Drug Addiction: Updating Actions to Habits to Compulsions Ten Years On

Barry J. Everitt and Trevor W. Robbins

Department of Psychology and Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge CB2 3EB, United Kingdom; email: bje10@cam.ac.uk, twr2@cam.ac.uk

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Abstract

A decade ago, we hypothesized that drug addiction can be viewed as a transition from voluntary, recreational drug use to compulsive drug-seeking habits, neurally underpinned by a transition from prefrontal cortical to striatal control over drug seeking and taking as well as a progression from the ventral to the dorsal striatum. Here, in the light of burgeoning, supportive evidence, we reconsider and elaborate this hypothesis, in particular the refinements in our understanding of ventral and dorsal striatal mechanisms underlying goal-directed and habitual drug seeking, the influence of drug-associated Pavlovian-conditioned stimuli on drug seeking and relapse, and evidence for impairments in top-down prefrontal cortical inhibitory control over this behavior. We further review animal and human studies that have begun to define etiological factors and individual differences in the propensity to become addicted to drugs, leading to the description of addiction endophenotypes, especially for cocaine addiction. We consider the prospect of novel treatments for addiction that promote abstinence from and relapse to drug use.

Contents

INTRODUCTION

The understanding of drug addiction has perhaps made most progress when conceived in terms of its underlying neuropsychological processes. Classic ideas of Pavlovian conditioning, positive reinforcement, opponent motivational processes, and cognitive control have all been shown to play a role not only in explaining apparently bizarre behavioral symptoms of drug abusers but also in relating the behavior to underlying dysfunctional neural networks. In our last major review of this area, more than a decade ago, we summarized the relevance of then-recent advances in specifying mechanisms of instrumental conditioning that produced both goal-directed behavior and stimulus-response habit learning (Everitt & Robbins 2005). We surmised that habits could be the building blocks of compulsive drug seeking. Compulsive behavior can be defined as the maladaptive persistence of responding despite adverse consequences (Dalley et al. 2011), and so clearly other factors must be involved. At the time, we suggested that aversive motivational states, as in withdrawal phenomena (Koob & LeMoal 1997), drug-induced sensitization (Robinson & Berridge 1993), and a loss of top-down inhibitory response control (Jentsch & Taylor 1999, Robbins & Everitt 1999) might all be contributory factors. One of the aims of this review is to re-examine the relative importance of these factors in the light of recent empirical evidence in experimental studies of both animals and humans. Pavlovian conditioning also evidently contributes to substance abuse and has formed the basis of attempts at remediation through extinction-based behavioral therapy; early work established the importance of such conditioning to both withdrawal and relapse to drug-seeking behavior, with the subjective correlate of craving (Tiffany 1990).

One of the current challenges to the field is indeed to understand how Pavlovian and instrumental conditioning processes interact during the course of drug abuse to produce compulsive behavior. One clue may reside in the importance of so-called Pavlovian-instrumental transfer (PIT), by which a conditioned stimulus (CS) exerts motivational influences on the expression of instrumental behavior. An important route by which such transfer occurs may also be the development of conditioned reinforcing properties of such CSs; in other words, the possibility that behavior may be maintained, especially over delays between drug taking, by the presentation of cues associated with drug-taking experiences, contingent upon responding

(Arroyo et al. 1998, Goldberg 1973). A further complication is the effect a drug itself has on such conditioned rewarding stimuli not only associated with drugs themselves but also with other positive reinforcers (e.g., Taylor & Robbins 1984). An exciting source of converging support has been the gradual identification of key neural systems underpinning these processes and interactions.

This approach has proved to be entirely contemporary in the face of two widely differing approaches to understand mental disorders, including addiction, exemplified by the new edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; Am. Psychiatr. Assoc. 2013) on the one hand, and the Research Domain Criteria (RDoC) project of the National Institutes of Health (Cuthbert 2014) on the other. The DSM method depends on a symptom-based categorization of mental disorders; the RDoC approach by contrast is dimensional, eschewing clinically expressed symptoms for objectively demonstrated deficits in neurobehavioral systems. Our own approach, and that of others, is intermediate between these two extremes: We seek to understand the symptomatic phenomena of drug addiction and abuse in terms of underlying neurobehavioral and neurocognitive systems. This enterprise appears to have borne some fruit; it is remarkable that the DSM-5 has abandoned former definitions of addiction in terms of substance dependence (a theoretically loaded term used in deference to stigmatizing views of the word addiction). A system of different substance use disorders of varying severity, culminating in addiction, is now defined according to the expression of a criterion number from a set of 11 basic symptoms (Am. Psychiatr. Assoc. 2013). In fact, although expressions of dependence, craving, and tolerance are among this set of symptoms, definitions of the majority of the set clearly reflect different aspects of compulsive behavior and failures of control. We thus take some encouragement for the field in continuing this neuroscientific program of investigation, which was begun in earnest in the 1990s, notably with the human neuroimaging work of Volkow and others, and is still gathering momentum.

LEARNING THEORY ACCOUNTS OF ADDICTION

From the initial important demonstration of the key role played by the mesolimbic dopamine (DA) system in the reinforcing—or rewarding—effects of addictive drugs (Roberts & Koob 1982, Wise 2008), neuroadaptations in nucleus accumbens function following repeated use have remained a major focus of cellular and molecular theories of addiction (Nestler 2004), as well as theories incorporating psychological mechanisms, including Pavlovian incentive motivational processes enhanced by incremental adaptations to repeated drug use (sensitization) (Leyton & Vezina 2014, Robinson & Berridge 1993) or opponent processes engaged by withdrawal (Koob & LeMoal 1997, Wikler 1965). However, it rapidly became apparent that responses to drugs can acquire motivational significance by being associated with environmental stimuli through Pavlovian conditioning (Gawin & Kleber 1986, O'Brien et al. 1998) and that these drug-associated CSs exert a marked influence on the instrumental behaviors of drug seeking and use (Everitt et al. 2001), induce subjective craving states, and precipitate relapse long into abstinence (Childress et al. 1999, Garavan et al. 2000, Grant et al. 1996).

As a result, concepts of addiction incorporating learning theory accounts of Pavlovian conditioning mechanisms (Everitt et al. 2001, Robinson & Berridge 1993, Saunders & Robinson 2013, Stewart et al. 1984) and, more recently, instrumental learning mechanisms (Everitt et al. 2001, Everitt & Robbins 2005, Robbins & Everitt 1999), have become more prominent. We have now reached a remarkable juncture at which learning theory accounts of addiction dominate the literature, whether based on motivational or hedonic mechanisms (Kalivas & Volkow 2005, Koob & Volkow 2010) or more sophisticated and evidence-based Pavlovian and instrumental learning mechanisms and interactions between them (Belin et al. 2009, Everitt & Robbins 2005, Hogarth

et al. 2010, Saunders & Robinson 2013). Moreover, this theoretical advance is compatible with an increasing focus on neuronal plasticity processes, such as long-term potentiation and long-term depression (Grueter et al. 2012, Hyman et al. 2006, Kauer & Malenka 2007, Luescher & Malenka 2011).

INSTRUMENTAL LEARNING AND ADDICTION

Our theorizing focused on the fact that the general concept of positive reinforcement conflates at least two different processes identified by contemporary analyses of instrumental conditioning with conventional reinforcers (Dickinson 1985, Dickinson & Balleine 1994): (*a*) a declarative associative process based upon knowledge of the relationship between instrumental behavior, or action (A) and its outcome (O), taking the form of intentional goal-directed actions maintained by a representation of the goal (A-O association), which, if devalued, results in markedly decreased instrumental responding; and (*b*) a stimulus-response (S-R) process by which a reinforcer strengthens an association between the response and the contextual and discrete stimuli present at the time of reinforcement. Instrumental behavior dependent on this associative structure takes the form of a habit that is elicited by the CSs independently of the value of the goal, such that its devaluation has little or no effect on instrumental seeking responses. These instrumental learning processes are generally engaged in parallel, but under some conditions (e.g., a degraded relationship between A and O, or after much repetition) the S-R habit response dominates so that instrumental behavior acquires autonomy and is elicited outside conscious awareness, persistent and resistant to extinction. Habits are not in themselves pathological, being an efficient mode of information processing, but carried to excess under certain circumstances become maladaptive (Robbins & Everitt 1999). The notion of transition and the imbalance between goal-directed and habitual drug seeking is central to our hypothesis but is insufficient in itself to explain compulsive drug seeking (Everitt & Robbins 2005, Robbins et al. 2008).

