Psychopharmacology (2005) 182: 579–587
DOI 10.1007/s00213-005-0107-3

ORIGINAL INVESTIGATION

Jeffrey W. Dalley · Kristjan Lääne · Yolanda Pena · David E. H. Theobald · Barry J. Everitt · Trevor W. Robbins

Attentional and motivational deficits in rats withdrawn from intravenous self-administration of cocaine or heroin

Received: 8 May 2005 / Accepted: 14 June 2005 / Published online: 27 July 2005

Abstract *Rationale:* Identifying the long-term neurocognitive sequelae of drug addiction may have important implications for understanding the compulsive, chronically relapsing nature of this brain disorder. *Objectives:* Our aim was to investigate the consequences of chronic intravenous self-administration of cocaine or heroin on visual attentional processes in rats. *Methods:* Adult male rats were pretrained on a five-choice serial reaction time task (5-CSRTT) of sustained visual attention and impulsivity and later trained to self-administer cocaine or heroin intravenously during multiple 'long-access' self-administration cycles. Control rats had identical training and surgical experience, but received passive infusions of saline during self-administration sessions. Executive cognitive processes of selection and inhibitory response control were evaluated 24 h after drug discontinuation and for a further 6 days prior to the next cycle of self-administration. *Results:* Findings indicate similar behavioural disturbances on the five-choice task in cocaine- and heroin-withdrawn rats with significantly impaired attentional accuracy, increased omissions and slower latencies to respond correctly during the early, but not late, withdrawal period. The self-administration of either drug was not associated with significant alterations in impulsive actions, and there was no evidence of persistent alterations in visual attentional performance. However, unlike rats self-administering cocaine, the motivation to collect food reward on the 5-CSRTT was significantly reduced in heroin-withdrawn animals for a period of at least 6 weeks. *Conclusions:* These data, together with recent findings of attentional dysfunction during the withdrawal of intravenous self-administration of amphetamine, suggest that generically different drugs of abuse produce similar disturbances in visual attentional performance during the early withdrawal period.

Keywords Cognitive sequelae · Drug addiction · Visual attention · Five-choice serial reaction time task · Impulsivity · Psychostimulants · Opiates

J. W. Dalley (✉) · K. Lääne · Y. Pena · D. E. H. Theobald · B. J. Everitt · T. W. Robbins
MRC Centre for Behavioural and Clinical Neuroscience,
Department of Experimental Psychology,
University of Cambridge,
Downing Street,
Cambridge, CB2 3EB, UK
e-mail: jwd20@cam.ac.uk
Tel.: +44-1223-765291
Fax: +44-1223-333564

Introduction

There is widespread support for the hypothesis that frontal lobe dysfunction plays a prominent role in compulsive brain disorders such as drug addiction (Volkow et al. 1993; Jentsch and Taylor 1999; Rogers et al. 1999; Lyvers 2000; Hester and Garavan 2004). Consistent with this view, brain imaging and neuropsychological investigations of human drug addicts have revealed specific patterns of impairment in executive control processes known to depend on the prefrontal cortex (PFC) and associated brain circuitry, including decision making, attention, memory function and inhibitory control (O'Malley et al. 1992; Berry et al. 1993; Rogers et al. 1999; Beatty et al. 1995; Rosselli and Ardila 1996; Bolla et al. 1999; Lyvers 2000; Ornstein et al. 2000; Hester and Garavan 2004). However, the hypothesis that chronic drug abuse per se leads to a dysregulation in frontally mediated self-control (e.g. Jentsch and Taylor 1999; Lyvers 2000) remains a contentious issue in drug addiction research. For example, it is difficult to rule out premorbid factors, such as residual attention-deficit/hyperactivity disorder and coexisting psychopathology, as explanations for observed neuropsychological impairment in chronic drug abusers. Indeed, neural and neurochemical abnormalities may be present prior to, rather than be a consequence of, long-term drug abuse. Determining the causal impact of long-standing drug self-administration on neurocognitive abilities thus requires experimental animal models to control drug exposure prior to cognitive testing.

