Published in final edited form as:

Neurosci Biobehav Rev. 2010 November ; 35(2): 212–219. doi:10.1016/j.neubiorev.2010.01.007.

Kicking the Habit: The Neural Basis of Ingrained Behaviors in Cocaine Addiction

R. Christopher Pierce^{1,*} and Louk J.M.J. Vanderschuren²

¹Department of Psychiatry, Center for Neurobiology and Behavior, University of Pennsylvania School of Medicine, 125 South 31st Street, Philadelphia, PA 19104 ²Rudolf Magnus Institute of Neuroscience, Department of Neuroscience and Pharmacology, University Medical Center Utrecht, Universiteitsweg 100, 3584 CG Utrecht, The Netherlands

Abstract

Cocaine addiction is a complex and multifaceted process encompassing a number of forms of behavioral plasticity. The process of acquiring and consuming drugs can be sufficiently risky and complicated that the casual drug user may choose not to act on every motivation to use drugs. The repetition of drug seeking and taking, however, often results in the gradual development of drug craving and compulsive drug seeking associated with addiction. Moreover, the complex sets of behaviors associated with drug addiction can become ingrained to such an extent that, when activated by drug-associated stimuli or exposure to the drug itself, the processes underlying drug seeking and taking are automatically engaged and very difficult to suppress. Here, we examine the hypothesis that aspects of cocaine seeking and taking become ingrained with repetition, thereby contributing to continued drug use despite a conscious desire to abstain. We also review emerging evidence indicating that neuronal circuits including the dorsolateral striatum play a particularly important role in the habitual aspects of drug seeking and taking.

Our lives are dominated by various habits, organized behaviors that have become automatic due to practice or mere repetition. It is easy to appreciate the adaptive benefit of ingrained behaviors. A hunter, for example, oftentimes must identify suitable prey, process distance and velocity, prepare and implement an attack in a fraction of a second. This would not be possible if many aspects of hunting had not become automatic with repetition. In addition, being able to perform a wide variety of behaviors automatically, without the need for continuous conscious monitoring, allows for energy-demanding cognitive processing resources to be utilized for sudden changes in the environment that require immediate attention or action. However, not all ingrained behaviors are necessarily beneficial; in fact, some of them are characterized as bad habits. Notably, although the phrase “kicking the habit” originally referred to muscle spasms observed in opiate addicts undergoing withdrawal, this expression is now commonly used to describe the cessation of chronic abuse of all classes of drugs. The habitual nature of drug abuse is exemplified by the fact that over time the behaviors associated with drug acquisition and consumption can result in the formation of complex sets of action plans that

© 2010 Elsevier Ltd. All rights reserved.

*To whom correspondence should be addressed: Chris Pierce, Center for Neurobiology and Behavior, University of Pennsylvania School of Medicine, 125 South 31st Street, Philadelphia, PA 19104, Phone: 215-746-8915, Fax: 215-573-7605, rcpierce@mail.med.upenn.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

become ingrained to the extent that, when activated, their suppression becomes difficult or impossible. This viewpoint was formalized in a cognitive model, which posited that drug use by addicted individuals is at least partially controlled by automatized action schemata (Tiffany, 1990). The general idea is that initial casual or recreational drug use is a willful act, driven by a representation of the outcome such as experiencing the positive subjective effects of the drug. However, after many cycles of drug seeking and taking, these behaviors become dominated by stimulus-response mechanisms, whereby at least certain aspects of drug seeking and taking become automatic processes (often triggered by drug-associated stimuli) that to a great extent are beyond the individual's control (Everitt and Robbins, 2005; Robbins and Everitt, 1999; Tiffany, 1990). This drug-directed form of habitual behavior can be viewed as an aberrant form of stimulus-response habit learning that is associated with overtraining in many forms of procedural learning (Dickinson, 1985; Packard and Knowlton, 2002; White and McDonald, 2002; Yin and Knowlton, 2006).

The overarching hypothesis examined in this review is that chronic drug abuse produces neuronal plasticity in brain circuits underlying stimulus-response habit learning. These changes result in maladaptive, drug-directed forms of automatic behavior that, in close interaction with certain goal-directed aspects of drug use, result in the addicted phenotype (Everitt and Robbins, 2005; Robbins and Everitt, 1999; Tiffany, 1990). This is not to say that stimulus-response habits in themselves equate to compulsive, addictive behaviors, that drug-associated habitual behaviors and addiction are synonymous or that addictive behavior no longer has goal-directed properties. Rather, it is suggested that automatic aspects of drug seeking and taking play a critical role in translating the powerful influence of drugs and drug-associated cues into action. That is, environmental stimuli and other factors that precipitate drug craving also trigger ingrained behaviors that facilitate drug seeking and taking. We argue that cocaine-induced changes in neuronal circuits including the ventral (i.e. nucleus accumbens) and dorsal striatum underlie the motivation/craving and habitual components of drug seeking behavior, respectively.

The Role of Ingrained Behaviors in Cocaine Addiction

The development of habitual behaviors requires repetition. It is interesting to note that the illicit drugs with the highest risk of addiction are those that have shorter half-lives (O'Brien, 2001). For example, although cocaine and amphetamine-like psychostimulants are all highly addictive, the risk of addiction for cocaine is substantially higher than other psychostimulants (O'Brien, 2001). Whereas psychostimulants have similar mechanisms of action in that they all increase extracellular levels of biogenic amines in the brain (Parsons et al., 1996; Ritz et al., 1988; Schmidt and Pierce, 2006), the half-life of cocaine is an hour or less compared to ten hours or more for amphetamine and its derivatives (including methamphetamine and MDMA) (O'Brien, 2001). The shorter half-life of cocaine, and therefore its shorter duration of action on aminergic neurotransmission, undoubtedly contributes to the binge consumption of this drug. Indeed, animal studies indicate that the pattern of cocaine taking is closely related to extracellular dopamine levels in the nucleus accumbens. That is, falling dopamine levels after cocaine is self-administered appear to trigger subsequent cocaine taking (Wise et al., 1995). Moreover, the rapid delivery of cocaine and other drugs of abuse more readily promotes forms of neuronal and behavioral plasticity associated with compulsive drug seeking/taking (Samaha et al., 2004; Samaha and Robinson, 2005). Consistent with the idea that repetitive drug use ingrains habitual aspects of drug seeking/taking thereby complicating efforts to remain abstinent, heavy tobacco smokers routinely administer nicotine hundreds of times per day and the risk of addiction for cigarette smoking is by far the highest of any drug of abuse (approximately double the risk of addiction for cocaine and alcohol) (O'Brien, 2001).