IMBALANCE BETWEEN GOAL-DIRECTED AND HABITUAL BEHAVIOR

There are now several demonstrations of habitual drug seeking behavior in animals, as well as neurobehavioral data in humans addicted to drugs, that indicate the dominant engagement of habit systems in the brain. However, a challenge for the field has been unambiguously to demonstrate S-R control over the seeking of intravenously self-administered drugs using the conventional techniques of reinforcer devaluation (through specific satiety or lithium chloride–induced malaise) or response contingency degradation that are readily achievable with ingestive reinforcers (Everitt 2014, Everitt & Robbins 2013). Such demonstrations underpin the somewhat counterintuitive conclusion that not all instrumental behavior is necessarily goal directed unless the performance of the behavior itself has become reinforcing. Descriptions of drug seeking by humans in motivational terms of "liking" and "wanting" may thus represent to some extent *post hoc* rationalizations of behavioral urges that we earlier characterized as "must do!" responses (Everitt & Robbins 2005).

Early demonstrations of the rapid resistance to devaluation of oral cocaine or alcohol (Dickinson et al. 2002, Miles et al. 2003) have been independently confirmed in the responding of rats for alcohol (Corbit et al. 2012) and for the intravenous (i.v.) self-administration of nicotine (Clemens et al. 2014). Using a novel method in which cocaine-seeking responses on one lever gave access to a second, "taking" lever delivering i.v. cocaine, we showed that devaluation achieved by extinguishing specifically the taking link of the chain reduced seeking early in training, which confirmed that it was goal directed (Olmstead et al. 2001). This demonstration was later

confirmed and extended by Zapata et al. (2010), who showed additionally that cocaine-seeking behavior became insensitive to devaluation, i.e., habitual, after extended training (Zapata et al. 2010). This effect of extended training to promote habitual drug seeking has further been shown in rats self-administering nicotine (Clemens et al. 2014).

Alcohol-dependent human subjects also exhibit overreliance on S-R representations, as shown in a computer-based task distinguishing between goal-directed and habitual control (Sjoerds et al. 2013). In fact, observations in humans and animals indicate that even noncontingent (i.e., not self-administered) addictive drug exposure can tip the balance between A-O and S-R associative mechanisms to favor the latter. Thus, for humans undergoing instrumental training for chocolate reward, noncontingent alcohol administration attenuated goal-directed control over chocolate choice and accelerated habit learning (Hogarth et al. 2013). In rats, noncontingent alcohol exposure accelerated the development of habitual control over natural reward seeking (Corbit et al. 2012), whereas repeated noncontingent amphetamine treatment resulted in extremely rapid development of habitual control over responding for sucrose (Nelson & Killcross 2006). Even posttraining cocaine administration was able to facilitate habitual responding for a natural reward (Schmitzer-Torbert et al. 2014). Hence, exposure to addictive drugs may impair the ability of outcome representations to control responding, leading to the dominant control over behavior by S-R contingencies. It is also possible that addictive drugs directly enhance habit learning for both drug and natural rewards (Everitt & Robbins 2013, Hogarth et al. 2013).

Major advances in understanding the neural basis of the transition from goal-directed to habitual drug seeking, as well as PIT and conditioned reinforcement, have depended on data from the response of animals and humans to food rewards. The goal-directed system in both rats and humans depends on interactions between the medial prefrontal cortex (mPFC) and the posterior dorsomedial striatum (pDMS) (Shiflett et al. 2010, Yin et al. 2005). In contrast, the habit system implicates the anterior dorsolateral striatum (aDLS), or putamen in humans, and perhaps motor cortical areas (Balleine & O'Doherty 2010, Yin et al. 2004). Significantly, electrophysiological data from animals learning and performing a T-maze, food-reinforced task have revealed a transition from activity in the DMS during acquisition and early performance that decreased with overtraining to be dominated by DLS activity mediating habitual performance (Thorn et al. 2010). The transition from goal-directed to habitual drug seeking maps well onto this conceptual landscape.

There is now considerable evidence that the aDLS is gradually engaged to underlie well-established, habitual drug seeking (Barker & Taylor 2014, Belin et al. 2009, Everitt 2014, Everitt & Robbins 2013). Initial observations of dorsal striatal DA release during the performance of a well-trained cocaine-seeking task (Ito et al. 2002) and decreases of such responding by intra-DLS DA receptor blockade (in the absence of effects in the nucleus accumbens) (Vanderschuren et al. 2005) have been reinforced by recent studies (Corbit et al. 2012, Zapata et al. 2010), but with the additional finding that aDLS DA receptor blockade earlier during acquisition of cocaine-seeking behavior was ineffective (Murray et al. 2012). Thus, the aDLS is not required for initial cocaine seeking, when it is goal directed, but gradually becomes dominant in the control over this behavior when it is well established and habitual (Murray et al. 2012). By contrast, DA receptor blockade in the pDMS impaired the acquisition of cocaine seeking when goal directed but had no effect after extended training (Murray et al. 2012). Zapata et al. (2010) additionally showed that well-trained cocaine seeking depended on the aDLS and that its inactivation reinstated sensitivity to devaluation—that is, rendered it goal directed.

The hypothesized devolution in control over alcohol seeking was further shown to proceed from the DMS to DLS (Corbit et al. 2012), with habitual responding depending on DLS α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and DA D2 receptors (Corbit et al. 2014). Other neurobiological data sit well with the recruitment by chronic drug exposure of DLS cellular

adaptations. Prolonged but not brief stimulant self-administration alters cellular plasticity markers in DLS neurons in rats (Jedynak et al. 2007) as well as striatal DA D2 receptors and metabolic markers in monkeys that spread from ventral to dorsal striatum after months, but not weeks, of cocaine self-administration (Letchworth et al. 2001). The escalation of cocaine intake after extended access is causally associated with specific micro-RNAs in the dorsal striatum (Jonkman & Kenny 2013), and chronic alcohol vapor exposure in mice facilitated DLS-dependent neuronal plasticity and learning suggested to be related to the progression to alcoholism (DePoy et al. 2013).

In humans, too, neuroimaging and behavioral studies have revealed the importance of dorsal striatal processes in individuals addicted to drugs. Cue-induced cocaine craving was associated with increased DA release and metabolic activity in the dorsal striatum (Garavan et al. 2000, Volkow et al. 2006). Alcohol-dependent subjects presented with alcohol-related CSs showed a shift in activation from the ventral to the dorsal striatum when compared to recreational alcohol drinkers (Vollstaedt-Klein et al. 2010). An overreliance on S-R habit learning in alcohol-dependent individuals was associated with the decreased activation of areas of the brain implicated in A-O, goal-directed learning, such as the ventromedial PFC and anterior putamen, but with the increased activation of the posterior putamen that mediates habit learning (Sjoerds et al. 2013). In human subjects engaged in learning a virtual maze task that could dissociate spatial and S-R response navigational strategies, response learners had increased dorsal striatal gray matter volume and activity measured using functional magnetic resonance imaging (fMRI), whereas spatial learners had increased hippocampal gray matter and activity. Furthermore, response learners had greater use of abused substances in comparison with spatial learners, including double the lifetime alcohol consumption, a greater number of cigarettes smoked, and a greater lifetime use of cannabis (Bohbot et al. 2013). Cocaine-dependent individuals and their non-cocaine-abusing siblings had a significantly enlarged left putamen (Ersche et al. 2011a, 2013a), suggesting that greater dorsal striatal (putamen) volume may be associated with a predisposition to acquire drug-seeking and -taking habits (see below).

