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Review

From the ventral to the dorsal striatum: Devolving views of their roles in drug addiction

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ABSTRACT

We revisit our hypothesis that drug addiction can be viewed as the endpoint of a series of transitions from initial voluntarily drug use to habitual, and ultimately compulsive drug use. We especially focus on the transitions in striatal control over drug seeking behaviour that underlie these transitions since functional heterogeneity of the striatum was a key area of Ann Kelley's research interests and one in which she made enormous contributions. We also discuss the hypothesis in light of recent data that the emergence of a compulsive drug seeking habit both reflects a shift to dorsal striatal control over behaviour and impaired prefrontal cortical inhibitory control mechanisms. We further discuss aspects of the vulnerability to compulsive drug use and in particular the impact of impulsivity. In writing this review we acknowledge the untimely death of an outstanding scientist and a dear personal friend.

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1. Introduction

Ann Kelley's research focused on the functions of the basal ganglia. This work ranged from her PhD thesis on the role of substance P in the ventral tegmental area (Kelley and Iversen, 1978) to post-doctoral discoveries with Walle Nauta about anatomical interactions of the amygdala with the nucleus accumbens (Kelley et al., 1982). Subsequently, she systematically mapped the striatum for the effects of amphetamine on conditioned reinforcement (Kelley and Delfs, 1991) and stereotyped behaviour (Kelley et al., 1988, 1997). In fact, her interests in feeding motivation stemmed from her observations on gnawing elicited within the striatum. She influenced our own work through her attempts to dissociate functions of the core and shell sub-regions of the nucleus accumbens (e.g. Maldonado-Irizarry and Kelley, 1995). She was also one of the first to highlight the apparently different effects of manipulating opioid (Bakshi and Kelley, 1993) and dopamine mechanisms within

the nucleus accumbens in control of eating and other aspects of appetitive motivation.

In addition to this research on the neurochemical coding of motivational and hedonic mechanisms in the nucleus accumbens, revealing distinct roles for opioid and dopaminergic transmission in core and shell (Baldo and Kelley, 2007), Ann Kelley's research also focused on the neural mechanisms within the nucleus accumbens of appetitive instrumental learning (Kelley, 2004). Her approach was informed historically by Thorndike's (1911) 'law of effect' – that the probability of a response being made is increased when followed by a reward (or 'satisfaction') and decreased when followed by 'discomfort'. Although intended to mark some distinction from pavlovian associations between stimuli, rather than responses, and outcomes, Kelley recognised that these processes are 'closely intertwined, both neurally and conceptually' (Kelley, 2004) and this same realisation has framed much of our own research on understanding the neural mechanisms underlying drug addiction. This has centred around the notion that addiction can be understood in terms of the operation of the brain's pavlovian and instrumental learning and memory systems and their subversion by the potent actions of self-administered addictive

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drugs on dopaminergic transmission within corticostriatal systems (Everitt and Robbins, 2005; Robbins and Everitt, 1999).

The hypothesis we advanced in 1999 and refined in 2005 was that drug addiction was the endpoint of a series of transitions from initial drug use, when a drug is voluntarily taken because it has reinforcing effects (that embody positive subjective states), through loss of control over this behavior as it emerges as a stimulus–response (S–R) habit, ultimately to become compulsive and not easily relinquished. Although the notion of progression from use to abuse to addiction was widely accepted, our experimental approach was different, bringing a contemporary animal learning theory analysis of pavlovian and instrumental learning processes and interactions between them that might underlie drug seeking and drug taking. Our overarching hypothesis was that the transition from voluntary to habitual and progressively compulsive drug use is the result of dynamic shifts in the neural loci of control over behaviour, from the ventral to dorsal striatum, mediated by its stratified dopaminergic innervation, together with a progressive decrease in prefrontal cortical control over drug seeking and drug taking behaviour (Everitt and Robbins, 2005; Everitt et al., 2008). In the period since, considerable evidence has accrued to support this hypothesis.

An important fundamental principle guiding our research and also Ann Kelley's (e.g. Kelley, 2004) was that the general concept of positive reinforcement conflates at least two different processes which have been identified by contemporary analyses of conditioning with conventional reinforcers (Dickinson, 1985; Dickinson and Balleine, 1994). The first is a cognitive process based upon knowledge of the relationship between instrumental behaviour and its outcome (i.e. reinforcer). When controlled by this process, instrumental behaviour takes the form of intentional, goal-directed actions which are performed because the animal 'knows' that these actions (A) give access to the reinforcer or outcome (O). The second is the stimulus–response (S–R) mechanism by which reinforcers strengthen an association between the response and the contextual and discriminative stimuli present at the time of reinforcement. Behaviour controlled by this process is composed of simple, habitual responses that are elicited automatically by these discriminative stimuli especially, we have argued, when presented response-contingently and acting as conditioned reinforcers (Everitt and Robbins, 2005).