One common way of testing the extent to which responding for a positive reinforcer occurs according to a stimulus-response (i.e. habitual) or action-outcome (i.e. goal-directed) associative structure is by evaluating instrumental responding for a devalued reinforcer (Adams, 1982; Dickinson, 1985; Killcross and Coutureau, 2003). Ingestive reinforcers, for example, can be devalued either by pre-feeding the subject with the food (or liquid) reinforcer, by degrading the taste of the reinforcer using bitter substances like quinine, or by associating the food with illness (induced by post-ingestion injection with lithium chloride, for example). If responding for the reinforcer is subsequently decreased, it is interpreted as being mediated by an action-outcome process, because behavior is driven by a representation of the value of the outcome, which is reduced by devaluing the reinforcer. On the other hand, if after devaluation the subject shows no difference in responding for valued and devalued reinforcers, responding is interpreted as being under the control of a stimulus-response process, independent of outcome value. Research in this area has shown that drug seeking can indeed become dependent on a habitual stimulus-response associative structure, and that this may occur more quickly for drugs than for food. Thus, it has been shown that lever pressing for food or sucrose was markedly suppressed after pairing with lithium chloride, whereas responding for cocaine and ethanol was impervious to this kind of devaluation (Dickinson et al., 2002; Miles et al., 2003). In these studies, both the drug (ethanol, cocaine) and natural (food, sucrose) reinforcers were ingestive rewards (i.e. ethanol, cocaine and sucrose solutions, food pellets, with clear and distinguishable taste characteristics). It is therefore unlikely that differences in stimulus associability (contiguity) explain the differential sensitivity to lithium devaluation between ethanol and cocaine on the one hand, and food pellets and sucrose on the other. Remarkably, both during taste aversion conditioning with lithium (which took place in four daily sessions) and during re-acquisition of responding for drug after the extinction test, responding for and intake of the drug solution associated with lithium-induced malaise was markedly decreased (Dickinson et al., 2002; Miles et al., 2003). This demonstrates that intake of the reinforcer itself can remain sensitive to devaluation even when responding for a drug reinforcer in extinction, using just the internal representation of the reinforcer to guide behavior, is impervious to devaluation. Thus, after relatively modest operant training under a random-interval schedule, responding for drugs relies on a stimulus-response associative structure of behavior, whereas intake of the drug is still a goal-directed action (Dickinson et al., 2002; Miles et al., 2003). It is possible that the pharmacological effects of the drug itself cause drug-directed behavior to change from a habitual to a goal-directed structure. This is not to say that drug intake always remains goal-directed. Insensitivity to devaluation of intake of a drug reinforcer has been observed in studies investigating the oral intake of ethanol and amphetamine, but this took prolonged drug experience to develop (Galli and Wolffgramm, 2004; Wolffgramm, 1991). In these experiments, rats became insensitive to the aversive properties of quinine since they did not reduce their intake of the drug solution after it had been rendered bitter. In early phases of the experiments, intake of the drug solution was reduced by quinine. In fact, the insensitivity to devaluation required no less than nine months of drug experience followed by an abstinence period to develop (Galli and Wolffgramm, 2004; Wolffgramm, 1991). On the other hand, as described above, the insensitivity to devaluation of operant responding for drug already developed after a relatively moderate amount of operant training (Dickinson et al., 2002; Miles et al., 2003). It should be born in mind that there are methodological differences between the studies by Dickinson et al. (2002) and Miles et al. (2003) on the one hand, and Galli and Wolffgramm (2004) and Wolffgramm (1991) on the other, such as differences in the devaluation procedure (lithium vs. quinine) and output parameters (lever pressing vs. drug intake). Nevertheless, these studies, taken together, suggest that operant responding for drugs (an act relatively distal from the actual subjective drug effects) more readily gains habitual properties than intake of the drug itself. This points to the possibility that the development of inflexible, habitual drug use occurs in several distinct phases, where distal drug cues or acts gain habitual properties before intake of the drug itself does, perhaps representing a gradual worsening of the addiction syndrome with increasing drug

experience. These results also clearly indicate that drug seeking progresses more readily from a goal-directed action-outcome to a habitual stimulus-response associative structure than the seeking of natural rewards.

Consistent with this notion, it has been shown that although instrumental behaviors directed at obtaining cocaine initially are goal-directed, after lengthy drug exposure aspects of these behaviors lose their flexibility and gain automatic, habitual characteristics (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). In order to evaluate continued drug seeking in the face of adverse consequences, which is one of the criteria of drug addiction as defined in the DSM-IV-TR (American Psychiatric Association, 2000), cocaine seeking in rats with a history of limited or extended cocaine self-administration was assessed in the presence of a footshock-associated conditioned stimulus (CS). Among animals with limited cocaine self-administration experience, the aversive CS markedly suppressed cocaine seeking. In contrast, the footshock-associated CS had no effect on cocaine seeking in rats with an extended cocaine self-administration history (Vanderschuren and Everitt, 2004). This progression from flexible to inflexible appetitive behavior was cocaine-specific since the footshock CS markedly suppressed sucrose seeking following a similarly extended period of sucrose ingestion (Vanderschuren and Everitt, 2004). Likewise, punishment of cocaine seeking with footshock markedly suppressed instrumental behavior in animals with limited drug experience, but a subgroup of animals subsequently displayed insensitivity to punishment, whereas animals responding for sucrose remained highly sensitive to footshock throughout lengthy training (Pelloux et al., 2007). Consonant with these results, pairing a footshock with delivery of cocaine suppressed self-administration to a much lesser extent after lengthy cocaine self-administration experience in rats that displayed high levels of cocaine-induced reinstatement (Deroche-Gamonet et al., 2004). Notably, only rats with prolonged cocaine self-administration experience were insensitive to devaluation of cocaine (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). This insensitivity to devaluation was not a consequence of exaggerated motivation for the drug. Vanderschuren and Everitt (2004) found no difference in rate of responding for cocaine (reflecting the motivation for the drug) between animals that displayed sensitivity (i.e. limited cocaine self-administration experience) and insensitivity (i.e. prolonged cocaine self-administration experience) to presentation of a footshock-associated cue during cocaine seeking. In the study by Deroche-Gamonet et al. (2004, see also Belin et al., 2009) the animals that showed willingness to endure footshock together with self-administered cocaine previously showed increased motivation for the drug. However, the increase in motivation for cocaine preceded the willingness to endure footshock by some 40 self-administration sessions, indicating that increased motivation for the drug occurs independently of willingness to endure footshocks. Thus, enhanced motivation for the drug may be necessary for habitual cocaine self-administration to develop, but it is not sufficient to explain its presence. Taken together, these results indicate that prolonged periods of drug taking result in the development of inflexible and habitual behaviors in that drug seeking and taking becomes insensitive to a variety of manipulations aimed at devaluing the drug reinforcer. These aspects of drug use may depend on nuclei involved in stimulus-response habit learning such as the dorsolateral striatum. Below, we review evidence that dorsolateral regions of the striatum become involved in drug seeking.