In a recent study (Dalley et al. 2005), we investigated this issue directly using a five-choice serial reaction time task (5-CSRTT) in rats, which engages executive control processes of attentional selection, inhibitory response con-

trol and monitoring, and which depends on neural systems including the PFC and striatum (Robbins 2002). Rats were trained on the 5-CSRTT to discriminate brief visual stimuli presented in a spatially unpredictable manner and to refrain from responding at inappropriate times before the onset of target stimuli (deemed 'impulsive' responding). In our initial analysis, we investigated the consequences of intravenous self-administration of D-amphetamine in rats pretrained on the 5-CSRTT on visual attentional performance (Dalley et al. 2005). It was shown that withdrawal from intravenous self-administration of amphetamine resulted in severe, but relatively temporary, disturbances in attentional performance that were overcome fully after several days of drug abstinence. The present study considers the hypothesis that attentional dysfunction associated with drug withdrawal is a phenomenon common to both opiate and psychomotor stimulant drugs of abuse. Despite reports of neuropsychological impairment among opiate addicts (Grant et al. 1978; Petry et al. 1998; Rogers et al. 1999; Ornstein et al. 2000), these are less well understood compared to psychomotor stimulant drugs of abuse (Zacny 1995; Rogers and Robbins 2001), and it is unclear whether related deficits in frontal lobe function are manifested before the onset of heroin use (Lyvers 2000). Research into the cognitive sequelae of chronic cocaine abuse is more extensive (e.g. O'Malley et al. 1992; Berry et al. 1993; Beatty et al. 1995; Rosselli and Ardila 1996; Bolla et al. 1999; Hester and Garavan 2004) but is nevertheless constrained by similar interpretative issues. Therefore, in the present investigation, we evaluated the effects of withdrawal from the intravenous self-administration of heroin or cocaine on the pretrained performance of rats on the 5-CSRTT.

Materials and methods

Subjects

Twenty-eight adult male Lister Hooded rats (Charles River, UK), weighing 368–425 g at the time of intravenous surgery, were used. They were housed in pairs in a temperature- and humidity-controlled room (22°C) under an alternating light/dark cycle (white lights off/red lights on from 7:30 a.m. to 7:30 p.m.). Subjects were each given 20 g of food per day (Purina Laboratory Chow), which was reduced to 14 g/day during behavioural testing on the 5-CSRTT. Water was provided ad libitum. All procedures conformed to the UK (1986) Animal (Scientific Procedures) Act (project licence PPL 80/1767).

5-CSRTT apparatus and training

The test apparatus consisted of eight five-choice chambers (25×25×25 cm), each housed within a ventilated, wooden, sound-attenuating box (see Dalley et al. 2005). A personal computer using WhiskerServer software written in C++ (version 2.2) and a FiveChoice client (version 2.7) controlled the apparatus (Cardinal and Aitken 2001). Subjects were trained to detect the location of a brief visual stimulus (0.5 s in duration) presented pseudorandomly in one of five apertures over a large number of trials, as described previously (Dalley et al. 2005). A number of performance measures were recorded, including choice accuracy (the proportion of correct responses to the total number of correct and incorrect responses), omissions (a failure to respond within the intertrial interval [ITI] and a short period thereafter), premature responding (responses made before the target stimulus), correct response latency (the time from the stimulus onset to a correct response) and magazine latency (the time from a correct response to the collection of food in the magazine). Subjects were considered to have acquired the task when their accuracy was greater than 80% and omissions were fewer than 20%. Thereafter, subjects were assessed for 14 days to determine the baseline performance. On days 3 and 10, longer 1-h sessions were used; these consisted of 100 trials and a fixed ITI of 7 s. The purpose of this procedure was to increase the sensitivity of the task to impulsive responding (see Dalley et al. 2002). Following intravenous surgery, rats were given 1 week to recover before being run on the 5-CSRTT for a further week of baseline testing. Subjects were randomly allocated to three groups: those destined to receive cocaine (n=10), those destined to receive heroin (n=9) and those destined to receive yoked infusions of saline (n=9).

Intravenous self-administration of cocaine and heroin

Chronic indwelling catheters were implanted into the right jugular vein under ketamine (Ketalar, 100 mg/kg, i.p.; Vet Drug, Bury, St. Edmunds, UK) and xylazine (Rompun, 12 mg/kg, i.p; Vet Drug) anaesthesia, supplemented with ketamine as needed (20 mg/kg, i.p.), as described previously (Caine et al. 1992; Dalley et al. 2005). Subjects were individually housed after surgery. Catheter patency was maintained by flushing once weekly with 0.2 ml of normal saline. Twelve dual-lever operant-conditioning chambers (24×20×22 cm; Med Associates, UK) were employed in the study. Infusions were delivered by a software-operated pump (Semat Technical, St. Albans, UK), as described previously (Dalley et al. 2005). Rats were trained to intravenously self-administer cocaine or heroin under a fixed ratio 1 (FR1) schedule. Acquisition was carried out over five daily sessions, with the daily number of infusions limited to 50 for cocaine (0.25 mg/infusion) and to 25 for heroin (0.04 mg/infusion). Subjects were then tested on the 5-CSRTT for seven consecutive days during withdrawal. Thereafter, the maximum number of infusions obtainable was increased to 150 for cocaine and to 75 for heroin. 'Long access' exposure to cocaine or heroin is known to produce an escalation in drug intake and a dysregulation of brain reward function not observed with a more restricted access (Ahmed and Koob 1999; Ahmed et