Our enhanced, but still incomplete, understanding of the neural basis of instrumental behaviour has depended upon studies with ingestive reinforcers, since the relative contribution of the S–R habit mechanism and the cognitive A–O process can be determined by the use of an outcome devaluation procedure in which, following instrumental (i.e. operant) training, the value of the outcome is changed and the impact this has on responding can be measured (Adams and Dickinson, 1981). If instrumental behaviour is controlled by the S–R mechanism, performance should be unaffected

by devaluation (see Table 1), whereas a change in the value of the outcome should reduce actions based on the A–O relationship. Such studies have shown that although instrumental learning may initially proceed via the cognitive A–O process (as studied by Kelley, 2004), its control passes to the S–R habit mechanism with extended training (Adams, 1982; Dickinson, 1985). One of the challenges in relating these concepts to the seeking and taking of drugs is that intravenously self-administered drugs of abuse, such as stimulants, apparently cannot be devalued by gastric malaise (by lithium chloride) nor by specific satiety, since pre-loading with stimulants or opiates markedly alters the propensity to respond, confounding any interpretation of the devaluation event.

2. The transition from voluntary to habitual drug seeking and its striatal locus of control

While it is well established that the ventral striatum, including the nucleus accumbens (Acb), plays a key role in mediating the reinforcing effects of stimulant drugs through its dopaminergic innervation (Wise, 2004), it has proven more problematic to define the neural basis of the acquisition of the instrumental behaviour of addictive drug self-administration because it is difficult to disentangle the neural mechanisms of instrumental conditioning from those mediating the rewarding and motor effects of the drugs. Whereas the acquisition of cocaine self-administration is impaired by manipulations that diminish the reinforcing effects of the drug, such as Acb dopamine (DA) depletion (Roberts and Koob, 1982) and DA receptor blockade (Robledo et al., 1992), it is not prevented by specific lesions of either the Acb core (AcbC) or shell (AcbS) (Ito et al., 2004), although this may possibly indicate the particular importance of the dopaminergic innervation of the olfactory tubercle component of the ventral striatum in stimulant reinforcement (Ikemoto, 2003).

However, we have made a distinction between the fundamental and widely studied behaviour of drug self-administration, in which each response is reinforced and there is thus a tight and predictable relationship between response and outcome (which we have termed 'drug taking'), and 'drug seeking' behaviour which models 'real world' foraging for drugs (Everitt and Robbins, 2000; Everitt et al., 2001). This seeking behaviour must be maintained over long periods of time during which instrumental responding is less predictably related to the drug outcome and is also greatly influenced by drug-associated, pavlovian CSs, that in humans are known to induce craving, drug seeking and relapse after abstinence (O'Brien et al., 1991; Childress et al., 1999; Garavan et al., 2000; Grant et al., 1996). We therefore invested considerable effort in establishing a second-order schedule of cocaine reinforcement in which rats respond for between 15 and 60 min prior to each cocaine infusion (or heroin, or highly palatable food delivery or, in earlier times, a female in heat and subsequent sex). The key feature of

Table 1
Procedures used to probe the associative structure underlying instrumental behavior.

Reinforcer devaluation procedure	Effect on instrumental responding	
	Action–outcome	Stimulus–response
(i) Lithium chloride post-ingestive malaise	Reduced responding	Responding persists
(ii) Specific satiety (free access to reinforcer and ingestion to satiety immediately before test)	Reduced responding	Responding persists
(iii) Instrumental contingency degradation (altering the probability of reinforcer delivery on one of two previously equally reinforced levers)	Reduced responding	Responding persists
(iv) Extinction of the taking response in a seeking-taking chained schedule. Extinction occurs in the absence of the seeking lever, so any change in responding depends upon 'knowledge' of the devalued taking response outcome.	Reduced responding	Responding persists

NB The test phase in (i), (ii) and (iv) occurs in the absence of the reinforcer (i.e. in extinction); (i) and (ii) involve affective devaluation (by directly reducing reward value); (iii) alters the relationship between response and outcome by intermittent non-contingent reinforcer delivery; (iv) alters the value of the outcome of the taking response, but measures its impact on making antecedent seeking responses that provide the opportunity to make the taking response.

this seeking behaviour is that it is sensitive not only to the contingency between instrumental responses and drug administration during its acquisition, but also to the presence of the CSs which, as conditioned reinforcers, have an increasingly dominant effect on the performance of seeking when it is well-established and, we have argued, habitual (Everitt et al., 2010). An important feature of drug seeking measured in this way is that, following acquisition of cocaine taking, the response contingencies in operation that determine when cocaine or heroin are self-administered intravenously can be altered, challenging the animal's A–O learning mechanism before progressing to S–R, habitual control. Using this behavioural approach, we have demonstrated the engagement of different sectors of the striatum during the transition from goal-directed to habitual drug seeking.