Neuronal Plasticity Underlying the Habitual Component of Cocaine Addiction

It is hypothesized that cocaine-induced plasticity in circuits including the ventral (i.e. nucleus accumbens) and dorsal striatum underlie the goal-directed and habitual components of drug seeking behavior, respectively. Both the ventral and dorsal striatum are influenced by topographically organized glutamatergic inputs from the cortex and dopaminergic afferents from the ventral midbrain (Alexander et al., 1990; Heimer et al., 1997; Porrino et al., 2004a; Schmidt et al., 2005; Voorn et al., 2004). An extensive literature clearly indicates that cocaine-

induced increases in extracellular dopamine levels in the nucleus accumbens play a major role in the initial reinforcing effects of cocaine (see Pierce and Kumaresan, 2006), that likely depend on a goal-directed associative structure. Based on anatomical as well as functional studies, the nucleus accumbens has been divided into the shell and core subregions, which are associated with the limbic system and basal ganglia, respectively (Everitt et al., 1999; Heimer et al., 1991; Rodd-Henricks et al., 2002; Zahm, 2000). The limbic shell has been implicated in the primary rewarding effects of various drugs of abuse including cocaine (Carlezon and Wise, 1996; Chevette et al., 2002; Ikemoto, 2003; Ito et al., 2004; Pierce and Kumaresan, 2006; Rodd-Henricks et al., 2002) (for a review see Pierce and Kumaresan, 2006), whereas the nucleus accumbens core mediates the incentive value of cocaine-conditioned stimuli (Di Ciano and Everitt, 2004a; Ito et al., 2004), among other functions (see also Bari and Pierce, 2005). The nucleus accumbens shell, which mediates some of the goal-directed aspects of cocaine use, is the most ventromedial portion of the striatum. The dorsal striatum comprises the caudate and putamen nuclei, analogous to what in rodents is termed the dorsomedial and dorsolateral striatum, respectively. The dorsomedial striatum is involved in the formation of action-outcome relationships (Kawagoe et al., 1998; Yin et al., 2005) as well as certain forms of behavioral flexibility (Kimchi and Laubach, 2009) and response inhibition (Eagle and Robbins, 2003). The most dorsolateral part of the striatum has been shown to play a critical role in stimulus-response habit learning, whereby behavior becomes automatic and is no longer driven by an action-outcome relationship (Faure et al., 2005; Iaria et al., 2003; Packard and Knowlton, 2002; Tricomi et al., 2009; White and McDonald, 2002; Yin and Knowlton, 2006; Yin et al., 2004; Yin et al., 2009).

The progression from goal-directed to habitual forms of drug seeking and taking appears to be mediated by the gradual recruitment of ventromedial-to-dorsolateral striatal regions with prolonged drug self-administration. In an elegant series of studies, it was shown that initial exposure to cocaine self-administration was correlated with changes in glucose utilization in the ventral striatum, whereas prolonged exposure resulted in a metabolic response that expanded to encompass the entire dorsal striatum, including its most caudal and lateral portions (Porrino et al., 2004a; Porrino et al., 2007). Thus, when adult rhesus monkeys were allowed only five days of experience with cocaine self-administration, significant alterations in functional activity were restricted to limbic nuclei including the nucleus accumbens core and shell as well as the ventromedial prefrontal cortex, which sends major glutamatergic projections to the nucleus accumbens (Porrino et al., 2002). After one hundred days of cocaine self-administration, the intensity and topography of changes in metabolic activity expanded markedly to encompass additional limbic structures such as the amygdala and hippocampus as well as the dorsolateral striatum (Beveridge et al., 2006; Porrino et al., 2004b). Parallel changes were found when the effects of cocaine self-administration on expression of dopamine transporters and D2 dopamine receptors in the striatum were assessed. Initially, cocaine taking induced down-regulation of dopamine transporter expression, but up-regulation was found after prolonged cocaine self-administration. This up-regulation was most pronounced in ventral portions of the striatum, but intensified and spread caudally and dorsally as cocaine experience progressed (Letchworth et al., 2001). Cocaine self-administration reduced D2 dopamine receptor densities, initially in ventral portions of striatum only, but with extended cocaine experience these changes also became larger and were found in caudal and dorsal striatal regions as well (Moore et al., 1998; Nader et al., 2002; Porrino et al., 2004b). Similar effects have been observed in humans, where decreases in D2 dopamine receptor binding were found throughout the striatum (including dorsolateral portions) in cocaine addicts (Martinez et al., 2004). It should be noted that many rodent studies examining the effect of cocaine exposure on dopamine receptor densities in the striatal complex have produced inconsistent findings (see Anderson and Pierce, 2005). These divergent results are likely due to multiple methodological differences including dose, route, extent of exposure to cocaine as well as the length of forced abstinence prior to tissue collection.

Collectively, these results indicate that the early phase of cocaine use primarily impacts the ventral striatum including the nucleus accumbens, which is involved in the regulation of behaviors related to motivation and reward as well as dysfunctional forms of neuronal plasticity associated with addiction resulting in dysphoria/anhedonia and drug craving (Kalivas et al., 2005; Pierce and Kumaresan, 2006; Porrino et al., 2007; Robbins and Everitt, 2002; Schmidt et al., 2005). The finding that chronic self-administration of cocaine resulted in the recruitment of dorsal regions of the striatum, whose functions include the processes underlying habit learning (Faure et al., 2005; Iaria et al., 2003; Packard and Knowlton, 2002; Tricomi et al., 2009; White and McDonald, 2002; Yin and Knowlton, 2006; Yin et al., 2004; Yin et al., 2009), is consistent with cocaine-associated plasticity in neuronal circuits underlying the development of automatic action patterns associated with cocaine seeking and taking.

Pathways Underlying the Flow of Information from Ventral to Dorsal Striatum

The evidence described above indicates that functional changes occur in the ventral striatum that spread progressively more dorsal and lateral over the course of prolonged cocaine use. To understand the mechanisms underlying these phenomena, it is important to note that there is substantial anatomical evidence that the neuronal circuits including ventral and dorsal subregions of the striatum are interconnected and process information via parallel as well as integrated feedforward connections (Alexander et al., 1990; Haber, 2003). Thus, the nucleus accumbens shell is connected to the dorsal medial prefrontal cortex (mPFC) via the medial ventral pallidum and the medial dorsal thalamus (Zahm, 2000). The dorsal mPFC, in turn, sends glutamatergic projections to the core of the nucleus accumbens as well as portions of the dorsal striatum (Haber, 2003; Haber et al., 2000; Heidbreder and Groenewegen, 2003; Zahm, 2000), with the dorsolateral striatum receiving some cortical input from the dorsal anterior cingulate, medial agranular and lateral orbital cortex, but mainly from sensorimotor cortex (Berendse et al., 1992; McGeorge and Faull, 1989; Voorn et al., 2004; Schilman et al., 2008). Thus, the shell is anatomically connected to the core and dorsal striatum via serial connections involving the ventral pallidum and thalamus (Zahm and Brog, 1992). There also is evidence that different striatal subregions are interconnected through an ascending spiral of pathways from the shell to the dorsal striatum via midbrain dopaminergic regions (Haber et al., 2000). Efferents from the shell project to the ventral tegmental area (VTA) and ventromedial substantia nigra pars compacta (SNc), which sends dopaminergic projections to the core (Haber et al., 2000). Efferents from the accumbens core include major projections to the lateral SNc, which sends dopaminergic projections to the dorsal striatum (Haber, 2003; Haber et al., 2000; Heimer et al., 1997; Zahm, 2000). Both the striatal-pallidal-thalamo-cortical and striatal-midbrain systems are depicted in a simplified manner in Figure 1, which highlights the pathways whereby information can flow hierarchically through the striatal complex from the shell to the core to the dorsal striatum (Haber, 2003; Heimer et al., 1997; Zahm, 2000).