al. 2000, 2002) and thus may result in differential effects on cognitive performance. These sessions consisted of five daily sessions (one 'cycle') that were repeated on four successive occasions. Testing on the 5-CSRTT took place 24 h after withdrawal, for a total of seven consecutive days. Control rats received an identical training on the 5-CSRTT and surgery but received yoked infusions of sterile saline (0.1 ml) during the self-administration sessions.

Since one major apparently long-lasting consequence of heroin withdrawal was a selective increase in magazine latencies (see Fig. 5), we determined if this deficit was still present following a further 1 month of drug withdrawal. Control and heroin rats were maintained in their home cages during this period, with food restricted to 18 g/day per subject but with water provided ad libitum. Retraining on the 5-CSRTT was conducted over three daily sessions, each consisting of 100 trials (ITI 5 s, stimulus duration 0.5 s). Comparisons between control and heroin rats were made on the third and final session.

Drugs

Cocaine and heroin hydrochloride (MacFarlen Smith, Edinburgh, UK) were dissolved in sterile 0.9% sodium chloride solution (Aquapharm; Animalcare, Dunnington, UK). Drug doses were calculated from the combined weight of the free base and salt.

Statistical analyses

Data were subjected to repeated-measures analysis of variance (ANOVA) using a general linear model (SPSS type III sum-of-squares method, version 11.5; SPSS, Chicago, IL, USA). Violations of the sphericity assumption within the repeated-measures ANOVAs were corrected using the Huynh–Feldt epsilon (ε) to adjust the degrees of freedom (Keppel 1991). Accuracy data were transformed using the formula $x'=2\text{arc}\sin[\sqrt{x}]$; correct responses and magazine latencies were subjected to logarithmic transformation. Significant interactions were assessed by ANOVA and independent t tests, where appropriate. All tests were performed at $\alpha=0.05$.

Results

Cocaine and heroin self-administration

Figure 1 shows the acquisition and rate of intravenous self-administration of cocaine or heroin. Active lever responses were significantly greater than inactive lever responses (cocaine $F_{1,9}=398.5$, $p<0.01$; heroin $F_{1,8}=133.2$, $p<0.01$), indicating that rats in both groups self-administered drugs intravenously. Cocaine rats self-administered approximately 20 infusions per hour—a rate of delivery that did not change significantly over the course of the experiment. In contrast, heroin rats showed 'within-cycle' *increases* in