In our earlier review (Everitt and Robbins, 2005) we discussed the data available at the time that could be seen as consistent with our hypothesis. Thus, we had shown that AcbC, but not AcbS, lesions impaired the acquisition of cocaine seeking and that this was likely due to a disruption of the control over instrumental responses by conditioned reinforcers (Ito et al., 2004) and an impaired ability to tolerate the delays to primary reinforcement in this task (Cardinal et al., 2001). However, when cocaine seeking behaviour was over-trained, its locus of control devolved to the anterior dorsolateral striatum (aDLS), being also greatly decreased by dopamine receptor blockade in the aDLS, but not in the AcbC (Vanderschuren et al., 2005). These data were in accord with our prior observation that well-established cocaine seeking under the second-order schedule is associated with increased extracellular dopamine in the aDLS, but not in the AcbC or AcbS (Ito et al., 2000, 2002). Interestingly, while AcbS lesions were without effect on the acquisition of cocaine seeking, they prevented the effects of self-administered cocaine from potentiating responding, recapitulating our earlier data demonstrating the role of the AcbC in conditioned reinforcement and AcbS dopamine in its potentiation (Taylor and Robbins, 1984; Parkinson et al., 1999), and reflecting dissociations in the functions of the core and shell nodes within limbic cortical-ventral striatal circuitry that complemented those demonstrated by Ann Kelley. Indeed, disconnecting the basolateral amygdala and AcbC using unilateral manipulations of each structure, but on opposite sides of the brain, also greatly impaired cocaine seeking, thereby showing the functional importance of the operation of this system (Di Ciano and Everitt, 2004). These data are consistent with the widely accepted view that the nucleus AcbC, with its afferents from the amygdala mediates the impact of CSs on appetitive behaviour, not only conditioned reinforcement, but pavlovian motivation (measured by pavlovian-instrumental transfer tasks) and conditioned pavlovian approach (reviews: Cardinal et al., 2002; Cardinal and Everitt, 2004; Blaiss and Janak, 2009). However, it left open the issue of the striatal locus (or loci) of instrumental A–O learning, rather than reinforcement and pavlovian-instrumental interactions, in the earliest stages of acquiring new drug seeking strategies when they are goal-directed.

This issue has become clearer from studies of responding for ingestive rewards, showing that early acquisition and performance depends upon the pDMS whereas habitual behaviour that develops after overtraining depends upon the aDLS (Balleine et al., 2009; Yin et al., 2006). In addition, both NMDA receptor blockade (Yin et al., 2005) and disruption of extracellular signal-regulated kinase (ERK) signalling in the pDMS, but not the aDLS, prevented A–O learning during the acquisition of food-reinforced responding which was shown to be immediately insensitive to outcome devaluation (Shiflett et al., 2010) (see Table 1). Conversely in overtrained rats, lesions, inactivation (Yin et al., 2006) or dopaminergic denervation (Faure et al., 2005) of the aDLS disrupted both the performance and establishment of S–R control over behaviour. It is important to realise here that there is no or little change in overall instrumental

response output following pDMS or aDLS lesions or inactivations, but the associative structure underlying responding is different, being either under the control of the value of the outcome (pDMS, A–O learning) or stimuli associated with the outcome (aDLS, S–R learning). This pDMS to aDLS shift in the control over behaviour has also been shown in spatial navigation tasks to reflect the transition from flexible, adaptive to inflexible, habitual performance (Packard and McGaugh, 1996; Lex et al., 2011).

We have therefore recently investigated the involvement of dopamine signaling in the pDMS and aDMS in the early and later, well-established stages of performance of cocaine seeking, revealing a double dissociation in their functional engagement at these time points (Murray et al., 2012). Bilateral infusions of the dopamine receptor antagonist α -flupenthixol into the pDMS dose-dependently impaired cocaine seeking only during early stage tests when animals had to adapt to a change in response contingency both for the CS and cocaine. But identical infusions had no effect when infused after extended training. In contrast, α -flupenthixol infusions into the aDLS had no effect during the early tests, but greatly reduced cocaine seeking at the later, well established or habitual stage, so confirming our earlier findings (Belin and Everitt, 2008; Vanderschuren et al., 2005). These effects on learning and performance could not be attributed to α -flupenthixol-induced changes in cocaine reinforcement (Veeneman et al., 2012), both because the effects on seeking were measured before any influence of self-administered cocaine infusion in each test session and also because α -flupenthixol had no measurable effect on taking responses when cocaine was self-administered after each response. Nor did the shift from pDMS to aDLS control simply reflect the impact of a long history of cocaine self-administration, since matching the total cocaine intake to that of the extended training group, but under a continuous (FR1) reinforcement schedule prior to the first seeking tests, resulted in the same sensitivity to pDMS α -flupenthixol infusions that was seen after a short cocaine taking history. Thus, the shift from pDMS to aDLS control over cocaine seeking resulted from an interaction between cocaine taking and extended training under an instrumental seeking schedule that facilitates the emergence of habitual control over behaviour (Belin et al., 2009; Dickinson, 1985).

Whilst there is now clear and consistent evidence of the transition from ventral to dorsomedial and dorsolateral striatum in the control over cocaine seeking behaviour, there is no direct evidence of a shift from A–O (or goal-directed) to S–R mechanisms. This reflects the special difficulty of implementing the usual criteria for establishing habit-like S–R representations (see Table 1) with intravenously (i.v.) self-administered drug reinforcers. For example, it is very difficult to devalue i.v. cocaine by lithium chloride (LiCl)-induced gastric malaise, there being little or no evidence of cross-modal associations between gastric malaise and the reinforcing effects of drugs mediated directly in the brain by an increase in dopamine transmission. Additionally, the use of 'satiety' (commonly used to define habitual responding with ingestive reinforcers) and contingency degradation (response-independent delivery of the drug) has proven difficult to employ in the drug-seeking context. However, we have shown that responding for oral cocaine became habitual and resistant to reinforcer devaluation by LiCl injection (Miles et al., 2003). Furthermore, responding for alcohol became resistant to LiCl-induced devaluation much more rapidly than responding for sucrose, suggesting that ingestion of an addictive drug leads to the more rapid instantiation of a S–R habit process than is the case for ingestive natural rewards (Dickinson et al., 2002).