These anatomical findings provide the substrates through which extensive cocaine experience progressively involves more dorsolateral striatal regions (Porrino et al., 2004a; Porrino et al., 2007). The cellular mechanisms underlying this progression are largely unknown. However, given the dense dopaminergic and glutamatergic input into the striatum and the role that these neurotransmitters play in neural plasticity, it is likely that changes in dopamine and glutamate transmission play significant roles in this process. Indeed, cocaine-induced increases in dopamine transmission in the nucleus accumbens shell are critically involved in the initial reinforcing effects of this drug (Caine et al., 1995; Ikemoto, 2003; Rodd-Henricks et al., 2002; for a review see Pierce and Kumaresan, 2006). Although cocaine does not have a direct influence on brain glutamate systems, repeated exposure to cocaine results in alterations in cortico-accumbal glutamatergic transmission in the nucleus accumbens (Baker et al., 2003; McFarland et al., 2003; Park et al., 2002; Pierce et al., 1996; Schmidt et al., 2005; Thomas et al., 2008; Wolf et al., 2004) as well as in the dynamics of glutamate input onto midbrain

dopaminergic regions (Kalivas and Duffy, 1998; Wang et al., 2005; You et al., 2007; Zhang et al., 1997). Repeated psychostimulant treatment results in hyper-responsiveness of dopaminergic inputs to both the ventral and dorsal striatum following a subsequent drug exposure (Kolta et al., 1985; Paulson and Robinson, 1995; for reviews see Pierce and Kalivas, 1997; Vanderschuren and Kalivas, 2000), and repeated amphetamine treatment has been shown to accelerate habit formation in rats (Nelson and Killcross, 2006; Nordquist et al., 2007). It is likely, therefore, that hyper-responsive striatal dopamine transmission promotes the development of habits (see Faure et al., 2005), perhaps by easing the way in which information is processed through the ventral-to-dorsal striatal spiraling pathways (Haber et al., 2000). Interestingly, increased dopamine transmission in the dorsal striatum is associated with the expression of species-specific stereotyped behaviors (Asher and Aghajanian, 1974; Kelly et al., 1975; Creese and Iversen, 1975), which supports the notion that the dorsal striatal dopamine regulates automatic non-goal-directed behaviors. In addition, a recent study showed that acquisition of automatized behavior is accompanied by changes in excitatory transmission that progresses from the dorsomedial to the dorsolateral striatum and, moreover, that adequate performance of this behavior was dopamine-dependent (Yin et al., 2009). These results, collectively, suggest that acquisition of habitual drug seeking and taking depends on plasticity in striatal dopamine and glutamate neurotransmission working in concert in progressively more dorsal and lateral regions.

Role of the dorsolateral striatum in cocaine seeking

Above, we have reviewed evidence that prolonged cocaine use causes functional changes in the striatum that progress from ventromedial to dorsolateral regions. The role of the ventromedial striatum in goal-directed aspects of cocaine seeking and taking is well established (Carlezon and Wise, 1996; Chevrette et al., 2002; Ikemoto, 2003; Ito et al., 2004; Rodd-Henricks et al., 2002; for a review see Pierce and Kumaresan, 2006), and results from recent behavioral studies indicate that changes in dopaminergic and glutamatergic transmission in the dorsolateral striatum contribute significantly to the influence of cocaine-associated environmental stimuli on drug seeking. Exposure to cues or contexts associated with drug taking is a major factor promoting the maintenance of drug use, as well relapse of drug seeking after detoxification (Shalev et al., 2002; Spealman et al., 1999). Laboratory studies using human (Panlilio et al., 2005) and animal (Di Ciano and Everitt, 2004b; Weiss et al., 2001) subjects indicate that operant responding for cocaine-paired cues can be remarkably persistent and resistant to extinction (although this behavior has goal-directed properties as well; Arroyo et al., 1998). Moreover, rodent experiments have shown that cue-induced cocaine seeking actually strengthens, or incubates, following extended periods of forced abstinence (Grimm et al., 2001; Lu et al., 2004). In keeping with the persistent influence that cocaine-associated cues have on drug seeking, perhaps endowing this behavior with habitual characteristics, it has been shown that the dorsolateral striatum plays an important role in behavior maintained by cocaine-associated cues. For example, cocaine self-administration maintained under a second-order schedule of reinforcement was accompanied by increased dopamine efflux in the dorsolateral striatum, but not the nucleus accumbens (Ito et al., 2000; Ito et al., 2002). Consistent with these findings, microinjection of a dopamine receptor or AMPA/kainate glutamate receptor antagonist directly into the dorsolateral striatum attenuated cocaine seeking maintained under a second-order schedule of reinforcement (Belin and Everitt, 2008; Vanderschuren et al., 2005). Inactivation of the dorsolateral striatum also was shown to reduce relapse to cocaine seeking driven by discrete or contextual cues (Fuchs et al., 2006; See et al., 2007). Studies in humans have shown increases in activity and dopamine transmission during cue-induced cocaine craving in the dorsal, but not ventral, striatum (Garavan et al., 2000; Volkow et al., 2006; Wong et al., 2006). It is possible, therefore, that cocaine craving precipitated by drug-associated cues triggers stimulus-response circuits including the dorsolateral striatum that encode automatic drug seeking and drug taking behaviors. Recent evidence also supports the

progressive involvement of ventral and dorsal striatal regions in cocaine seeking. Using a disconnection procedure in which the accumbens core was unilaterally lesioned pre-training and a dopamine receptor antagonist was microinjected into the contralateral dorsolateral striatum, cocaine seeking was decreased following extensive training under a second order schedule of reinforcement (Belin and Everitt, 2008). Taken together, these results indicate important roles for both ascending striatal-pallidal-thalamo-cortical and striatal-midbrain systems in the transition from goal-directed to maladaptive habitual drug seeking.

Concluding remarks, caveats and remaining issues

The evidence reviewed above is consistent with the notion that repeated exposure to cocaine and repetition of all of the behaviors associated with drug seeking and taking result in the modification of neuronal transmission in the limbic system and basal ganglia, among other areas, producing increasingly ingrained sets of behavioral sequences. These habitual behaviors can be activated by drug-associated stimuli and contribute significantly to the process whereby the motivation (or craving) to use cocaine is put into action. The initial rewarding effects of cocaine are due to neurochemical changes in the ventral striatum (including subregions of the nucleus accumbens) and regions of the dorsal striatum and associated structures appear to be engaged when aspects of drug seeking and taking become ingrained. A simplified neuronal schematic outlining the pathways that appear to be modified during the transition from casual cocaine use to habitual cocaine seeking and taking is presented in Figure 1.

In sum, there is evidence to support three main points: i) Drug seeking and taking becomes inflexible or habitual after prolonged use; ii) After lengthy exposure to self-administered cocaine, drug-induced neuronal activation patterns and adaptive changes spread from ventromedial into dorsolateral striatal regions; iii) The dorsolateral striatum plays an important role in drug seeking in drug-experienced animals, especially in well-established drug seeking driven by drug-associated environmental stimuli. These converging lines of evidence provide substantial experimental support for the hypothesis that when patterns of drug intake become ingrained, they come to rely on dorsal striatal mechanisms. There are, however, several remaining questions that need to be addressed in future studies, which are discussed below.