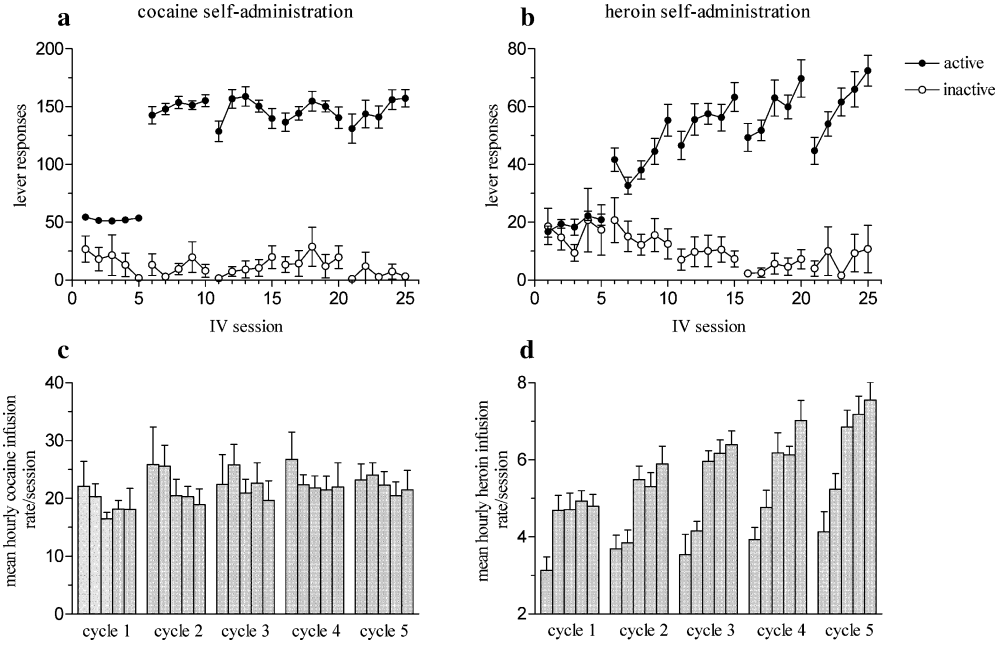

Fig. 1 Number of active and inactive lever-press responses during cocaine (**a**) and heroin (**b**) intravenous self-administration maintained under an FR1 schedule of reinforcement (mean±SEM; cocaine $n=10$ and heroin $n=9$). The data are grouped as cycles of five consecutive daily intravenous sessions, each separated by 9 days during which time 5-CSRTT testing took place. During the first cycle, the number of infusions in each 5-h session was limited to 50 and 25 for cocaine (250 μg/infusion) and heroin (40 μg/infusion), respectively; for the remaining cycles, access was increased to 150 and 75 infusions, respectively, with a session duration of 8 h. The lower *bar graphs* show the average rate of drug self-administration (number of infusions/h±SEM) for cocaine (**c**) and heroin (**d**) collapsed over the entire session

both the mean hourly rate of self-administration and the number of active lever responses. In the case of infusion rates (see Fig. 1d), this was revealed by a significant cycle×session interaction ($F_{16,128}$=2.3, p<0.01), main effects of session for cycle 2 ($F_{4,32}$=4.1, p<0.01), cycle 3 ($F_{4,32}$=8.7, p<0.01), cycle 4 ($F_{4,32}$=11.4, p<0.01) and cycle 5 ($F_{4,32}$=16.7, p<0.01), and by significant post hoc differences between sessions 1 and 5 for each of the five cycles. There was also a main effect of cycle ($F_{4,32}$=21.0, p<0.01), the nature of which was determined by calculating for each rat a mean rate of self-administration per cycle. This analysis revealed significant differences (all p<0.01), respectively, between cycle 1 and cycles 3, 4 and 5; between cycle 2 and cycles 3, 4 and 5; but not between cycle 3 and cycles 4 and 5. A similar analysis of the main effect of cycle for active lever responses ($F_{4,32}$=49.1, p<0.01) showed similar results, except that responses for cycle 2 were greater than cycle 1 (p<0.01). Thus, in contrast to cocaine, heroin self-administration *increased* both within each cycle and at least across the first two cycles of long-access exposure.

Attentional accuracy

The effects of cocaine and heroin withdrawal on choice accuracy are shown in Fig. 2. Prior to intravenous drug exposure, there were no significant differences between future control, cocaine and heroin rats. The main effect of cocaine and heroin withdrawal was *reduced* accuracy, especially on the first withdrawal day. Initial analyses revealed a significant group×session×cycle interaction ($F_{48,600}$= 2.7, p<0.01) and significant group×session interactions for the five cycles. Examining each cycle in turn revealed a significant session×group interaction for the heroin group relative to controls for cycle 1 ($F_{6,96}$=2.5, p=0.025) but no significant pairwise differences. A similar analysis for cycle 2 revealed a main effect of session ($F_{6,150}$=9.2, p<0.01) but no other significant effects. However, for cycle 3, there were significant session×group interactions for both the cocaine ($F_{6,102}$=3.2, p=0.007) and heroin ($F_{6,96}$=4.2, p<0.01) groups and significant differences for both groups during the first day of withdrawal compared with controls (cocaine p=0.028; heroin p<0.01). For the remaining two cycles, there were again significant session×group interactions for the cocaine (cycle 4 $F_{6,102}$=4.1, p<0.01; cycle 5 $F_{6,102}$=4.3, p=0.01) and heroin (cycle 4 $F_{6,96}$=2.6, p=0.021; cycle 5 $F_{6,96}$=8.9, p<0.01) groups and a reduced accuracy relative to controls on the first drug-free day (cocaine cycle 4 p<0.01; cocaine cycle 5 p<0.01; heroin cycle 4 p=0.035; heroin cycle 5 p<0.01).