Nonetheless, a devaluation procedure also used in studies of ingestive rewards has been employed to reveal the shift from goal-directed to habitual cocaine seeking under a seeking-taking chained schedule (see Table 1) in which animals performed a drug

seeking response in the initial link of the chain, which then gave access to a drug-taking response in the second link, performance of which delivered cocaine (Olmstead et al., 2001). After a brief history of self-administration, cocaine seeking was shown to be goal-directed since performance was sensitive to devaluation by extinguishing the taking link in the absence of opportunity to make a seeking response (Olmstead et al., 2001). The key point in interpreting this result is that the seeking response was never directly reinforced by cocaine, it only provided the opportunity to make the taking response. Thus, the propensity to make seeking responses depends upon the value of the outcome of the taking response (i.e. cocaine) once the opportunity to make it had been earned. Extinction of the taking response resulted, on first presentation of the seeking lever, in a marked reduction in responding suggesting that seeking behaviour was driven by the value of the outcome. This devaluation effect demonstrated that cocaine seeking at an early stage of performance is mediated by the value of the seeking response outcome.

Our seeking-taking procedure was adopted subsequently by Toni Shippenberg and colleagues to do the experiment that we should have completed earlier, namely to allow animals to self-administer cocaine over a much extended period in order to see whether cocaine seeking became habitual and insensitive to devaluation. Zapata et al. (2010) confirmed our earlier result that cocaine seeking is goal-directed early after acquisition, but further showed that it became insensitive to devaluation of the taking link after a prolonged drug taking history. In addition, they were able to demonstrate that inactivation of the aDLS reinstated sensitivity of seeking to the devaluation manipulation, so that it again became goal-directed, a result that is consistent with that from studies with an ingestive reward (Yin et al., 2004, 2005; Balleine et al., 2009).

The shift from DMS to DLS control over responding for an addictive drug has now also been studied in detail for alcohol, with the advantage that a devaluation manipulation (a satiety procedure involving 45 min of free access to alcohol before test; see Table 1) was employed with this orally ingested drug to make possible an assessment of sensitivity or resistance to reinforcer devaluation after one, two, four or eight weeks of training (Corbit et al., 2012). It was demonstrated that instrumental alcohol seeking became insensitive to devaluation after 4 weeks of training (similar to the results of Dickinson et al., 2002), with the S–R process overshadowing the A–O process to gain full control over behaviour by eight weeks. This behavioural transition from goal-directed to habitual control over alcohol seeking was further shown to be mirrored by a shift from the DMS to the DLS. Thus, whereas inactivation of the DMS prevented the expression of an ethanol devaluation effect following two weeks of training, this manipulation was ineffective after 8 weeks of training when inactivation of the DLS restored sensitivity to devaluation, having had no behavioural consequences at the earlier stage (Corbit et al., 2012). Thus goal-directed and habitual alcohol seeking depend, as we have argued for cocaine seeking, on DMS and DLS processes that are likely engaged in parallel, but with the aDLS-dependent S–R process eventually exerting dominant control over behaviour.

The recruitment of the aDLS by prolonged self-administration of psychostimulant drugs is also correlated with a progressive increase in dendritic spines and implied neural plasticity in the DLS, as compared to the DMS (Jedynak et al., 2007). Similarly, in monkeys self-administering cocaine, adaptations in metabolic markers, the DA transporter and D2 DA receptors that were initially restricted to more ventral parts of the striatum were, after prolonged cocaine administration, increasingly prominent in the dorsal and lateral anterior striatum (Letchworth et al., 1999, 2001; Porrino et al., 2004). We earlier showed increased extracellular DA in the DLS, but not in the AcbS or AcbC after several weeks of cocaine seeking experience (Ito et al., 2000, 2002), data that are consistent

with the finding that prior administration of cocaine results in a shift in the balance of CS-evoked firing from ventral to dorsal striatum (Takahashi et al., 2007). Habitual control over behaviour is also associated with on-line transitions in electrophysiological activity between the DMS and DLS in a T-maze task in rats, such that DMS neuronal activity was actively engaged during acquisition and early behavioural performance, but then progressively decreased over training, eventually leaving DLS activity to drive habitual performance (Thorn et al., 2010). These experimental data provide a context for the observations that cue-induced craving in human cocaine addicts is associated with increased metabolic activity and dopamine release in the dorsal striatum (Garavan et al., 2000; Volkow et al., 2006; Wong et al., 2006). Moreover, Ersche et al. (2012a,b) recently reported that the left putamen was significantly enlarged both in cocaine-dependent individuals and their non-drug abusing siblings, suggesting an endophenotype for drug addiction that is associated with a predisposition to acquire the drug seeking and taking habits characteristic of the addicted state.

