka RC (2012) Input-specific control of reward and aversion in the ventral tegmental area. *Nature* 491:212–217. [CrossRef Medline](#)

- Lee BR, Ma YY, Huang YH, Wang X, Otaka M, Ishikawa M, Neumann PA, Graziane NM, Brown TE, Suska A, Guo C, Lobo MK, Sesack SR, Wolf ME, Nestler EJ, Shaham Y, Schlüter OM, Dong Y (2013) Maturation of silent synapses in amygdala-accumbens projection contributes to incubation of cocaine craving. *Nat Neurosci*. Advance online publication retrieved September 29, 2013. doi:10.1038/nn.3533.
- Licata SC, Rowlett JK (2008) Abuse and dependence liability of benzodiazepine-type drugs: GABA(A) receptor modulation and beyond. *Pharmacol Biochem Behav* 90:74–89. [CrossRef Medline](#)
- Lüscher C, Malenka RC (2011) Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. *Neuron* 69:650–663. [CrossRef Medline](#)
- Lüscher C, Ungless MA (2006) The mechanistic classification of addictive drugs. *PLoS Med* 3:e437. [CrossRef Medline](#)
- Mameli M, Balland B, Luján R, Lüscher C (2007) Rapid synthesis and synaptic insertion of GluR2 for mGluR-LTD in the ventral tegmental area. *Science* 317:530–533. [CrossRef Medline](#)
- Mameli M, Halbout B, Creton C, Engblom D, Parkitna JR, Spanagel R, Lüscher C (2009) Cocaine-evoked synaptic plasticity: persistence in the VTA triggers adaptations in the NAc. *Nat Neurosci* 12:1036–1041. [CrossRef Medline](#)
- Mameli M, Bellone C, Brown MT, Lüscher C (2011) Cocaine inverts rules for synaptic plasticity of glutamate transmission in the ventral tegmental area. *Nat Neurosci* 14:414–416. [CrossRef Medline](#)
- McCutcheon JE, Loweth JA, Ford KA, Marinelli M, Wolf ME, Tseng KY (2011) Group I mGluR activation reverses cocaine-induced accumulation of calcium-permeable AMPA receptors in nucleus accumbens synapses via a protein kinase C-dependent mechanism. *J Neurosci* 31:14536–14541. [CrossRef Medline](#)
- Mogenson GJ, Jones DL, Yim CY (1980) From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol* 14:69–97. [CrossRef Medline](#)
- O'Connor EC, Chapman K, Butler P, Mead AN (2011) The predictive validity of the rat self-administration model for abuse liability. *Neurosci Biobehav Rev* 35:912–938. [CrossRef Medline](#)
- Papp E, Borhegyi Z, Tomioka R, Rockland KS, Mody I, Freund TF (2012) Glutamatergic input from specific sources influences the nucleus accumbens-ventral pallidum information flow. *Brain Struct Funct* 217:37–48. [CrossRef Medline](#)
- Pascoli V, Turiault M, Lüscher C (2011) Reversal of cocaine-evoked synaptic potentiation resets drug-induced adaptive behaviour. *Nature* 481:71–75. [CrossRef Medline](#)
- Redish AD, Jensen S, Johnson A (2008) A unified framework for addiction: vulnerabilities in the decision process. *Behav Brain Sci* 31:415–437. [CrossRef Medline](#)
- Robinson TE, Berridge KC (2001) Incentive-sensitization and addiction. *Addiction* 96:103–114. [CrossRef Medline](#)
- Rocha BA, Fumagalli F, Gainetdinov RR, Jones SR, Ator R, Giros B, Miller GW, Caron MG (1998) Cocaine self-administration in dopamine-transporter knockout mice. *Nat Neurosci* 1:132–137. [CrossRef Medline](#)
- Saal D, Dong Y, Bonci A, Malenka RC (2003) Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron* 37:577–582. [CrossRef Medline](#)
- Schultz W (2011) Potential vulnerabilities of neuronal reward, risk, and decision mechanisms to addictive drugs. *Neuron* 69:603–617. [CrossRef Medline](#)
- Sesack SR, Grace AA (2010) Cortico-basal ganglia reward network: microcircuitry. *Neuropsychopharmacology* 35:27–47. [CrossRef Medline](#)
- Shaham Y, Shalev U, Lu L, De Wit H, Stewart J (2003) The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology (Berl)* 168:3–20. [CrossRef Medline](#)
- Stewart J, de Wit H, Eikelboom R (1984) Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychol Rev* 91:251–268. [CrossRef Medline](#)
- Stuber GD, Sparta DR, Stamatakis AM, van Leeuwen WA, Hardjoprajitno JE, Cho S, Tye KM, Kempadoo KA, Zhang F, Deisseroth K, Bonci A (2011) Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. *Nature* 475:377–380. [CrossRef Medline](#)
- Tan KR, Brown M, Labouèbe G, Yvon C, Creton C, Fritschy JM, Rudolph U, Lüscher C (2010) Neural bases for addictive properties of benzodiazepines. *Nature* 463:769–774. [CrossRef Medline](#)
- Tsai HC, Zhang F, Adamantidis A, Stuber GD, Bonci A, de Lecea L, Deisseroth K (2009) Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. *Science* 324:1080–1084. [CrossRef Medline](#)
- Ungless MA, Whistler JL, Malenka RC, Bonci A (2001) Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. *Nature* 411:583–587. [CrossRef Medline](#)
- Valjent E, Bertran-Gonzalez J, Aubier B, Greengard P, Hervé D, Girault JA (2010) Mechanisms of locomotor sensitization to drugs of abuse in a two-injection protocol. *Neuropsychopharmacology* 35:401–415. [CrossRef Medline](#)
- Vanderschuren LJ, Everitt BJ (2004) Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science* 305:1017–1019. [CrossRef Medline](#)
- Vengeliene V, Celerier E, Chaskiel L, Penzo F, Spanagel R (2009) Compulsive alcohol drinking in rodents. *Addict Biol* 14:384–396. [CrossRef Medline](#)
- Wagner FA, Anthony JC (2002) From first drug use to drug dependence; developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. *Neuropsychopharmacology* 26:479–488. [CrossRef Medline](#)
- Wise RA (1987) The role of reward pathways in the development of drug dependence. *Pharmacol Ther* 35:227–263. [CrossRef Medline](#)
- Yuan T, Mameli M, O'Connor EC, Dey PN, Verpelli C, Sala C, Perez-Otaño I, Lüscher C, Bellone C (2013) Expression of cocaine-evoked synaptic plasticity by GluN3A-containing NMDA receptors. *Neuron*, in press.
- Zweifel LS, Argilli E, Bonci A, Palmiter RD (2008) Role of NMDA receptors in dopamine neurons for plasticity and addictive behaviors. *Neuron* 59:486–496. [CrossRef Medline](#)