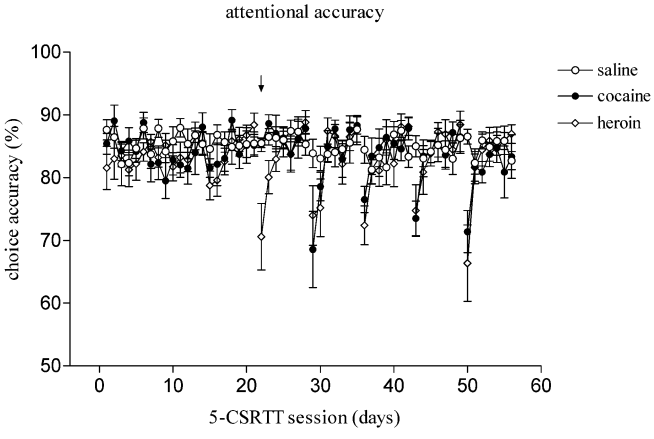

Fig. 2 Symmetrical impairments in attentional accuracy on the 5-CSRTT following discontinuation of intravenous self-administration of cocaine and heroin. Accuracy was computed as the percentage of correct responses to the total correct and incorrect responses and was thus independent of motor performance. Control ('saline') animals received passive yoked infusions of sterile 0.9% saline during active self-administration sessions. Predrug baseline accuracy was determined over a period of 3 weeks (sessions 1–21). The *arrow* depicts the first test session on the 5-CSRTT, which was conducted 24 h after the last intravenous self-administration session. Testing took place for a further 6 days before subjects experienced an additional 'cycle' of five consecutive days of intravenous drug administration (see Fig. 1). Access was increased during cycles 2–5 with a longer session time (8 h), and an increase in the number of reinforcements was potentially obtainable

Omissions

A further main of effect of cocaine and heroin withdrawal was a sharp but transient rise in omissions (see Fig. 3). ANOVA revealed a significant interaction between group, session and cycle ($F_{48,600}$=1.65, p=0.005) and significant group×session interactions for each of the five cycles (all p<0.02). During cycle 1, omissions varied significantly only in the heroin group (session×group interaction $F_{6,96}$= 3.12, p<0.01), with a near significant difference between heroin and control rats on the first day of withdrawal

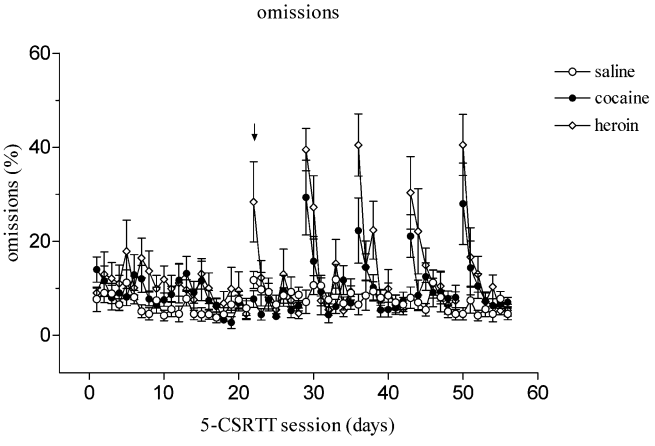

Fig. 3 Increased omissions on the 5-CSRTT following the withdrawal of intravenous self-administration of cocaine and heroin compared with control subjects receiving intravenous passive infusions of sterile 0.9% saline. An omission was recorded when no response was made within a 5-s period from the onset of the target stimulus. Omissions were calculated as a percentage of total trials initiated, including those that were ultimately 'correct', 'incorrect' or 'omissions' and thus can never exceed 100%. The *arrow* depicts the first test session on the 5-CSRTT following the withdrawal of cocaine and heroin self-administration (see Fig. 2)