These observations supporting the increasing importance of the dorsal striatum in well-established, or habitual, drug seeking raise the issue of how, in neural terms, such a shift in the locus of control from ventral to dorsal striatum might occur. We hypothesized (Everitt and Robbins, 2005; Belin and Everitt, 2008) that it could be mediated by the striato-nigro-striatal ascending, or ‘spiralling’ dopamine-dependent circuitry that functionally links domains of the ventral and dorsal striatum, initially revealed in the primate brain (Haber et al., 2000), but also seen in the rat brain (Ikemoto, 2007). We investigated the functional importance of this link by ‘disconnecting’ the ventral from the dorsal striatum by infusing the dopamine receptor antagonist, alpha-flupenthixol into the aDLS, contralateral to a selective lesion of the AcbC, thus effectively compromising any recruitment of dopamine transmission in the aDLS by antecedent activity in the AcbC on one side of the brain, but blocking the consequences of it in the intact aDLS (Belin and Everitt, 2008). This disconnection resulted in an identical degree of reduction in well-established cocaine seeking to that observed after bilateral infusions of alpha-flupenthixol into the aDLS (Belin and Everitt, 2008; Murray et al., 2012; Vanderschuren et al., 2005). Thus, the long-term performance of instrumental seeking responses for cocaine depends upon a striatal network involving interactions between the AcbC and dopamine transmission in the aDLS. Direct evidence that the AcbC regulates DA release in the aDLS was provided by an *in vivo* voltammetric study of DA release in both structures during cocaine self-administration in rats; a specific lesion of the AcbC prevented a late-emerging (after 3 weeks of self-administration) DA transient in the ipsilateral, but not contralateral DLS, thereby indicating AcbC control over DA function in the DLS interacting with the duration of the history of cocaine self-administration (Willuhn et al., 2012).

Evidence from computational modelling and functional imaging studies has provided further evidence that ventral striatal processes may drive nigro-dorsal striatal activity to guide decision making (Kahnt et al., 2009). Taken together with the data summarised above, this suggests that a distributed ventral striatal–posterior dorsomedial striatal network is engaged in the acquisition and early performance of cocaine seeking under A–O control, but that an AcbC–aDLS circuit dominates well-established habitual performance (Murray et al., 2012).

3. Impulsivity and compulsive drug seeking in addiction

Having argued and, together with others, experimentally demonstrated that drug seeking becomes habitual, being evoked and maintained by drug associated CSs in the drug user’s environment so that drug seeking persists even when the drug’s value

may have decreased (e.g. through tolerance), it should be acknowledged that there is nothing aberrant or unusual about devolving behavioural control to a dorsal striatal S–R ‘habit’ mechanism. This also occurs, as we have seen, in individuals responding for ingestive rewards although it may develop more rapidly when the reinforcer is an addictive drug (Dickinson et al., 2002; Corbit et al., 2012). Habits also dominate behaviour in other aspects of our everyday lives (Duhigg, 2012). Automatisation of behaviour frees up cognitive processes to enable us to respond to rapidly changing contingencies and expectations in the environment. However, we have argued (Everitt and Robbins, 2005; Everitt et al., 2008) that it is perhaps the *compulsive* nature of CS-evoked drug seeking habits that is at the core of drug addiction. Thus, individuals addicted to drugs seek and take them compulsively, at the expense of other sources of reinforcement and despite negative outcomes that include risk to the individual in terms of deterioration in their personal physical and mental health, and when negotiating the dangerous environments in which they must forage to fuel their compulsive habit. However, not all individuals that experiment with drugs, or even take them on a frequent basis become dependent. Only some individuals are vulnerable to lose control over their drug intake, a proportion that is often estimated to be about 20% of those initially exposed to addictive drugs (Anthony et al., 1994). What do we know about this vulnerability at a psychological or neurobiological level of analysis?

We have developed a model of compulsive cocaine seeking, defined as persistent responding for the drug despite the threat or reality of an aversive outcome. Rats were trained on the cocaine seeking-taking chained schedule described above (Olmstead et al., 2000), but intermittent punishment of the seeking response was subsequently introduced (i.e. on 50% of the seeking bouts, the outcome was not the opportunity to take cocaine, but instead delivery of a mild footshock; Pelloux et al., 2007). Introduction of punishment resulted in the suppression of cocaine seeking, or abstinence, in all animals after acquisition of the seeking-taking chain and a relatively short cocaine self-administration history. But after an extended (Pelloux et al., 2007; Vanderschuren and Everitt, 2004) or escalated (Jonkman et al., 2012a,b; Pelloux et al., 2012) self-administration history a sub-group of 17–20% of individuals were completely resistant to punishment, continuing to seek and take drugs despite the ongoing, daily experience of the negative outcome. The degree of cocaine exposure, rather than the degree of conditioning through pavlovian pairings of CS and drug, was shown to be critical in determining the propensity to persist in seeking cocaine under punishment (Jonkman et al., 2012a,b). In related research, Deroche-Gamonet et al. (2004), identified the emergence of three addiction-like behavioural criteria in rats, but again only after about 40 days of cocaine self-administration: (i) an increased motivation to take the drug measured as break-points under a progressive ratio of cocaine reinforcement, (ii) an inability to refrain from drug-seeking during signalled periods of drug unavailability and (iii) persistent responding for cocaine even when it was punished by mild footshock. Having established these procedures for measuring compulsive cocaine seeking, we have begun to investigate the predisposing, or vulnerability, factors involved and the underlying neural mechanisms.