The lion's share of the evidence discussed here was obtained from cocaine-using subjects. It is important to determine if the dorsolateral striatal regions engaged by prolonged cocaine use also underlie the development of inflexible behavioral patterns associated with other drugs of abuse. It is clear that drugs of abuse such as heroin, alcohol, amphetamine and nicotine also evoke addictive behavior characterized by inflexible and habitual patterns of intake (American Psychiatric Association, 2000; Nutt et al., 2007; O'Brien, 2001). Indeed, results from animal studies indicate that prolonged alcohol and amphetamine intake in rats becomes inflexible and habitual (Dickinson et al., 2002; Galli and Wolffgramm, 2004; Miles et al., 2003; Wolffgramm, 1991). There is also some evidence to support the involvement of dorsolateral striatal regions in addictive behavior maintained by other drugs of abuse. Thus, stimulation of dorsolateral striatal dopamine D1 receptors is necessary for relapse to heroin seeking evoked by a drug-associated context (Bossert et al., 2009). Furthermore, studies in humans have demonstrated activation of the dorsolateral striatum by alcohol- and tobacco-associated cues (Grusser et al., 2004; McClernon et al., 2009).

For the most part, the available evidence shows that the dorsolateral striatum is involved in addictive behavior maintained or evoked by drug-associated cues. In principle, this is consistent with the notion of a dorsolateral striatum-mediated stimulus-response associative structure of behavior where exposure to reward-associated cues results in the execution of an ingrained response, irrespective of the current value of the outcome or cost of the response. In the case of addictive behaviors, it is easy to appreciate that responding for drugs under a second-order

schedule of reinforcement has habitual properties. Establishment of this behavior takes extensive training during which the animal receives hundreds of drug-cue pairings. Furthermore, responding for drug-associated cues themselves is persistent in the absence of further presentations of the primary drug reinforcer and it is relatively resistant to extinction (Di Ciano and Everitt, 2004b; Weiss et al., 2001; Panlilio et al., 2005). However, responding for drugs under a second-order schedule of reinforcement also has goal-directed properties, mediated by drugs and conditioned reinforcers (Arroyo et al., 1998). In fact, responding under a second-order schedule of reinforcement having both goal-directed and habitual properties is consistent with the findings that responding for cocaine under a second-order schedule of reinforcement depends on the nucleus accumbens core (Di Ciano and Everitt, 2001) and the dorsolateral striatum (Vanderschuren et al., 2005), likely working in concert (Belin and Everitt, 2008). Indeed, responding for cocaine-associated cues in the absence of cocaine reinforcement also depends on both the nucleus accumbens core and the dorsolateral striatum (Di Ciano et al., 2008). However, involvement of the dorsolateral striatum in a certain behavior does not necessarily mean that this behavior is habitual, as there is recent evidence to suggest that the dorsolateral striatum has functions that extend beyond habitual behaviors (Corbit and Janak, 2007; Luo et al., 2009).

On the other hand, the demonstration that dorsolateral striatal mechanisms also underlie forms of cue-evoked drug-seeking that require only limited self-administration training followed by extinction of operant behavior (Bossert et al., 2009; Fuchs et al., 2006; See et al., 2007) suggests that either striatally driven habits can develop after quite limited drug experience or that the dorsolateral striatum is also involved in certain non-habitual aspects of addictive behavior, such as the general appetitive arousal evoked by reward-associated cues (Corbit and Janak, 2007). In some cases responding was not reinforced by presentations of drug-associated cues but evoked by placement in a self-administration environment (Fuchs et al., 2006; See et al., 2007) and this drug-context-evoked responding extinguished upon repeated testing (See et al., 2007) as did responding for heroin-associated cues in a self-administration environment using a within-session paradigm (Bossert et al., 2009). Thus, it remains unclear if all dorsolateral striatum-dependent operant behavior is indeed habitual (see also Kantak et al., 2002). Therefore, an essential line of future research would be to investigate whether drug seeking that is inflexible in the sense that it is insensitive to punishment (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004) also depends on dorsolateral striatal mechanisms.

Another issue is whether habitual addictive behavior is specific to drug-associated cues or whether it also extends to the drug itself. There is evidence from animal studies that cocaine self-administration under a simple fixed-ratio 1 schedule depends on stimulation of dorsal striatal dopamine receptors (McGregor and Roberts, 1995; Vanderschuren et al., 2005 but see also Caine et al., 1995). In addition, self-administration of cocaine by experienced cocaine users was found to decrease neural activity and increase dopamine transmission in both the ventral and dorsolateral striatum (Cox et al., 2009; Risinger et al., 2005). In his original proposal, Tiffany (1990) stated that automatized drug use is stimulus-bound (i.e. evoked by drug-associated stimuli), but the automaticity applies to both the procurement and consumption of drugs. Thus, habitual forms of drug use not only involve drug seeking (the dependent measure used in most experiments focused on the dorsolateral striatum reviewed above) but also drug taking, as in tobacco chain smoking as well as binge cocaine or alcohol use. Thus far, however, there is relatively little evidence for the involvement of the dorsolateral striatum in the habitual aspects of drug taking.

One last point that we wish to address refers to the title of this paper. If cessation of chronic drug use is indeed a matter of “kicking the habit”, then interfering with habitual aspects of drug addiction pharmacologically or through cognitive-behavioral therapy could be an effective strategy for the treatment of addiction. Indeed, the development of habitual behavior need not

be irreversible. Recent studies indicate that although the development of a stimulus-response habit requires substantial training (i.e. drug taking in the context of addiction), goal-directed action outcome and habitual stimulus-response systems appear to function in parallel, rather than sequentially. For example, interfering with the neural mechanisms underlying action-outcome learning facilitates the development of stimulus-response habits (Killcross and Coutureau, 2003; Tran-Tu-Yen et al., 2009; Wassum et al., 2009; Yin et al., 2005). Conversely, if the neural circuitry underlying the expression of habits is inactivated after the habit has developed, then behavior becomes goal-directed again (Coutureau and Killcross, 2003; Yin et al., 2006). It is crucial, therefore, to understand the neural mechanisms of habitual drug seeking because drug-directed habits appear to develop more rapidly than habitual behavior centered on natural rewards and their neural bases may not be identical. Nevertheless, this opens the possibility of therapeutically blocking habitual aspects of drug use such that these behaviors revert to being goal-directed, thereby allowing the addicted individual to regain control over drug intake. The recent finding that the neural systems underlying action-outcome and stimulus-response learning are not only anatomically but also pharmacologically dissociable (Wassum et al., 2009) indicates that this may not just be a hypothetical avenue for the treatment of addiction.