TRANSITION FROM VENTRAL TO DORSAL STRIATUM

Our emphasis on shifts within dorsal striatal instrumental learning systems has deflected detailed consideration of the contribution of ventral striatal (nucleus accumbens)–mediated processes by which addictive drugs exert their reinforcing effects as Pavlovian unconditioned stimuli (Di Chiara & Imperato 1988, Ikemoto & Wise 2004) as well as their conditioned associations, for example, as PIT and expressed in instrumental responding as conditioned reinforcement (Cardinal et al. 2002, Corbit & Balleine 2005, Hall et al. 2001). However, it is evident that not only is there a shift of control within the dorsal striatum, but that ventral striatal processes initially recruit and eventually become dominated by—yet continue to influence—the dorsal striatum. Thus, we (Everitt & Robbins 2005) hypothesized that the intrastriatal shift in the control over drug seeking and taking might have a neuroanatomical basis in the circuitry that connects the ventral to the dorsal striatum via recurrent connections with midbrain DA neurons (Haber et al. 2000).

Recent evidence for this scheme has depended on a novel procedure to disconnect ventral from dorsal striatum by combining a specific unilateral lesion of the nucleus accumbens core with contralateral DLS DA receptor blockade, thereby disabling this system bilaterally (Belin & Everitt 2008). This disconnection reduced well-established habitual cocaine seeking at a time point previously shown to depend on the aDLS, but importantly had no effect on a newly acquired instrumental seeking response. That processing in the nucleus accumbens core can indeed influence DA transmission in the aDLS was further demonstrated using in vivo voltammetry in rats self-administering cocaine in which late-developing, drug CS-evoked DA transients in the aDLS

were completely prevented by a specific nucleus accumbens core (NAcbC) lesion (Willuhn et al. 2012). Remarkably, functional coupling between the ventral and the dorsal striatum has also been shown in former heroin addicts, together with decreased functional coupling between the striatum and the PFC (Xie et al. 2014). Neurocomputational models of addiction have successfully incorporated this concept (Dezfouli et al. 2009, Piray et al. 2010), which may be linked to earlier notions of a reinforcement learning model, which assigns the role of critic to the nucleus accumbens that modulates the actor role over action selection assigned to the dorsal striatum (O'Doherty et al. 2004). Repeated drug taking may result in a failure of the critic properly to direct action selection by the actor, thus rendering choices and actions rigid and independent of the value of outcomes (Belin et al. 2013).

Ventral striatal mediation of drug-associated conditioned reinforcement and PIT also depends upon its afferents from the amygdala (Cardinal et al. 2002). However, the neural circuitry by which the amygdala influences habitual instrumental behavior in the DLS is unclear, since it does not project there directly. The two main routes by which amygdala-DLS interactions could occur are (*a*) via glutamatergic basolateral amygdala (BLA) projections to the NAcbC, which can thereby influence the spiraling dopaminergic circuitry linking the core with the DLS, and (*b*) via the central amygdala (CeN) projections directly to the substantia nigra pars compacta that dopaminergically innervates the DLS. The latter amygdala CeN-DLS system has been shown functionally to be important for Pavlovian conditioned orienting (Han et al. 1997) and for the acquisition of food-reinforced habits (Lingawi & Balleine 2012). By disconnecting either the BLA or the CeN from the DLS (by combining a unilateral lesion of either the CeN or BLA with infusion of a DA receptor antagonist into the contralateral aDLS), Murray and colleagues (2013) have demonstrated the functional importance of this polysynaptic and indirect circuitry in the acquisition and maintenance of cue-controlled cocaine-seeking habits. Moreover, it was further shown electrophysiologically that activation of the BLA can both up- and downregulate cortically driven aDLS medium spiny neuron activity via its projections to the NAcbC (Belin-Rauscent et al. 2013).

MODULATORS OF HABIT

The strength and persistence of habits can be modulated by motivational processes. Drug-associated CSs can retrieve representations of a drug's identity and, through specific PIT, elicit and potentiate instrumental responses for the same drug outcome (Hogarth et al. 2013). Through general PIT, CSs can retrieve the drug's affective value and hence a motivational state that is similar to that elicited by the drug itself, but which has a general excitatory effect on responses for both the same and other goals. Although both forms of PIT can readily be demonstrated for ingestive rewards (Cardinal & Everitt 2004, Saunders & Robinson 2013) including alcohol (Milton et al. 2012), we previously drew attention to the fact that neither effect had been seen in individuals' responding for i.v. drug reinforcement (Everitt & Robbins 2005), though some reports of this effect have appeared more recently (reviewed by Saunders & Robinson 2013). Hogarth and colleagues (2013) have in particular pointed out that early in training, drug CSs can indeed retrieve the drug's specific identity to produce specific transfer effects, whereas extended exposure to drugs, including their self-administration, results in such CSs failing to retrieve the drug's specific identity, instead retrieving the drug's affective value to exert a general PIT effect on drug seeking. Such a shift from specific to general PIT can therefore explain the effect of drug CSs in an addicted individual's environment to potentiate habitual drug responding during delays to drug reinforcement that are bridged by either the same or other CSs acting as conditioned reinforcers of drug-seeking responses. Indeed, it has been shown that CS-potentiated smoking

in humans was unaffected by satiety and therefore independent of the current incentive value of the drug (cigarette puffs), instead reflecting a general motivational enhancement of habitual drug use (Hogarth et al. 2010). This account is neurally compatible with the shift from DMS- to DLS-dependent mechanisms recruited by Pavlovian CS processing in the nucleus accumbens via the spiraling dopaminergic circuitry linking ventral and dorsal striatum (Belin et al. 2009, Everitt & Robbins 2013).

Negative emotional states, such as those instantiated by stress, can also influence habit learning. Thus, rats subjected to chronic stress rapidly developed insensitivity to outcome value and were relatively impervious to changes in A-O contingency. These changes biased rats toward habitual behavioral strategies and resulted in atrophy of the mPFC and the associative striatum and hypertrophy of the DLS (Dias-Ferreira et al. 2009). An intriguing possibility, then, is that drug withdrawal stress that is known to result in raised reward thresholds and long-term changes in hedonic state (Koob 2008) may, through activation of stress systems in the amygdala (Koob 2008), also influence the development of S-R drug-seeking habits by facilitating its coupling with the DLS (Lingawi & Balleine 2012, Murray et al. 2013). Indeed, instrumental avoidance learning, which presumably contributes to withdrawal-motivated negative reinforcement, becomes impervious to extinction and may resemble compulsive habits in OCD (Gillan et al. 2015).

Incremental responses to addictive drugs and drug-associated CSs that collectively reflect the process of sensitization are widely assumed to lead to a pathological motivation for drugs, or drug wanting (Kalivas & Volkow 2005, Robinson & Berridge 1993). The phenomenon of sensitization has now clearly been demonstrated in humans exposed relatively few times to amphetamine, leading to very long-lasting enhancements in striatal DA responses to both drugs and drug CSs (Leyton 2007, Leyton & Vezina 2014, Vezina & Leyton 2009). One consequence of this process is that drug CSs, through their enhanced ability to increase DA release in the ventral striatum, may lead to subjective craving states and what might be assumed to be a voluntary urge to seek and take drugs (Leyton & Vezina 2014). Paradoxically, long-term drug use in humans is associated with decreased striatal dopaminergic function both in terms of reduced D2 DA receptors and DA release (a hypodopaminergic state), including lower craving responses to drug cues (Volkow et al. 2007). This paradox may be resolved by considering individual differences in the propensity to attribute incentive salience to drug-associated CSs and hence the marked variation in craving responses to drug cues in addicted individuals (Saunders & Robinson 2013). However, the enhanced DA transmission underlying sensitization is not restricted to the ventral striatum but is also seen in the dorsal striatum and is associated with the potentiated expression of motor stereotypies. The latter depend upon the dorsal striatum (Kelly et al. 1975) and are putatively a form of compulsive responding. Stimulant sensitization may therefore lead both to potentiated motivational and Pavlovian associative processes and a parallel enhancement of S-R learning mediated by upregulation of DA in the ventral and dorsal striatum, respectively.