In terms of vulnerability, we have shown in a series of studies that a high level of impulsivity in rats confers vulnerability to several key aspects of cocaine, but not heroin, seeking and taking behaviour (Dalley et al., 2007; Belin and Everitt, 2008; Economidou et al., 2009; McNamara et al., 2010). Thus, highly impulsive responding in an attentional task (the 5-choice serial reaction time task, 5-CSRTT) in about 7% of a Lister hooded rat population, which is associated with low dopamine D2 receptor availability in the NAc but not DS, predicted subsequent (i) escalated responding for i.v. cocaine on a binge access schedule (Dalley

et al., 2007), (ii) an increased propensity to relapse after abstinence (Economidou et al., 2009) and (iii) a tendency to respond compulsively for cocaine under punishment after a prolonged period of access to the drug (Everitt et al., 2008). The results of these studies provide experimental evidence that high levels of impulsivity can antedate the onset of compulsive drug use, thereby emphasizing the importance of pre-existing impulsivity seen in individuals addicted to drugs (Dom et al., 2006; Jentsch and Taylor, 1999; Ersche et al., 2012b; Verdejo-Garcia and Perez-Garcia, 2007; Chakroun et al., 2004). The latter study used an endophenotype design to show that another measure of impulsivity, prolonged stop-signal reaction times, in a commonly used test of response inhibition (stop-signal task), was significantly greater not only in chronic cocaine abusers, but also in their non-drug abusing siblings.

Demonstrating that impulsivity is a factor underlying the tendency to escalate drug intake and to relapse after abstinence indicates that impulsivity might be a therapeutic target for the pharmacological treatment of addiction. Intriguingly, the anti-ADHD drug atomoxetine (a selective noradrenaline reuptake inhibitor) remediated high levels of impulsivity both when administered systemically and also when infused into the shell sub-region of the accumbens (Fernando et al., 2012; Economidou et al., 2012). Systemic atomoxetine also greatly reduced cocaine- and heroin-seeking under a second-order schedule of i.v. drug self-administration (Economidou et al., 2012), but not compulsive cocaine seeking (Pelloux et al., 2012). These results perhaps suggest a role for atomoxetine in the treatment of those individuals who are addicted to cocaine, but who do not show a compulsive pattern of use (Ersche et al., 2012a,b).

There are several possible origins of compulsion within the brain that are not mutually exclusive. The neuroadaptations occurring during behavioural sensitization to stimulant drugs have been argued to underlie an extreme incentive motivational state of drug ‘wanting’ (Robinson and Berridge, 1993). Those addicted to drugs may experience this state especially when exposed to drug-associated cues, which leads to over-activation of the sensitized dopaminergic innervation of the Acb, in which plasticity-associated structural changes in dendritic spines result from a sensitisation treatment regimen (Ferrario et al., 2005). One interpretation of compulsive drug seeking, then, is that it is a behavioural manifestation of this potentiated motivational state; its impact on the motivation to seek drugs has been demonstrated in some studies (see Vezina, 2004). However, stimulant sensitization also leads to the more rapid instantiation of S–R habits (Nelson et al., 2006) and it is not easy to differentiate at the behavioural level between an increased tendency to repeat drug seeking responses elicited and maintained by drug-associated CSs – what we have called the ‘must do!’ of *compulsive* habits (Everitt and Robbins, 2005) – from an increased desire for a drug.

An alternative, potentially powerful source of the motivation is negative reinforcement – the alleviation or avoidance through self-medication of the negative affective state resulting from withdrawal from drugs, perhaps resulting in a persistent hedonic allostatic state of dysphoria or anhedonia (Koob and Le Moal, 2005; Koob and Volkow, 2010). The neural counter-adaptations correlating with this state are prevalent in the central and extended amygdala as well as within the reward system (Koob, 2008). These positive and negative reinforcement mechanisms induced by short-term (sensitisation) and long-term (tolerance, withdrawal and hedonic allostasis) exposure to addictive drugs are not either/or, and addiction may reflect a combination of increased incentive motivation mediated by the up-regulation of ventral striatal DA transmission, by strongly consolidated S–R habits mediated by the dorsal striatal, DA-dependent mechanisms, and the drive engendered by negative emotional states in extra-striatal networks.

However, there may be additional neural mechanisms underlying the compulsive drug seeking seen in drug addiction. Indeed, it is significant that chronic stimulant abusers have elevated scores on the OCDUS scale for measuring compulsive drug use, which captures behavioural predispositions in drug taking rather than reflecting subjective motivational responses based on 'liking' or 'wanting' (Ersche et al., 2010). Moreover, stimulant abusers and their siblings have a propensity to exhibit obsessive-compulsive like or ritualistic behaviours as measured by the Padua Inventory for Obsessive-Compulsive Disorder ritualistic behaviors, indicative of a possible overlap between these disorders (Ersche et al., 2011a, 2012b). We and others have hypothesized that the compulsive nature of drug seeking and taking might arise in part as the direct or indirect consequence of toxic drug effects based on impaired top-down control by prefrontal cortical processes and a shift in the balance of behavioral control from PFC to striatum (Jentsch and Taylor, 1999; Robbins and Everitt, 1999; Everitt and Robbins, 2005; Olausson et al., 2007).