References

- Anderson SM, Pierce RC. Cocaine-induced alterations in dopamine receptor signaling: implications for reinforcement and reinstatement. *Pharmacology and Therapeutics* 2005;106:389–403. [PubMed: 15922019]
- Adams CD. Variations in the sensitivity of instrumental responding to reinforcer devaluation. *Quarterly Journal of Experimental Psychology* 1982;34B:77–98.
- Alexander GE, et al. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res* 1990;85:119–146. [PubMed: 2094891]
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR Fourth Edition (Text Revision)*. 2000.
- Arroyo M, et al. Acquisition, maintenance and reinstatement of intravenous cocaine self-administration under a second-order schedule of reinforcement in rats: effects of conditioned cues and continuous access to cocaine. *Psychopharmacology* 1998;140:331–344. [PubMed: 9877013]
- Asher IM, Aghajanian GK. 6-Hydroxydopamine lesions of olfactory tubercles and caudate nuclei: effect on amphetamine-induced stereotyped behavior in rats. *Brain Res* 1974;82:1–12. [PubMed: 4373138]
- Baker DA, et al. Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. *Nat Neurosci* 2003;6:743–749. [PubMed: 12778052]
- Bari AA, Pierce RC. D1-like and D2 dopamine receptor antagonists administered into the shell subregion of the rat nucleus accumbens decrease cocaine, but not food, reinforcement. *Neuroscience* 2005;135:959–968. [PubMed: 16111825]
- Belin D, Everitt BJ. Cocaine seeking habits depend upon dopamine-dependent serial connectivity linking the ventral with the dorsal striatum. *Neuron* 2008;57:432–441. [PubMed: 18255035]
- Belin D, et al. Pattern of intake and drug craving predict the development of cocaine addiction-like behavior in rats. *Biol Psychiatry* 2009;65:863–868. [PubMed: 18639867]
- Berendse HW, et al. Topographical organization and relationship with ventral striatal compartments of prefrontal corticostriatal projections in the rat. *J Comp Neurol* 1992;316:314–347. [PubMed: 1577988]
- Beveridge TJ, et al. Chronic cocaine self-administration is associated with altered functional activity in the temporal lobes of non human primates. *Eur J Neurosci* 2006;23:3109–3118. [PubMed: 16820001]
- Bossert JM, et al. Role of dopamine D(1)-family receptors in dorsolateral striatum in context-induced reinstatement of heroin seeking in rats. *Psychopharmacology (Berl)* 2009;206:51–60. [PubMed: 19506837]

- Caine SB, et al. Effects of the dopamine D-1 antagonist SCH 23390 microinjected into the accumbens, amygdala or striatum on cocaine self-administration in the rat. *Brain Res* 1995;692:47–56. [PubMed: 8548319]
- Carlezon WA Jr, Wise RA. Rewarding actions of phencyclidine and related drugs in nucleus accumbens shell and frontal cortex. *J Neurosci* 1996;16:3112–3122. [PubMed: 8622141]
- Chevrette J, et al. Both the shell of the nucleus accumbens and the central nucleus of the amygdala support amphetamine self-administration in rats. *Pharmacol Biochem Behav* 2002;71:501–507. [PubMed: 11830184]
- Corbit LH, Janak PH. Inactivation of the lateral but not medial dorsal striatum eliminates the excitatory impact of Pavlovian stimuli on instrumental responding. *J Neurosci* 2007;27:13977–13981. [PubMed: 18094235]
- Coutureau E, Killcross S. Inactivation of the infralimbic prefrontal cortex reinstates goal-directed responding in overtrained rats. *Behav Brain Res* 2003;146:167–174. [PubMed: 14643469]
- Cox SM, et al. Striatal dopamine responses to intranasal cocaine self-administration in humans. *Biol Psychiatry* 2009;65:846–850. [PubMed: 19249751]
- Creese I, Iversen SD. The pharmacological and anatomical substrates of the amphetamine response in the rat. *Brain Res* 1975;83:419–436. [PubMed: 234270]
- Deroche-Gamonet V, et al. Evidence for addiction-like behavior in the rat. *Science* 2004;305:1014–1017. [PubMed: 15310906]
- Di Ciano P, Everitt BJ. Dissociable effects of antagonism of NMDA and AMPA/KA receptors in the nucleus accumbens core and shell on cocaine-seeking behavior. *Neuropsychopharmacology* 2001;25:341–360. [PubMed: 11522463]
- Di Ciano P, Everitt BJ. Direct interactions between the basolateral amygdala and nucleus accumbens core underlie cocaine-seeking behavior by rats. *J Neurosci* 2004a;24:7167–7173. [PubMed: 15306650]
- Di Ciano P, Everitt BJ. Conditioned reinforcing properties of stimuli paired with self-administered cocaine, heroin or sucrose: implications for the persistence of addictive behaviour. *Neuropharmacology* 2004b;47 Suppl 1:202–213. [PubMed: 15464138]
- Di Ciano P, Robbins TW, Everitt BJ. Differential effects of nucleus accumbens core, shell, or dorsal striatal inactivations on the persistence, reacquisition, or reinstatement of responding for a drug-paired conditioned reinforcer. *Neuropsychopharmacology* 2008;33:1413–1425. [PubMed: 17712353]
- Dickinson A. Actions and habits: the development of behavioural autonomy. *Philos Trans R Soc Lond B Biol Sci* 1985;308:67–78.
- Dickinson A, et al. Alcohol seeking by rats: action or habit? *Q J Exp Psychol B* 2002;55:331–348. [PubMed: 12350285]
- Eagle DM, Robbins TW. Inhibitory control in rats performing a stop-signal reaction-time task: effects of lesions of the medial striatum and D-amphetamine. *Beh Neurosci* 2003;117:1302–1317.
- Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 2005;8:1481–1489. [PubMed: 16251991]
- Everitt BJ, et al. Associative processes in addiction and reward. The role of amygdala-ventral striatal subsystems. *Ann N Y Acad Sci* 1999;877:412–438. [PubMed: 10415662]
- Faure A, et al. Lesion to the nigrostriatal dopamine system disrupts stimulus-response habit formation. *J Neurosci* 2005;25:2771–2780. [PubMed: 15772337]
- Fuchs RA, et al. Different neural substrates mediate cocaine seeking after abstinence versus extinction training: a critical role for the dorsolateral caudate-putamen. *J Neurosci* 2006;26:3584–3588. [PubMed: 16571766]
- Galli G, Wolffgramm J. Long-term voluntary D-amphetamine consumption and behavioral predictors for subsequent D-amphetamine addiction in rats. *Drug Alcohol Depend* 2004;73:51–60. [PubMed: 14687959]
- Garavan H, et al. Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. *Am J Psychiatry* 2000;157:1789–1798. [PubMed: 11058476]
- Grimm JW, et al. Neuroadaptation. Incubation of cocaine craving after withdrawal. *Nature* 2001;412:141–142. [PubMed: 11449260]