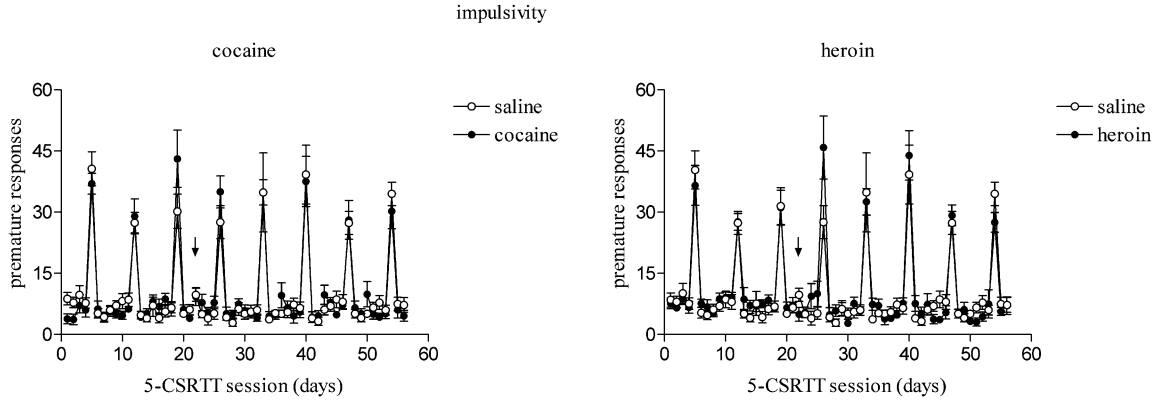

Fig. 4 Lack of effect of cocaine and heroin self-administration on 'impulsive' premature responding on the 5-CSRTT. The *arrow* depicts the transition between the predrug baseline evaluation on the 5-CSRTT and the first test day conducted 24 h after the last self-administration session. Data are the mean number of premature responses per session (±SEM). The sharp peaks in premature responding relate to sessions where the ITI (i.e. the period separating the start of each trial and the onset of the target stimulus) was increased to 7 s

(p=0.075). For subsequent cycles, cocaine and heroin withdrawal was associated with reliable increases in omissions. Specifically, omissions in cocaine rats were significantly increased relative to controls on the first withdrawal day for cycle 2 (p=0.011), cycle 3 (p=0.014) and cycle 4 (p=0.004) and on the first (p=0.006) and third (p=0.027) days of cycle 5. Omissions increased significantly in heroin rats on the first and second days of cycle 2 (p<0.01), on day 1 of cycle 3 (p<0.01) and on days 1 and 3 of the final two cycles (all p<0.05).

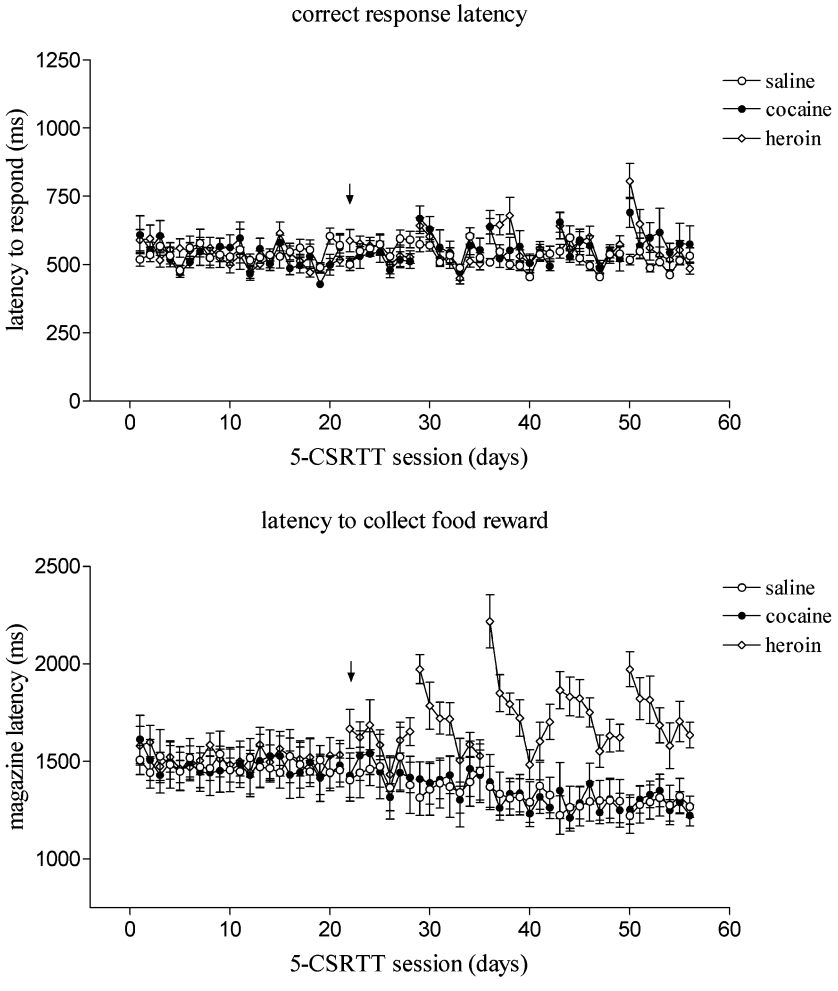

Fig. 5 Differential effects of cocaine and heroin withdrawal on mean latencies (±SEM) to respond correctly (*upper graph*) and to collect earned food pellets from the magazine (*lower graph*). Baseline data were collected for 3 weeks prior to cocaine and heroin self-administration. The *arrow* marks the first withdrawal day following the acquisition of intravenous self-administration (i.e. cycle 1; see Fig. 1). It can been seen that heroin withdrawal produces large and sustained increases in the latency to collect food reward

Impulsivity

Figure 4 shows the effects of cocaine and heroin withdrawal on impulsive responding. There were no significant differences between future control, cocaine and heroin rats on this measure of impulsivity prior to drug exposure, nor were there significant differences between the three groups during drug withdrawal (group $F_{2,25}$=0.06, p=0.94; cycle×group $F_{8,100}$=1.3, p=0.25; cycle×session×group $F_{48,600}$=1.3, p=0.11).