There are abundant data suggesting PFC, especially orbitofrontal (OFC), dysfunction in humans addicted to cocaine and other drugs (Volkow and Fowler, 2000; Volkow et al., 2002, 2004; Rogers et al., 1999; Ersche et al., 2005, 2008). There is reduced activity of the OFC in cocaine and methamphetamine abusers which correlates with reduced D2/3 dopamine receptors in the striatum (Volkow et al., 2001) and reduced OFC grey matter volume (Ersche et al., 2011a,b, 2012a,b). There are several reports of impaired behavioural and cognitive functions, including poor behavioural adjustment to environmental contingencies (Bechara, 2005), impaired probabilistic reversal learning in cocaine abusers (Ersche et al., 2008, 2012a), possibly due to reduced inhibitory control and deficits in decision-making on computerized versions of a gambling task (Ersche et al., 2005; Rogers et al., 1999) that are indicative of OFC dysfunction, since similar changes in behaviour are seen in individuals with OFC damage (Rogers et al., 1999). This has encouraged the view that chronic drug taking may be causal in inducing these prefrontal cortex-dependent deficits. But suboptimal prefrontal cortical, including OFC and anterior cingulate cortex, function (Hester and Garavan, 2004; Kaufman et al., 2003; Matochik et al., 2003; Volkow and Fowler, 2000) may also represent a pre-existing vulnerability trait that results in poor decisions and/or a lack of sensitivity to the consequences of such decisions, and hence drug abuse leading to addiction (Ersche et al., 2012a,b). However, evidence against that view comes from a recent endophenotype study of non drug-abusing stimulant abusers (Ersche et al., 2012b) in which grey matter changes in the OFC and anterior cingulate cortex were not observed in the siblings. Rather, increases occurred in the medial temporal lobe and putamen and reductions in the superior temporal gyrus, post-central gyrus and insula. The increases in the putamen are consistent with the function of this dorsal striatal area, that is homologous with the DLS in the rat brain, subserving habit learning and its implication in response control. The siblings also had reduced white matter in prefrontal cortical areas probably innervating the right inferior frontal gyrus and pre-supplementary motor area, regions known to be implicated in response control on such tests as the stop-signal reaction time task (Aron et al., 2003; Aron and Poldrack, 2006; Duann et al., 2009).

Experimental studies primarily involving psychostimulant treatment of rats and monkeys even after brief periods of exposure have supported the view that disrupted OFC function may indeed be a consequence of toxic drug effects during an addict's history of drug abuse (Jentsch and Taylor, 1999; Schoenbaum et al., 2006). Short-term experimenter- or self-administered cocaine or amphetamine enhanced the development of impulsivity (Jentsch and Taylor, 1999; Roesch et al., 2007) which, as we have seen, may result in loss of control over cocaine intake and a tendency to compulsive cocaine seeking (Dalley et al., 2007; Belin et al., 2008).

Reversal learning is impaired by cocaine treatment in monkeys (Jentsch et al., 2002) and rats (Schoenbaum et al., 2004), and is seen in cocaine-dependent humans (Ersche et al., 2008). Rats having self-administered and then been withdrawn from cocaine exhibited both increased extinction responding and a marked deficit in reversal learning during withdrawal (Calu et al., 2007). Schoenbaum and colleagues have emphasized both the similarity between OFC lesions and these apparently long-lasting effects of relatively short-term treatment with cocaine, but also showed that the deficit in reversal learning is reflected in a change in the properties of OFC neurons, which do not develop appropriate responses to cues predicting outcomes (Stalnaker et al., 2006).

Other considerations implicate the orbitofrontal cortex in compulsivity related to chronic drug abuse. Obsessive-compulsive disorder (OCD), perhaps the prototypical compulsive syndrome, is associated, like drug abuse, with altered OFC-striatal function (Menzies et al., 2007). Of especial significance is the recent study by Meunier et al. (2012) which used measures of functional connectivity obtained in resting state to compare patients with obsessive-compulsive disorder to those with stimulant dependence. Remarkably, both groups had reduced connectivity in only two OFC regions of 50 defined cortical nodes. Moreover, this reduced connectivity significantly correlated in both cases with increased compulsivity, whether for OCD (Y-Box scale) or for the patients with stimulant dependence (OCDUS scale). Thus, increased compulsivity appears to be related to reduced OFC connectivity, as we would have predicted. The parallels between chronic stimulant abuse and OCD are further emphasised by the discovery of reduced D2 striatal receptors in patients with OCD (Denys et al., 2004; Perani et al., 2008), as also occurs in cocaine or methamphetamine abusers (see above Volkow et al., 2001). The significant association between striatal D2/3 receptor number and orbitofrontal metabolism in stimulant abusers (Volkow et al., 2001) has not yet been confirmed in patients with OCD, but seems likely given the changes in OFC structure and function associated with that disorder.

Another possible behavioural index of compulsivity is perseverative responding in reversal learning (rewarded with food). Again, as might be predicted, experimental lesions of the OFC impair reversal learning (e.g. Dias et al., 1996; Chudasama and Robbins, 2003; Clarke et al., 2008). Patients with OCD (and their non-OCD siblings) also exhibit reduced activation of the OFC (Chamberlain et al., 2008). OCD has been linked with serotonergic dysfunction and indeed is generally treated with serotonin selective reuptake inhibitors (SSRIs). Again, consistent with reversal learning representing a possible marker of compulsivity, Clarke et al. (2004) found that serotonin or 5-HT depletion in the marmoset prefrontal cortex impaired reversal learning. Hence, 5-HT might modulate the top-down inhibitory functions of the OFC and be implicated in compulsive behaviour.