- Grusser SM, et al. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. *Psychopharmacology (Berl)* 2004;175:296–302. [PubMed: 15127179]
- Haber SN. The primate basal ganglia: parallel and integrative networks. *J Chem Neuroanat* 2003;26:317–330. [PubMed: 14729134]
- Haber SN, et al. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci* 2000;20:2369–2382. [PubMed: 10704511]
- Heidbreder CA, Groenewegen HJ. The medial prefrontal cortex in the rat: evidence for a dorso-ventral distinction based upon functional and anatomical characteristics. *Neurosci Biobehav Rev* 2003;27:555–579. [PubMed: 14599436]
- Heimer L, et al. Specificity in the projection patterns of accumbal core and shell in the rat. *Neuroscience* 1991;41:89–125. [PubMed: 2057066]
- Heimer L, et al. The accumbens: beyond the core-shell dichotomy. *J Neuropsychiatry Clin Neurosci* 1997;9:354–381. [PubMed: 9276840]
- Iaria G, et al. Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. *J Neurosci* 2003;23:5945–5952. [PubMed: 12843299]
- Ikemoto S. Involvement of the olfactory tubercle in cocaine reward: intracranial self-administration studies. *J Neurosci* 2003;23:9305–9311. [PubMed: 14561857]
- Ito R, et al. Differential control over cocaine-seeking behavior by nucleus accumbens core and shell. *Nat Neurosci* 2004;7:389–397. [PubMed: 15034590]
- Ito R, et al. Dopamine release in the dorsal striatum during cocaine-seeking behavior under the control of a drug-associated cue. *J Neurosci* 2002;22:6247–6253. [PubMed: 12122083]
- Ito R, et al. Dissociation in conditioned dopamine release in the nucleus accumbens core and shell in response to cocaine cues and during cocaine-seeking behavior in rats. *J Neurosci* 2000;20:7489–7495. [PubMed: 11007908]
- Kalivas PW, Duffy P. Repeated cocaine administration alters extracellular glutamate in the ventral tegmental area. *J Neurochem* 1998;70:1497–1502. [PubMed: 9523566]
- Kalivas PW, et al. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. *Neuron* 2005;45:647–650. [PubMed: 15748840]
- Kantak, et al. Stimulus-response functions of the lateral dorsal striatum and regulation of behavior studied in a cocaine maintenance/cue reinstatement model in rats. *Psychopharmacology* 2002;161:278–287. [PubMed: 12021831]
- Kawagoe R, Takikawa Y, Hikosaka O. Expectation of reward modules cognitive signals in the basal ganglia. *Nat Neurosci* 1998;1:411–416. [PubMed: 10196532]
- Kelly PH, Seviour PW, Iversen SD. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. *Brain Res* 1975;94:507–522. [PubMed: 1171714]
- Killcross S, Coutureau E. Coordination of actions and habits in the medial prefrontal cortex of rats. *Cereb Cortex* 2003;13:400–408. [PubMed: 12631569]
- Kimchi EY, Laubach M. Dynamic encoding of action selection by the medial striatum. *J Neurosci* 2009;29:3148–3159. [PubMed: 19279252]
- Kolta MG, et al. Time course of the development of the enhanced behavioral and biochemical responses to amphetamine after pretreatment with amphetamine. *Neuropharmacology* 1985;24:823–829. [PubMed: 4058677]
- Letchworth SR, et al. Progression of changes in dopamine transporter binding site density as a result of cocaine self-administration in rhesus monkeys. *J Neurosci* 2001;21:2799–2807. [PubMed: 11306632]
- Little KY, et al. Brain dopamine transporter messenger RNA and binding sites in cocaine users: a postmortem study. *Arch Gen Psychiatry* 1998;55:793–799. [PubMed: 9736005]
- Luo S, et al. Behavioral and neural evidence of incentive bias for immediate rewards relative to preference-matched delayed rewards. *J Neurosci* 2009;29:14820–14827. [PubMed: 19940177]

- Lu L, et al. Incubation of cocaine craving after withdrawal: a review of preclinical data. *Neuropharmacology* 2004;47 Suppl 1:214–226. [PubMed: 15464139]
- Martinez D, et al. Cocaine dependence and d2 receptor availability in the functional subdivisions of the striatum: relationship with cocaine-seeking behavior. *Neuropsychopharmacology* 2004;29:1190–1202. [PubMed: 15010698]
- McClernon FJ, et al. 24-h smoking abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. *Psychopharmacology (Berl)* 2009;204:25–35. [PubMed: 19107465]
- McFarland K, et al. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci* 2003;23:3531–3537. [PubMed: 12716962]
- McGeorge AJ, Faull RL. The organization of the projection from the cerebral cortex to the striatum in the rat. *Neuroscience* 1989;29:503–537. [PubMed: 2472578]
- McGregor A, Roberts DC. Effect of medial prefrontal cortex injections of SCH 23390 on intravenous cocaine self-administration under both a fixed and progressive ratio schedule of reinforcement. *Behav Brain Res* 1995;67:75–80. [PubMed: 7748503]
- Miles FJ, et al. Oral cocaine seeking by rats: action or habit? *Behav Neurosci* 2003;117:927–938. [PubMed: 14570543]
- Moore RJ, et al. Effect of cocaine self-administration on dopamine D2 receptors in rhesus monkeys. *Synapse* 1998;30:88–96. [PubMed: 9704885]
- Nader MA, et al. Effects of cocaine self-administration on striatal dopamine systems in rhesus monkeys: initial and chronic exposure. *Neuropsychopharmacology* 2002;27:35–46. [PubMed: 12062905]
- Nelson A, Killcross S. Amphetamine exposure enhances habit formation. *J Neurosci* 2006;26:3805–3812. [PubMed: 16597734]
- Nordquist RE, et al. Augmented reinforcer value and accelerated habit formation after repeated amphetamine treatment. *Eur Neuropsychopharmacol* 2007;17:532–540. [PubMed: 17275266]
- Nutt D, et al. Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet* 2007;369:1047–1053. [PubMed: 17382831]
- O'Brien, CP. Drug Addiction and Drug Abuse. Goodman and Gilman's the pharmacological basis of therapeutics. Hardman, JG.; Limbird, LE.; Gilman, AG., editors. New York, NY: McGraw-Hill; 2001. p. 621–642.
- Packard MG, Knowlton BJ. Learning and memory functions of the Basal Ganglia. *Annu Rev Neurosci* 2002;25:563–593. [PubMed: 12052921]
- Panlilio LV, et al. Human cocaine-seeking behavior and its control by drug-associated stimuli in the laboratory. *Neuropsychopharmacology* 2005;30:433–443. [PubMed: 15536497]
- Park WK, et al. Cocaine administered into the medial prefrontal cortex reinstates cocaine-seeking behavior by increasing AMPA receptor-mediated glutamate transmission in the nucleus accumbens. *J Neurosci* 2002;22:2916–2925. [PubMed: 11923456]
- Parsons LH, et al. Extracellular serotonin is decreased in the nucleus accumbens during withdrawal from cocaine self-administration. *Behav Brain Res* 1996;73:225–228. [PubMed: 8788507]
- Paulson PE, Robinson TE. Amphetamine-induced time-dependent sensitization of dopamine neurotransmission in the dorsal and ventral striatum: a microdialysis study in behaving rats. *Synapse* 1995;19:56–65. [PubMed: 7709344]
- Pelloux Y, et al. Compulsive drug seeking by rats under punishment: effects of drug taking history. *Psychopharmacology (Berl)* 2007;194:127–137. [PubMed: 17514480]
- Pierce RC, Kalivas PW. A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. *Brain Res Brain Res Rev* 1997;25:192–216. [PubMed: 9403138]
- Pierce RC, Kumaresan V. The mesolimbic dopamine system: The final common pathway for the reinforcing effect of drugs of abuse? *Neurosci Biobehav Rev* 2006;30:215–238. [PubMed: 16099045]
- Pierce RC, et al. Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. *J Neurosci* 1996;16:1550–1560. [PubMed: 8778304]