Response and magazine latencies

Figure 5 shows the effects of cocaine and heroin withdrawal on latencies to respond correctly and to collect earned food from the magazine. Correct response latencies increased significantly in both cocaine and heroin rats during withdrawal. Initial analyses revealed a significant overall interaction between cycle, session and group ($F_{48,600}$=1.7, ε=0.81, p=0.007) and significant three-way interactions for cocaine ($F_{24,408}$=1.6, p=0.046) and heroin ($F_{24,384}$=2.0, p<0.01) rats relative to controls. Significant effects on correct response latencies were evident only during the final three cycles, with each case being significant for the first test session only (all p<0.03). Although magazine latencies were not significantly affected by cocaine withdrawal, they did increase in rats withdrawn from heroin. This was confirmed by a main effect of group ($F_{1,16}$=11.2, p<0.01) and a significant cycle×session×group interaction ($F_{24,384}$=1.8, p=0.02) for the comparison between control and heroin rats. For all cycles, except the first, there were significant main effects of group (all p<0.035) and significant session×group interactions (all p<0.016). Post hoc tests revealed that latencies were significantly elevated compared with controls on the first 4 days of cycles 2–5 (all p<0.02), as well as on the final 2 days of cycles 4 and 5 (all p<0.027). The final day of cycle 3 was also significant (p=0.011).

Despite increased magazine latencies in rats withdrawn from heroin, there were no significant changes in body weight during the course of the study. The body weights of cocaine and heroin rats on the first week of baseline testing were 418±14 and 420±10 g, respectively; on test day 35 (see Fig. 5) were 421±6 and 413±6 g, respectively; and on test day 56 were 426.7±5 and 414.9±10 g, respectively. Figure 6 shows that magazine latencies remained persistently elevated in heroin-withdrawn rats for at least 6 weeks.

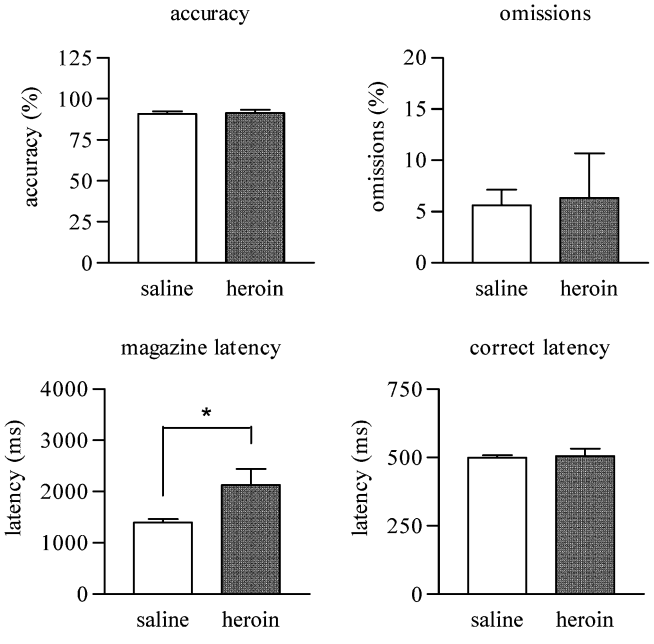

Fig. 6 Performance of control and heroin rats on the 5-CSRTT following 1 month of drug withdrawal. Subjects previously exposed to long-access intravenous self-administration of heroin show a persistent and selective impairment in the latency to collect earned food reward from the magazine (*p<0.05)