FROM HABIT TO COMPULSION

Compulsive drug seeking despite negative consequences is now a major criterion of substance use disorder. However, the fact that not everyone initially or recreationally taking drugs ultimately exhibits compulsive drug seeking (Anthony et al. 1994) has provided a challenge for its experimental investigation. This challenge has recently been met by the demonstration that in rats (as in humans), about 20% exhibit compulsive drug seeking despite adverse consequences, but only after chronic drug use (Belin et al. 2008, Deroche-Gamonet et al. 2004, Pelloux et al. 2007).

Thus in the three-criteria addiction model (Belin et al. 2008, Deroche-Gamonet et al. 2004), 20% of rats having self-administered cocaine for 100, but not 40, days continued to respond for

cocaine despite receiving mild footshock punishment; they also persisted in responding when a CS signaled that cocaine was unavailable and showed increased motivation for cocaine. Contemporaneously, we modified our previously established cocaine seeking-taking chained schedule (Olmstead et al. 2001) to introduce unpredictable footshock punishment and therefore required rats to risk these adverse consequences when seeking the opportunity to take cocaine (Pelloux et al. 2007). After a brief cocaine history, all rats stopped seeking cocaine when the punishment contingency was introduced (i.e., they abstained from drug use), but after a long history of cocaine self-administration, some 20% of rats continued to seek cocaine (i.e., were compulsive) (Pelloux et al. 2007). The compulsive cocaine seeking was not necessarily associated with increased motivation for the drug nor with impaired fear conditioning. The extent of exposure to cocaine, rather than the degree of conditioning through Pavlovian pairings of CS and drug, was further shown to be a critical factor in determining the development of cocaine seeking under punishment (Jonkman et al. 2012b). Compulsive cocaine seeking in a vulnerable subgroup of rats has now been demonstrated in different strains of rats and in different laboratories (Belin et al. 2008, Cannella et al. 2013, Chen et al. 2013, Deroche-Gamonet et al. 2004, Pelloux et al. 2007) using three-criteria or seeking-under-threat-of-punishment procedures.

Initial neural investigation of compulsive cocaine seeking revealed the involvement of a discrete aDLS domain specifically in punished, but not unpunished, cocaine seeking (Jonkman et al. 2012a), thus identifying a link to the neural basis of drug-seeking habits. Pelloux and colleagues (2012) also showed reduced levels of serotonin (5-HT) utilization across prefrontal cortical areas, as well as decreased DA utilization in the dorsal striatum, selectively in compulsive but not in noncompulsive rats, despite a very similar history of cocaine exposure. It was demonstrated that the low levels of 5-HT utilization were causal in compulsive cocaine seeking by showing that forebrain 5-HT depletion, or systemic treatment with a 5-HT2C receptor antagonist, after a short cocaine history, when none of the rats were compulsive, resulted in increased levels of seeking under punishment. Of translational interest was that treatment with a serotonin-selective 5-HT reuptake inhibitor, citalopram, dose-dependently reduced compulsive seeking in rats that had developed this behavior after a long drug-taking history (Pelloux et al. 2012).

In replicating our observation of a compulsive cocaine-seeking subpopulation of rats after a long history of cocaine exposure, Chen and colleagues (2013) showed that in vivo optogenetic stimulation of the prelimbic cortex decreased compulsive cocaine seeking in compulsive animals, whereas the 80% subpopulation of rats that had suppressed their cocaine seeking during punishment subsequently increased their cocaine seeking under punishment (i.e., became compulsive) after optogenetic inhibition of the prelimbic cortex. These data (Chen et al. 2013, Jonkman et al. 2012a, Pelloux et al. 2012), together with the demonstration of anaplasticity in NAcb neurons in three-criteria "addicted" rats (Kasanetz et al. 2010), suggest altered corticostriatal mechanisms and disrupted top-down or inhibitory control in compulsive cocaine seeking.

ADDICTION AND TOP-DOWN CONTROL

Addiction to drugs has long been presumed in the popular imagination to represent a failure of will by which the addict's propensity to seek and take drugs is not appropriately regulated by volitional processes (Leshner 1997). Whilst this view is controversial and has been held by some to impede progress in the biological understanding and treatment of addiction, the past decade has seen increasing evidence, via a range of neuroimaging modalities, of changes in brain structure and function in addicted individuals that illuminate its underlying motivational control processes. This evidence has been paralleled by enhanced interest in the role of cortical processes in the

regulation of conditioned behavior, including drug seeking and taking as well as their underlying Pavlovian and instrumental processes, in experimental animals.

Although the emphasis has been on the role of limbic-striatal mechanisms, these have increasingly been considered in the context of neural circuits involving cortical, and especially prefrontal, regions. A general theme has been that loss of fronto-executive inhibitory control produces a dominance of subcortically mediated responding, including S-R habit learning, potentially exacerbating the drive to compulsive behavior (Jentsch & Taylor 1999, Robbins & Everitt 1999). However, a range of processes, including attention, memory, and other aspects of executive function besides inhibitory control, are mediated by cortically dominant circuits. For example, apparent loss of control could result not only from exacerbated habitual behavior, but also from an impairment of goal-directed behavior, with the consequent imbalance favoring habit learning. Important questions have been the degree to which such processes contribute to addiction and the extent to which they result from chronic drug taking, or are present premorbidly, and hence represent predispositions leading to susceptibility to substance use disorders.

A previous review (Robbins et al. 2008) surveyed the results of more than 20 studies using structural MRI of substance abusers, including abusers of stimulant drugs, nicotine, opiates, cannabis, and alcohol. Results were variable, but the general trend was of loss of cortical gray matter volume and white matter in alcoholics, sometimes globally (Fein et al. 2002) but often in specific regions, for example, especially in frontal and parietal regions, the dorsal hippocampus (Jang et al. 2007, Mechtcheriakov et al. 2007), and striatum (Sullivan et al. 2005). There are also reported losses in the cingulate cortex and PFC in nicotine smokers (Brody et al. 2004, Gallinat et al. 2006).

Findings in stimulant (methamphetamine or cocaine) abusers were relatively consistent, often including loss of prefrontal or cingulate gray matter in combination with increases in the basal ganglia (i.e., caudate, putamen, globus pallidus). The latter are especially relevant in the context of the S-R habit hypothesis advanced previously (Everitt & Robbins 2005), which would predict greater changes in the putamen relative to the caudate.

Focusing on stimulants, Ersche and colleagues (2013b) performed a voxel-based meta-analysis of 16 suitable magnetic resonance structural imaging studies comprising 494 stimulant-dependent individuals and 428 controls. These investigators concluded that gray matter decreased significantly in stimulant-dependent individuals in four cortical regions: the insula, ventromedial PFC, inferior frontal gyrus, and pregenual anterior cingulate gyrus, as well as the anterior thalamus. These reductions in these five areas concur well with the regions commonly implicated using perfusion methods and metabolic imaging (e.g., with positron emission tomography). Volkow & Fowler (2000) made the seminal observation that striatal D2 DA receptor downregulation is related to orbitofrontal cortex (OFC) hypometabolism—clearly implicating the OFC as a component of fronto-striatal circuitry that is modulated by striatal DA. Ersche et al. (2012a) supplemented these studies by demonstrating loss of white matter in chronic stimulant abusers in such structures as the frontal lobes.