- Porrino LJ, et al. Metabolic mapping of the effects of cocaine during the initial phases of self-administration in the nonhuman primate. *J Neurosci* 2002;22:7687–7694. [PubMed: 12196592]
- Porrino LJ, et al. The expanding effects of cocaine: studies in a nonhuman primate model of cocaine self-administration. *Neurosci Biobehav Rev* 2004a;27:813–820. [PubMed: 15019430]
- Porrino LJ, et al. Cocaine self-administration produces a progressive involvement of limbic, association, and sensorimotor striatal domains. *J Neurosci* 2004b;24:3554–3562. [PubMed: 15071103]
- Porrino LJ, et al. The effects of cocaine: a shifting target over the course of addiction. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31:1593–1600. [PubMed: 17900777]
- Risinger RC, et al. Neural correlates of high and craving during cocaine self-administration using BOLD fMRI. *Neuroimage* 2005;26:1097–1108. [PubMed: 15886020]
- Ritz MC, et al. Cocaine self-administration appears to be mediated by dopamine uptake inhibition. *Prog Neuropsychopharmacol Biol Psychiatry* 1988;12:233–239. [PubMed: 3387585]
- Robbins TW, Everitt BJ. Drug addiction: bad habits add up. *Nature* 1999;398:567–570. [PubMed: 10217139]
- Robbins TW, Everitt BJ. Limbic-striatal memory systems and drug addiction. *Neurobiol Learn Mem* 2002;78:625–636. [PubMed: 12559840]
- Rodd-Henricks ZA, et al. Cocaine is self-administered into the shell but not the core of the nucleus accumbens of Wistar rats. *J Pharmacol Exp Ther* 2002;303:1216–1226. [PubMed: 12438546]
- Samaha AN, Robinson TE. Why does the rapid delivery of drugs to the brain promote addiction? *Trends Pharmacol Sci* 2005;26:82–87. [PubMed: 15681025]
- Samaha AN, et al. The rate of cocaine administration alters gene regulation and behavioral plasticity: implications for addiction. *J Neurosci* 2004;24:6362–6370. [PubMed: 15254092]
- Schilman EA, et al. The orbital cortex in rats topographically projects to central parts of the caudate-putamen complex. *Neurosci Lett* 2008;432:40–45. [PubMed: 18248891]
- Schmidt HD, Pierce RC. Systemic administration of a dopamine, but not a serotonin or norepinephrine, transporter inhibitor reinstates cocaine seeking in the rat. *Behav Brain Res* 2006;175:189–194. [PubMed: 16978714]
- Schmidt HD, et al. Anatomy and pharmacology of cocaine priming-induced reinstatement of drug seeking. *Eur J Pharmacol* 2005;526:65–76. [PubMed: 16321382]
- See RE, et al. The role of dorsal vs ventral striatal pathways in cocaine-seeking behavior after prolonged abstinence in rats. *Psychopharmacology (Berl)* 2007;194:321–331. [PubMed: 17589830]
- Shalev U, et al. Neurobiology of relapse to heroin and cocaine seeking: a review. *Pharmacol Rev* 2002;54:1–42. [PubMed: 11870259]
- Spealman RD, et al. Pharmacological and environmental determinants of relapse to cocaine-seeking behavior. *Pharmacol Biochem Behav* 1999;64:327–336. [PubMed: 10515309]
- Thomas MJ, et al. Neuroplasticity in the mesolimbic dopamine system and cocaine addiction. *Br J Pharmacol* 2008;154:327–342. [PubMed: 18345022]
- Tiffany ST. A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. *Psychol Rev* 1990;97:147–168. [PubMed: 2186423]
- Tran-Tu-Yen DA, et al. Transient role of the rat prelimbic cortex in goal-directed behaviour. *Eur J Neurosci* 2009;30:464–471. [PubMed: 19614748]
- Tricomi E, et al. A specific role for posterior dorsolateral striatum in human habit learning. *Eur J Neurosci*. 2009
- Vanderschuren LJ, Kalivas PW. Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. *Psychopharmacology (Berl)* 2000;151:99–120. [PubMed: 10972458]
- Vanderschuren LJ, Everitt BJ. Drug seeking becomes compulsive after prolonged cocaine self-administration. *Science* 2004;305:1017–1019. [PubMed: 15310907]
- Vanderschuren LJ, et al. Involvement of the dorsal striatum in cue-controlled cocaine seeking. *J Neurosci* 2005;25:8665–8670. [PubMed: 16177034]
- Volkow ND, et al. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J Neurosci* 2006;26:6583–6588. [PubMed: 16775146]

- Voorn P, et al. Putting a spin on the dorsal-ventral divide of the striatum. *Trends Neurosci* 2004;27:468–474. [PubMed: 15271494]
- Wang B, et al. Cocaine experience establishes control of midbrain glutamate and dopamine by corticotropin-releasing factor: a role in stress-induced relapse to drug seeking. *J Neurosci* 2005;25:5389–5396. [PubMed: 15930388]
- Wassum KM, et al. Disruption of endogenous opioid activity during instrumental learning enhances habit acquisition. *Neuroscience* 2009;163:770–780. [PubMed: 19619616]
- Weiss F, et al. Enduring resistance to extinction of cocaine-seeking behavior induced by drug-related cues. *Neuropsychopharmacology* 2001;25:361–372. [PubMed: 11522464]
- White NM, McDonald RJ. Multiple parallel memory systems in the brain of the rat. *Neurobiol Learn Mem* 2002;77:125–184. [PubMed: 11848717]
- Wilson JM, et al. Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. *Nat Med* 1996;2:699–703. [PubMed: 8640565]
- Wise RA, et al. Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. *Psychopharmacology (Berl)* 1995;120:10–20. [PubMed: 7480530]
- Wolf ME, et al. Psychomotor stimulants and neuronal plasticity. *Neuropharmacology* 2004;47 Suppl 1:61–79. [PubMed: 15464126]
- Wolffgramm J. An ethopharmacological approach to the development of drug addiction. *Neurosci Biobehav Rev* 1991;15:515–519. [PubMed: 1792014]
- Wong DF, et al. Increased occupancy of dopamine receptors in human striatum during cue-elicited cocaine craving. *Neuropsychopharmacology* 2006;31:2716–2727. [PubMed: 16971900]
- Yin HH, Knowlton BJ. The role of the basal ganglia in habit formation. *Nat Rev Neurosci* 2006;7:464–476. [PubMed: 16715055]
- Yin HH, et al. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. *Eur J Neurosci* 2004;19:181–189. [PubMed: 14750976]
- Yin HH, et al. Inactivation of dorsolateral striatum enhances sensitivity to changes in the action-outcome contingency in instrumental conditioning. *Behav Brain Res* 2006;166:189–196. [PubMed: 16153716]
- Yin HH, et al. The role of the dorsomedial striatum in instrumental conditioning. *Eur J Neurosci* 2005;22:513–523. [PubMed: 16045504]
- Yin HH, et al. Dynamic reorganization of striatal circuits during the acquisition and consolidation of a skill. *Nat Neurosci* 2009;12:333–341. [PubMed: 19198605]
- You ZB, et al. A role for conditioned ventral tegmental glutamate release in cocaine seeking. *J Neurosci* 2007;27:10546–10555. [PubMed: 17898226]
- Zahm DS. An integrative neuroanatomical perspective on some subcortical substrates of adaptive responding with emphasis on the nucleus accumbens. *Neurosci Biobehav Rev* 2000;24:85–105. [PubMed: 10654664]
- Zahm DS, Brog JS. On the significance of subterritories in the "accumbens" part of the rat ventral striatum. *Neuroscience* 1992;50:751–767. [PubMed: 1448200]
- Zhang XF, et al. Increased responsiveness of ventral tegmental area dopamine neurons to glutamate after repeated administration of cocaine or amphetamine is transient and selectively involves AMPA receptors. *J Pharmacol Exp Ther* 1997;281:699–706. [PubMed: 9152375]

Figure 1.

Anatomical circuits proposed to underlie the progressive recruitment of more dorsal regions of the striatum during the transition from casual cocaine use to habitual cocaine seeking and taking. See the text for additional details.