Patients with chronic stimulant abuse also exhibit enhanced perseverative responding in association with reduced activity in the anterior head of the caudate nucleus (Ersche et al., 2008, 2011b). Intriguingly, both of these deficits are reversed by treatment with the dopamine D2 receptor agonist pramipexole, consistent with the possible restoration of D2 signalling in these addicted individuals sufficient to restore normal orbitofrontal-striatal function. Importantly, no such improvement was seen in patients with OCD (Ersche et al., 2011b), suggesting some dissociation between these two phenotypes, despite their many commonalities as seen throughout this review.

The involvement of 5-HT in compulsive cocaine seeking has also been demonstrated in an experimental study in rats (Pelloux et al., 2012). The sub-population of rats exhibiting compulsive self-administration behaviour in the face of punishment after an escalated history of intake showed a marked reduction in 5-HT

utilisation in prefrontal cortical areas, as well as in the amygdala and dorsal striatum, together with reductions in dorsal striatal DA turnover (Pelloux et al., 2012). These deficits occurred in the 20% of compulsive rats, but not in those that suppressed their cocaine seeking under punishment, despite the same extent of cocaine exposure, suggesting an interaction between toxic drug effects and a predisposing factor. This deficit in 5-HT was shown causally to be related to compulsive seeking as depleting the forebrain of 5-HT using the serotonin toxin 5,7-dihydroxytryptamine induced resistance to punishment of seeking in rats after a brief cocaine history when none normally show a compulsive tendency. Compulsive cocaine seeking was reduced by treatment with a selective SSRI, citalopram (Pelloux et al., 2012), suggesting a potential therapeutic use of SSRIs as an abstinence promoting treatment in cocaine abusers, especially those with a compulsive pattern of use (Ersche et al., 2010). Treatment with a 5-HT_{2C} receptor antagonist also induced a compulsive tendency in rats after a short cocaine history, whilst a 5-HT_{2C} receptor agonist reinstated sensitivity to punishment in rats in which this behaviour had been induced by prior forebrain 5-HT depletion (Pelloux et al., 2012). Consequently, 5-HT, putatively in the OFC, can be linked to the development of compulsive drug-seeking, and a SSRI might also be a plausible treatment to reduce compulsive drug-seeking in humans. However, treatment of addicted individuals with lower, antidepressant doses of SSRIs has not generally been regarded as a successful addiction therapy, but perhaps the use of higher doses such as those employed in the treatment of OCD, may have better efficacy (Moeller et al., 2007; Vayalapalli, 2011). It is notable that early *post mortem* studies of chronic methamphetamine abusers reported evidence of reduced 5-HT markers in the PFC (Wilson et al., 1996) and other studies have found increased levels of 5-HT transporters in cocaine and alcohol abusers (Little et al., 1998; Jacobsen et al., 2000).

We have also shown that the dorsal striatum mediates the performance of a well-established cocaine seeking habit under punishment by selectively inactivating the aDLS or the midlateral striatum in rats responding for cocaine in the seeking–taking task at three timepoints: (i) after the acquisition of cocaine seeking, (ii) after extended cocaine self-administration and finally (iii) after the introduction of intermittent, seeking-contingent foot shock punishment (Jonkman et al., 2012a,b). The results showed that inactivation of the aDLS selectively disrupted punished drug seeking, but did not affect unpunished drug seeking, even after extended training. Inactivation of the midlateral striatum, an area that would also have been affected by alpha-flupenthixol infusions in our earlier studies (Vanderschuren et al., 2005; Belin and Everitt, 2008; Murray et al., 2012) disrupted drug seeking at all stages of training. The effect of inactivating the aDLS under punishment conditions was present before delivery of the first shock in the session, and responding reverted to baseline the next day. Thus, it seems that inactivation of the aDLS enhanced the influence of recalled threat of the negative consequences of cocaine seeking (Jonkman et al., 2012a,b). These results suggest a novel differentiation of function in the sensorimotor striatum, where the aDLS selectively mediates the rigidity of responding after over-training and under the threat of punishment, while the midlateral striatum mediates responding itself at all stages of training, reflecting its motor cortical connectivity. The relationship between changes in prefrontal cortical function, including reductions in 5-HT utilisation to this emergent involvement of a specific region of the dorsal striatum in cocaine seeking under punishment remains to be established.

A more general question arising from the research summarised above is the relationship of other neuropsychiatric disorders to other syndromes in which impulsivity or compulsivity and their mediation by fronto-striatal mechanisms form a prominent part, such as gambling (Grant and Potenza, 2012) or compulsive

eating (Smith and Robbins, *in press*). It is perhaps too early to be confident that this is the case, but there are some intriguing behavioral and neural parallels with what we have described here for drug addiction. Given the focus of Ann Kelley's work on the neural mechanisms of food-motivated behavior, this may not perhaps be altogether surprising.

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