The key questions arising from such analyses, whether of stimulant or other substance use disorders, are the nature of the functions that these regions mediate and the origin of the reductions. These can be addressed by means of correlation with salient epidemiological, clinical, and neuropsychological assessments; by reference to studies of effects of cortical brain damage; and by the design of studies utilizing fMRI.

In general, the changes in frontal brain function are consistent with impairments in decision-making cognition in chronic drug abusers (Rogers et al. 1999), and these impairments resemble in some ways the effects of frontal lesions in clinical patients (see also Bechara et al. 2001, Clark et al. 2008). Deficits in decision making can be due to disruption of several distinct contributory processes. The ventromedial PFC (and medial OFC) is implicated in reward-related processing

in fMRI studies (both in the anticipation of reward and in its reinforcing outcome). Damage to the ventromedial PFC in humans causes impairments in the assessment of value and choice outcomes, as well as gross impairments in decision-making tasks such as the Iowa Gambling Task and the Cambridge Gambling Task (Bechara et al. 2001, Clark et al. 2008). Functional imaging of stimulant and opiate abusers has shown changes in the way the OFC is activated during risky decision making (Ersche et al. 2005). The consequent deficits in decision-making cognition are of considerable clinical importance, as they evidently exacerbate the general functional difficulties of chronic drug abusers, whether these difficulties are caused by the drugs themselves or pre-existing dispositions. Impairments in the representation of goals at the cortical level may also lead to the "narrowing" of options open to chronic drug abusers and thus help to determine the compulsive focus on drug-seeking behavior.

The possibility that the insula was implicated in processing the visceral sequelae of drug taking (helping to translate sensations into subjective feelings) was raised by Everitt & Robbins (2005), and the past decade has seen a large increase in studies of the role of the insula in addiction (Paulus & Stewart 2014). The insular cortex may play an ancillary role in effective decision making via its mediation of hypothetical somatic markers that contribute to affective states influencing risky choice behavior (Clark et al. 2008, Verdejo-Garcia & Bechara 2009). Somatic markers are essentially interoceptive Pavlovian cues that can both elicit conditioned responses and contribute to PIT. Such cues, as well as more readily identified exteroceptive CSs, are well known to elicit drug-seeking behavior and concomitant subjective craving, as well as aversive withdrawal phenomena, both mediated in part via limbic-striatal circuitry including the amygdala. This may explain the remarkable observation of a blockade of craving in nicotine-dependent individuals following damage to the insula caused, for example, by strokes (Naqvi et al. 2007). A subsequent analysis of neuroimaging studies by Naqvi & Bechara (2009) has provided broad support for this original observation over a number of drug classes, including nicotine, cocaine, alcohol, and heroin. Of the 16 studies examined, the insula was the only brain region to be consistently activated by urges to seek drugs, although the anterior cingulate and OFC were often activated, too. Animal studies involving inactivation of the insula have suggested a causal role in an animal model of craving (Contreras et al. 2007).

The somatic marker hypothesis of addiction (Naqvi & Bechara 2010, Verdejo-Garcia et al. 2006) thus essentially seeks to explain core aspects of addiction in terms of an aberrant emotional or homeostatic guidance of decision making that leads to craving and impulsive behavior (i.e., relapse). The insula clearly plays an important role in the functioning of neural circuitry linking to limbic and striatal (i.e., the nucleus accumbens) structures, thus also providing a powerful source of motivational Pavlovian influences over instrumental choice, including craving. However, we doubt that the insula exerts the crucial lack of control over instrumental behavior that is evident in addictive individuals.

Interoception is often linked to notions of awareness and insight, although these notions are not synonymous. The lack of insight, often attributed to addicted individuals as well as individuals with other neuropsychiatric disorders, is problematic, for example, when assessing the adverse consequences of drug taking, including impaired social behavior. A lack of conscious awareness may be symptomatic of habitual behavior, which, by its nature, is implicit and autonomous. It is also consistent with generalized impairments in goal-directed behavior or instrumental control over actions, which may signal the lack of agency generally associated with mPFC function (Balleine & O'Doherty 2010). Error processing especially implicates sectors of the anterior cortex, and hence its dysfunction would promote unawareness of error feedback. A recent review has speculated on the nature of the neural networks contributing to insight that probably include the insula and anterior cingulate cortex (Goldstein et al. 2009). It should be noted that those hypotheses

that postulate self-medication by drug abusers, for example, to alleviate withdrawal syndromes or amotivational/avolitional states such as reward deficiency, would appear to be opposed to these notions of impaired insight.

In addition to impairments in decision making, drug abusers are commonly impaired in several facets of "cold" executive function, including working memory, cognitive flexibility, and response inhibition (Friedman et al. 2006, Ornstein et al. 2000, Rogers & Robbins 2001). Of these, impairments of inhibitory response control are of obvious interest as potentially leading to relapse, impulsivity, and compulsion (Morein-Zamir & Robbins 2014).

In humans, the anterior cingulate and inferior frontal cortex (especially in the right hemisphere) are generally considered to be cortical components of a neural circuit mediating inhibitory response control, which also includes the striatum, subthalamic nucleus, and supplementary motor cortex. The impairments are most often quantified in terms of go/no-go or stop-signal reaction time performance (Aron et al. 2014) but may have an obvious influence on decision making, especially decision making involving conflict or the need to reflect on information processing. Disruptions in the activity of this network may therefore lead to forms of impulsive behavior that occur when a subject is unable to cancel an initiated response. Such impulsive behavior may also occur in attention-deficit/hyperactivity disorder as well as in drug abuse (Robbins et al. 2012). fMRI studies showing impaired go/no-go responding in parallel with underactivation of PFC circuitry in stimulant abusers have also revealed, rather surprisingly and significantly, remediation both in terms of activation and behavioral performance following cocaine treatment within the scanner (Garavan et al. 2008)—suggestive of a possible therapeutic role for catecholamine agents and not inconsistent with the so-called self-medication hypothesis. The enhancement of inhibitory control may have arisen as a direct consequence of catecholamine-induced modulation of PFC functioning or alternatively as a reduction of a hypothetical withdrawal state, although it is evident that stimulant drugs can enhance similar performance in healthy volunteers (de Wit et al. 2000, Fillmore et al. 2005).

In another study with therapeutic implications, attention to drug cues that normally elicit craving in stimulant drug abusers was associated with activation of the (left) inferior frontal cortex and was remediated in some patients by treatment with a D2 DA receptor agonist (Ersche et al. 2011b). Other aspects of impulsivity that depend, for example, on the temporal discounting of reward (and hence tolerance to reward delay) may implicate additional cortico-striatal circuitry that targets the nucleus accumbens (Dalley et al. 2011).

In animal studies, there has been considerable research on the role of fronto-striatal circuitry in mediating inhibitory control in the special case of relapse into drug seeking/taking. The often-used extinction-reinstatement model is based on the fact that extinction (in this case of instrumental responding, not Pavlovian CS extinction) is a form of inhibitory control over learned associations. The mechanisms known to mediate the extinction of Pavlovian fear, which include the mPFC (comprising the prelimbic and infralimbic cortex in rodents), have similarly been implicated, along with the nucleus accumbens (especially the core subregion), in the recovery, renewal, or reinstatement of self-administration behavior after a period of extinction (Kalivas & McFarland 2003). However, it is possible that the role of the mPFC is not limited to extinction alone, but may represent more general behavioral regulatory roles, including the balance between goal-directed and habitual behavior (see above).

Inhibitory control may also be recruited in the regulation of compulsive behavior, which can be defined as the maladaptive persistence of responding (Dalley et al. 2011). If the substrate of compulsive behavior is in part habitual, the precise neural circuitry mediating inhibitory control is less clear but may also implicate such structures as the lateral and medial OFC. Thus, reversal learning, which involves the suppression of perseverative tendencies in parallel with new learning,

appears to depend on OFC projections (Chudasama & Robbins 2003, Dias et al. 1996) to the dorsomedial striatum (Castañé et al. 2010, Clarke et al. 2008) as well as interactions with other regions of the striatum, including the putamen (Groman et al. 2013). Such reversal learning for monetary reward can be quite seriously impaired in human drug abusers (Ersche et al. 2008) as well as in monkeys exposed to chronic cocaine administration (Jentsch et al. 2002). Functional connectivity studies of chronic stimulant abusers, in parallel with studies of patients with obsessive-compulsive disorder (OCD), have shown that frontal zones of connectivity including the OFC are correlated in both cases with measures of compulsivity [the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and the Obsessive Compulsive Drug Use Scale (OCDUS)] in the stimulant abusers (Meunier et al. 2012). Such studies encourage the notion that compulsivity associated with a neural circuit regulated by the OFC may be a general construct of neuropsychiatric disorders, including addiction. These cortical regions are also implicated in the production of compulsive stimulant drug seeking in rats that results in adverse consequences such as electric footshock (Chen et al. 2013; Pelloux et al. 2012, 2013).

These aspects of impaired executive function are clearly relevant to addiction, but their precise causal role remains unclear. They may form part of a general cognitive-deficit syndrome, including other impairments (for example, in memory), that has profound implications for rehabilitation. Thus, to what extent are cortical changes associated with such cognitive changes irreversible or subject to recovery with abstinence? Alternatively, a subset of the deficits may not only exacerbate the drive to compulsive behavior but also may be present in the drug abuser prior to drug exposure; in other words, some deficits may play a causal role in addiction. Specifically, the loss of top-down control may represent a critical step by which habits gain control over behavior due to an imbalance with goal-directed behavior, and the performance of these habits may become less subject to cognitive or inhibitory control imposed by the PFC, with dysregulated, perseverative behavior being a prominent consequence. A critical question then becomes the precise timing of changes in top-down control from the PFC during the hypothesized devolution of control from ventral to dorsal striatum. As discussed in the next section, these important issues of causality and development of addiction are now beginning to be addressed in both human and animal studies.

ETIOLOGICAL FACTORS AND INDIVIDUAL DIFFERENCES: ADDICTION ENDOPHENOTYPES

Dissecting causality in studies of addiction is especially difficult because of multiple factors: genetics, early experience, acute pharmacological actions of abused drugs, potential neurotoxic effects of the drugs themselves as well as the effects of withdrawal, and long-term chronic effects of relapse and abstinence. Such difficulties are highlighted by problems of interpretation of some of the most seminal findings in the field: downregulation of D2 DA receptors in chronic cocaine, methamphetamine, and alcohol abusers (e.g., Volkow et al. 2007). Are such changes causes or consequences of drug abuse? This general question can be posed of virtually all studies of drug abusers in the absence of prospective data on their preabuse state, but it is in fact difficult to address. The common finding of impulsivity in drug abusers might also reflect a premorbid condition that actually contributes to drug seeking rather than resulting from it.

One useful approach in neuropsychiatry has been to determine intermediate phenotypes or endophenotypes (Gottesman & Gould 2003). Endophenotypes are core characteristics, for example, behavioral or neural, found in first-degree relatives as well as their drug-abusing proband. Generally, expression of the characteristic is intermediate between that of the proband and healthy controls. Endophenotypes are commonly interpreted as reflecting genetic influences, but of course it is entirely plausible that they arise from common environmental, for example, familial, effects.

Moreover, the most parsimonious interpretation of an endophenotype is that it cannot have arisen from drug taking because it is pre-existing; nonetheless, it could itself be further influenced by subsequent drug exposure.

Addiction Endophenotypes in Experimental Animals

The obvious difficulties of studying the period of pre-exposure to drugs of abuse in human participants do not, of course, apply to experimental animals. Consequently, the field has recently been stimulated by many studies of neurobehavioral characteristics of rodents and nonhuman primates that are predictive of the propensity to take drugs. One of the original studies identified a group of high-reactive (HR) rats that were susceptible to i.v. self-administration of low doses of d-amphetamine based on their levels of locomotor activity in a novel situation (Piazza et al. 1989). Originally, these rats were suggested to be sensation seeking, although it is not quite clear on what theoretical basis this dimension was invoked. They exhibited a number of neurobiological changes, including paradoxical susceptibility to stress; increases in the corticosteroid response to novelty were paralleled by a propensity to corticosterone self-administration (Piazza et al. 1993). Subsequently, the importance of stress as a candidate endophenotype for stimulant abuse was highlighted by studies in monkeys (Morgan et al. 2002) and exposure to social defeat stress in rodents (Covington & Miczek 2005).

Recent studies have focused on the trait of impulsivity [measured as excessive premature responses in a test of sustained attention, the 5-choice serial reaction time task (5-CSRTT)], finding that high impulsives exhibited escalation and greater intake of cocaine in a binge-access paradigm (Dalley et al. 2007). These high-impulsive rats also exhibited, prior to any cocaine experience, reductions in D2/3 receptor binding in the ventral but not dorsal striatum, analogous to what had been shown in chronic stimulant abusers (Volkow et al. 2007) and also in rhesus monkeys subsequently exhibiting high levels of stimulant self-administration (Nader et al. 2010). High-impulsive rats were not, however, high reactive and further differed from that phenotype in showing compulsive cocaine administration when risking punishment through mild electric footshock (Belin et al. 2008). Hence, high impulsivity was hypothetically linked to compulsive drug seeking; however, the important issue remains as to whether this is indeed a causal association.

The high-impulsive rat phenotype has been subsequently refined. These rats do not exhibit obvious alterations in appetitive Pavlovian conditioning (autoshaping or sign tracking) and are not especially susceptible to novelty stress or anxiety (Molander et al. 2011) or to impairments on the rodent stop-signal reaction time task, another index of impulsive action (Robinson et al. 2009). They do, however, exhibit steeper reward discounting compared to controls, enhanced intake of nicotine or sucrose, and a mild preference for novelty (see review by Dalley et al. 2011). Other studies (Perry & Carroll 2008) have also shown that changes in the temporal discounting of reward, sometimes defined as impulsive choice, can be predictive of future drug self-administration. Most recently, a similar high-impulsive phenotype based on premature responding in the 5-CSRTT has been shown in the ethanol-preferring B6 strain of mice (Sanchez-Roige et al. 2014), although the high-impulsive rat does not exhibit binge self-administration of heroin (McNamara et al. 2010), indicating that this relationship does not exist for all major drugs of abuse.

Although high impulsivity in rodents predicts vulnerability to compulsive cocaine seeking, whereas high reactivity in rats mainly alters initial responsivity to stimulants, these are not the only rodent behavioral endophenotypes to confer susceptibility to stimulant drug effects. Escalation of cocaine intake has also been reported in highly anxious rats, as measured by their tendency to avoid open arms of the elevated plus maze (Dilleen et al. 2012), and in novelty-preferring rats, as indexed by their choice of a novel side of a test chamber (Belin et al. 2011). Moreover, risky behavior in a

decision-making task (Mitchell et al. 2014), associated with lower striatal D2 mRNA expression, led to enhanced adult intake of cocaine. The experience of cocaine self-administration also enhanced risky decision making in adults; perhaps these rats would have also exhibited compulsive cocaine self-administration despite adverse consequences, but this has not yet been tested. High-impulsive rats exhibit mild tendencies for novelty preference in several contexts, but the propensity for impulsivity is only weakly related to novelty preference (Molander et al. 2011). Thus, impulsivity is dissociable from other candidate endophenotypes of novelty preference and anxiety, as well as sensation seeking, suggested for the HR rat.

The picture has been further complicated by a program of genetic selective inbreeding leading to the production of HR and low-reactive (LR) rats (indexed by locomotor hyperactivity in novel settings) that also exhibit differential behavioral sequelae of appetitive Pavlovian conditioning. HR rats tend to orient to discrete cues predictive of food (sign trackers), whereas LR rats tend to approach a food magazine directly (goal trackers) (Flagel et al. 2011, 2014). Similar to findings in earlier work on HR rats, they exhibit greater sensitivity to stimulant-induced sensitization and greater self-administration as well as a greater propensity to relapse (as indexed by extinction reinstatement) and evidence for enhanced motivation for cocaine. However, the propensity of HR rats for compulsive stimulant seeking has not yet been investigated in detail. Their tendency to impulsivity is equivocal; they display increased motor impulsivity [as measured by overresponding on a differential reinforcement of lower rates of behavior (DRL) schedule] but decreased temporal discounting of reward (Flagel et al. 2014).

Overall, it would appear that the response to stimulants and the propensity to compulsive stimulant seeking, although clearly interactive to some extent, may be differentially affected by a range of trait-like influences in rodents. Impulsivity, risk taking, novelty preference, locomotor activity, and anxiety may all be reflected in these responses, to different degrees. Their influence on other forms of drug taking may also differ; there are some indications that responses to nicotine and alcohol may be similarly affected to responses to stimulants such as cocaine. The overlapping influence of the various endophenotypes probably reflects subtle differences in underlying neural networks, which almost certainly center on the nucleus accumbens (Dalley et al. 2011).

Thus, the neuroendophenotype of the high-impulsive rats is associated with specific changes in D2/3 receptor autoradiography and DAT immunocytochemistry in the nucleus accumbens shell as well as with gray matter reduction in the nucleus accumbens core (Caprioli et al. 2014, Dalley et al. 2011). There is no evidence from in vivo microdialysis studies of altered presynaptic levels of accumbens DA (Dalley et al. 2007). Recent work is characterizing differential electrophysiological activity in these regions between high and low impulsives (Donnelly et al. 2014). There are also concomitant changes in top-down influences of the anterior cingulate and mPFC and bottom-up regulatory monoaminergic projections (Dalley et al. 2011).

The nucleus accumbens is also a major focus for changes (e.g., in DA function) in HR rats as well as in high-impulsive rats. However, both outbred and inbred HR rats are hyperdopaminergic in terms of response to systemic DA D2 agonists such as quinpirole, fast-scan cyclic voltammetry, and an increased proportion of high-affinity D2 receptors (with no changes in total D2 binding) (Flagel et al. 2014). Rats classified as high impulsives on the basis either of 5-CSRTT or delayed discounting performance also exhibit differential patterns of DA release in the nucleus accumbens. There is apparently greater release in the nucleus accumbens shell and lower release in the core in the 5-CSRTT high impulsives, and lower DA release in both subregions in steep-discounting rats (Diergaarde et al. 2008). High impulsives (5-CSRTT) are also hypersensitive to quinpirole, but the nature of this effect differs between the shell and core subregions. Clearly, a full understanding of the possible differences between these various trait-like characteristics must depend on a systematic comparison using the same methods to assess DA

function. However, it does appear that different modulations of DA function in the nucleus accumbens result in subtly different behavioral phenotypes that participate in different stages of the development of compulsive stimulant self-administration, including its initiation, development, and maintenance. The analysis of rodent endophenotypes for other drugs of abuse has not perhaps proceeded to such an intensive degree as for stimulants, but it promises to do so in the future.

The ultimate test of the validity of these candidate endophenotypes would be to demonstrate that their amelioration leads also to reductions in compulsive drug use. Amelioration of high impulsivity has been reported for rats chronically self-administering cocaine (Dalley et al. 2007) and for experimenter-administered methylphenidate, the D2/3 receptor agonist quinpirole or atomoxetine (Fernando et al. 2012). Methylphenidate also caused an upregulation of D2/3 receptors in high-impulsive rats but the opposite neural (and behavioral) effects in controls (Caprioli et al. 2014). Such ameliorative effects may also depend on noradrenergic mechanisms, as the selective noradrenaline reuptake blocker atomoxetine was effective whether administered systemically (Robinson et al. 2008) or into the shell of the nucleus accumbens (Economidou et al. 2012). The implications of these findings for the treatment of substance use disorders remains to be explored in detail, although it is of interest that relapse from punishment-induced suppression of cocaine self-administration is especially significant for high-impulsive rats and that this disinhibition is susceptible to blunting by systemic atomoxetine (Economidou et al. 2009).

Endophenotypes for Human Substance Use Disorders

Identifying reliable endophenotypes for addiction would benefit the field in several ways: (*a*) More accurate phenotypes may lead to more successful searches for genome-wide association and candidate genes, (*b*) stratification of clinical populations would lead to more sensitive clinical trials, (*c*) endophenotypes may allow predictions of future vulnerability to substance use disorders, and (*d*) as previously discussed, defining endophenotypes also enables a limited analysis to be performed of possible etiological factors in addiction.

Some of the animal work reviewed above has inspired a fresh look at possible human equivalents. This has been facilitated in the area of impulsivity, where several objective measures can be implemented in both humans and experimental animals, including the serial reaction time task, the stop-signal reaction time task, and temporal discounting of reward (Dalley et al. 2011). A recent example has been the finding that not only chronic stimulant abusers exhibit deficits in tests of inhibitory control such as the stop-signal reaction time task, but also their nondrug-abusing siblings, as compared to controls (Ersche et al. 2012a, 2013b). These deficits were correlated with the degree of white matter loss in frontal regions in siblings as well as stimulant abusers. There were also changes in siblings in such regions as the amygdala and putamen, both of which had greater volume. However, regions of gray matter loss in probands, including the OFC and anterior insula, did not show any change in the relatives. These changes may well occur as a consequence of stimulant drug taking, especially as some of the changes (e.g., in the OFC) were related to duration of drug use as well as to measures of compulsive behavior (Ersche et al. 2011a). This is consistent with longitudinal findings in rhesus monkeys exposed to cocaine self-administration (Porrino et al. 2010). Thus, study of possible endophenotypes may help to chart the progression of changes in brain structure and function over the course of addiction.

Recreational stimulant abusers who take the drugs regularly without fulfilling DSM criteria for stimulant dependence provide informative comparisons. These individuals exhibited increased gray matter volume in the OFC, anterior cingulate, and insula, suggestive of possible resilience to the compulsive drug-seeking characteristic of addiction. These individuals seem unlikely to

be at an earlier point on a trajectory to drug dependence; the results highlight how individual neurobiological differences may drastically affect outcome after drug abuse (Ersche et al. 2013b).

An alternative approach is prospective: Is it possible to detect markers of future drug abuse in adolescent populations? The IMAGEN project, in which 2,000 healthy adolescents aged 14 years were screened for brain structure, functional brain imaging, neuropsychological test performance, drug-taking history, and genomics, has addressed this question. One finding pertinent to the impulsivity endophenotype is that the neural circuits activated by the stop-signal reaction time task do have some predictive associations with incipient drug taking propensity at that age (Whelan et al. 2012). Thus, activity in lateral orbital frontal circuits during successful response inhibition was directly related to self-reported experimentation with alcohol and nicotine. Moreover, as the drug use extended to illicit substances, there was also a significant relationship with hyperactivity in right inferior frontal and anterior cingulate circuits known to mediate successful stop-signal reaction time task performance.

Independent studies have shown that chronic cocaine users exhibit hypoactivity in the same regions, and so from this cross-sectional perspective there may be a gradual evolution of the activity of this region. Further evidence is provided by the important observation that the siblings of chronic stimulant abusers exhibit hyperactivity of similar circuits (Morein-Zamir et al. 2013), suggesting that this activity may be initially compensatory, hypothetically resisting craving or the temptation to seek drugs, only later showing reductions. This is of course highly speculative, and longitudinal studies of adolescent drug users are now clearly required. Moreover, other candidate endophenotypes in humans should be examined to establish their validity and utility. An alternative way of addressing the issue of loss of top-down control is to examine the neural changes occurring during successful abstinence as well as over the long term (Garavan et al. 2013).

PROSPECTS FOR NEW TREATMENTS OF ADDICTION

Despite major advances in understanding the neuropsychological and molecular mechanisms involved in drug addiction, few if any new medications have been introduced clinically, in particular those that might prevent relapse and prolong periods of abstinence. The considerable interest in preventing relapse by diminishing the impact of drug-associated CSs on craving and drug seeking has led to the preclinical identification of novel pharmacological treatments (reviewed in Everitt 2014), but there is little evidence to suggest that they will reach the stage of clinical trials and regulatory approval. There is some optimism that repurposing already approved medications, such as those used in the treatment of impulsive and compulsive disorders, may result in novel proabstinence treatments (Everitt 2014), but a challenge for this treatment approach is the requirement for frequent, perhaps daily, dosing and attendant problems of side effects and compliance.

However, there has been a recent resurgence of interest in psychological approaches to diminishing the impact of drug CSs on relapse. Cue exposure therapy—that is, extinction of the CS through repeated nonreinforced presentations—has been frequently attempted, but a meta-analysis of a substantial literature has indicated that overall it results in little benefit (Myers & Carlezon 2012), in part because of the contextual specificity of extinction learning (Conklin & Tiffany 2002); however, the view is perhaps less pessimistic for alcoholics (Glautier et al. 1994, MacKillop & Lisman 2008, Stasiewicz et al. 2007). Attempts to enhance drug CS extinction with the glutamate receptor agonist D-cycloserine, following demonstrations of enhanced Pavlovian fear extinction (Davis 2002, Lee et al. 2006b), have also generally been unsuccessful (Myers & Carlezon 2012) and may even result in an increase, not a decrease, in craving elicited by later exposure to the CS (Price et al. 2013), an explanation for which is discussed below.

A new approach to treatment with great potential involves targeting memory reconsolidation, the process set in motion by the reactivation of a memory by presenting drug CSs but insufficiently to engage extinction learning. This reactivation causes the memory trace to become labile in the brain, a state from which it must be restabilized through de novo protein synthesis in order to persist. The phenomenon has long been known (Lewis 1979) but was relatively ignored until its rediscovery through the demonstration that conditioned fear memory reconsolidation could be prevented by intra-amygdala protein synthesis inhibition in conjunction with memory reactivation (Nader et al. 2000). Subsequently, fear memory reconsolidation was shown to require expression of the immediate-early gene *zif268* (Lee et al. 2004), intracellular signaling molecules (Tronson & Taylor 2007), and activity at *N*-methyl-D-aspartate (NMDA) receptors (Lee et al. 2006b) and β-adrenergic receptors (Debiec & Ledoux 2004).

Against this background, we investigated whether drug memories might undergo reconsolidation. This was a major challenge because, unlike Pavlovian fear conditioning that requires only one or two CS-unconditioned stimulus pairings, instrumental drug self-administration must take place repeatedly, involving hundreds of CS-drug pairings, for a drug CS alone to elicit drug seeking and relapse (Lee & Everitt 2007). We showed that a small number of cocaine CS presentations in rats that had self-administered the drug daily for two weeks of more (several hundred cocaine-CS pairings) could indeed reactivate and destabilize the memory, such that knockdown of *zif268* in the amygdala prevented reconsolidation as assessed by a major decrease in the subsequent ability of the CS to act as a conditioned reinforcer and support cocaine seeking or to precipitate relapse (Lee et al. 2005).

There has been considerable focus on the neurochemical mechanisms that initiate or modulate drug memory reconsolidation, both to link them to intracellular signaling pathways (Barak et al. 2014, Miller & Marshall 2005, Milton et al. 2008a) and also to identify therapeutic leads (Milton & Everitt 2010). NMDA receptor or β-adrenoceptor antagonists given at memory reactivation can prevent cocaine or alcohol memory reconsolidation, with the result that drug CSs have a much reduced capacity or no capacity to elicit drug seeking or relapse when presented subsequently (Lee et al. 2006a; Milton 2013; Milton et al. 2008a,b). Heroin conditioned-withdrawal memories similarly undergo reconsolidation following reactivation (Hellemans et al. 2006). Moreover, Pavlovian associations underlying sign tracking, PIT, and conditioned reinforcement (the main properties of drug CSs involved in maintaining drug seeking and precipitating relapse) also undergo NMDA- or β-adrenoceptor-dependent reconsolidation, indicating that these Pavlovian influences on drug seeking and relapse can all be diminished by a single or few treatments given at a CS-drug memory reactivation (Milton 2013, Milton & Everitt 2010).

Memory retrieval does not always labilize the memory trace in the brain, and this likely explains failures to see reconsolidation blockade when amnestic drugs are given in association with retrieval under some conditions (Milton et al. 2012). Especially important is the finding that fear (Lee et al. 2006b) and drug memory (Lee et al. 2009) reconsolidation can be enhanced by NMDA receptor agonism at reactivation, thereby potentiating the impact of the CS at subsequent test. This may explain the paradoxical effect of D-cycloserine to increase craving to later presentations of a cocaine CS—the opposite of the intended effect to enhance drug CS extinction (Price et al. 2013). This should remind us that we are far from being able to specify precisely the conditions under which memory is destabilized to undergo reconsolidation and to delineate this from those conditions under which extinction is engaged. Reconsolidation and extinction are dissociable and mutually exclusive processes in terms of their molecular basis (Merlo et al. 2014) and are bidirectionally modulated by NMDA receptor agonism and antagonism (Lee et al. 2006b).

Therapeutically, targeting reconsolidation of drug memories as a means of reducing the propensity for drug CSs to elicit craving and relapse has the obvious advantage that only single,

or very few, drug treatments in association with drug memory retrieval are needed. Furthermore, reconsolidation blockade appears not to be context dependent, so therapy in the clinic could be effective in the addict's environment. Additionally, problems of compliance that come with daily and long-term treatments would be avoided, and the single or few drug treatments could take place during psychological therapy sessions, such as cognitive behavioral or cue-exposure therapies. A promising place to begin overdue clinical studies would be β-adrenoceptor antagonist treatment at drug memory reactivation, since these drugs are clinically approved and safe.

A surprising observation may, however, suggest that the story is not over for cue exposure therapy. If fear extinction is carried out soon after a brief memory reactivation in both rats and humans, the fear memory is not only extinguished but also seemingly erased, as it does not spontaneously recover or renew, which it does after extinction alone (Monfils et al. 2009, Schiller et al. 2010). Thus, if repeated or long-term exposure to a CS occurs during the time window (approximately four hours) when reconsolidation takes place following brief memory reactivation, extinction becomes much more effective in diminishing the memory—so-called superextinction. In an ambitious combined animal and human study, it has been shown that a superextinction protocol can impair cocaine and heroin memories in rats having self-administered the drugs, and also in a heroin-dependent inpatient population (Xue et al. 2012). In the addicted individuals, the treatment sessions involved memory reactivation by viewing a brief video featuring drug taking, followed after a short delay by longer exposure to the same video (extinction). At subsequent test, there was both decreased autonomic reactivity and craving following cue exposure and a significant decrease in relapse up to six months later. This remains the only study of its kind and clearly requires replication, but like reconsolidation-based approaches, it suggests great promise of psychological treatments to prevent relapse and promote abstinence from drug use.

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