Discussion

There has been much interest in determining the residual effects of chronic drug abuse on neuropsychological test performance as a basis for understanding why some individuals continue to abuse drugs despite obvious harm to themselves and others. It has been hypothesized that repeated drug use interferes with 'executive' functions known to depend on interrelated areas of the PFC, including self-control (Jentsch and Taylor 1999; Lyvers 2000). Consistent with this notion, chronic cocaine and heroin abusers often show impaired performance on tests of executive function, including working memory, decision making, planning and attentional set-shifting (Berry et al. 1993; Rosselli and Ardila 1996; Bolla et al. 1999; Ornstein et al. 2000; Rogers and Robbins 2001; Hester and Garavan 2004). However, evidence for enduring executive dysfunction in abstinent drug addicts has been less well substantiated despite research indicating a reduced metabolism in the orbital PFC of chronic cocaine abusers 3–4 months after drug discontinuation (Volkow et al. 1993). Even more problematic is the frequently encountered coexistent psychopathology that may precede drug addiction (Khantzian 1985; Levin and Kleber 1995; Sim et al. 2002; Dawe and Loxton 2004). Using a task in which proficient performance depends on the integrity of the PFC and striatum (Robbins 2002), the present study addresses these issues by allowing controlled drug access to subjects premorbidly assessed for cognitive capabilities. We were especially interested in understanding whether a high access to cocaine and heroin, which previously has been shown to escalate drug self-administration (Ahmed and Koob 1999; Ahmed et al. 2000) and promote lasting changes in brain reward function (Ahmed et al. 2002), affects cognitive functions known to depend on the PFC.

The main findings of this investigation show that visual attentional performance is disrupted by the acute withdrawal of either cocaine or heroin self-administration. These data thus extend previous findings of attentional dysfunction in rats withdrawn from chronic amphetamine

(Dalley et al. 2005) and nicotine (Shoaib and Bizarro 2005) and suggest, therefore, that common neurobiological substrates may underlie opiate- and stimulant-induced disturbances in visual attention, despite clear dissimilarities in the neural systems mediating the reinforcing effects of these drugs (Ettenberg et al. 1982; Pettit et al. 1984). One possibility is that this deficit in some way involves reduced dopamine transmission in some as yet unspecified brain areas, in addition to the nucleus accumbens (Parsons et al. 1991; Pothos et al. 1991; Rossetti et al. 1992; Maisonneuve et al. 1995; Kuhar and Pilotte 1996). However, the present findings are unlikely to result from impaired motivation or non-specific disturbances in motor behaviour. Thus, it is difficult to argue for a general involvement of motivational variables when magazine latencies were unaffected in the cocaine-withdrawn group. Moreover, since responses to correct and incorrect target locations require the same motor effort, it is improbable that general deficiencies in motor ability mediated the decline in accurate responding. Rather, the corresponding increase in omissions makes it more likely that the acute withdrawal of cocaine or heroin adversely affected active processes of attentional selection (Lyvers 2000; Robbins 2002). These data thus provide further insights into the wide-ranging effects of opiate and stimulant withdrawal on mood and arousal, including anhedonic-like states in rats (Markou and Koob 1991; Koob and Le Moal 1997) and depressive symptoms mixed with anxiety, irritability and inattentiveness in human drug addicts (Gawin and Kleber 1986; Berry et al. 1993). They also suggest that such disturbances during the acute period of stimulant or opiate withdrawal may be sensitive to amelioration by further drug intake. Further experiments are needed to determine whether contingent drug access would be sufficient to restore attentional capabilities in cocaine- and heroin-withdrawn rats in ways that potentially could contribute to the long-term maintenance of drug intake. Such findings would clearly be consistent with elements of the self-medication hypothesis of drug addiction (Khantzian 1985).

In the present study, increasing the access time to cocaine produced no significant increase in the rate of cocaine self-administration, a finding that is somewhat at odds with previous investigations that also used an FR1 schedule and a cocaine infusion dose of 0.25 mg (Ahmed and Koob 1999; Ahmed et al. 2002; Ben-Shahar et al. 2004). A comparison between these studies and the present study, however, reveals a number of procedural dissimilarities that may have contributed to this discrepancy, not the least of which includes differences in the strain of rat used and the precise conditions under which high access to cocaine was made available. For example, in the present study, the number of cocaine infusions in each session was restricted whereas no constraint was imposed in previous studies, which were limited instead by a fixed session time of 6 h. However, our failure to observe cocaine escalation is unlikely the result of ceiling effects because the majority of subjects in the present study did not receive the maximum permissible number of infusions during the long-access sessions. A further distinction relates to the training history of the animals. Rats in the present study received no lever-press training for food to facilitate subsequent cocaine self-administration, nor did they experience a limited 1-h access to cocaine self-administration prior to cocaine availability being increased, unlike earlier studies. Finally, rats in the present study experienced intermittent cycles of high-access cocaine self-administration that were each separated by a period of withdrawal. Therefore, the development of cocaine (administered intravenously) escalation may depend on several experimental variables, in addition to increased cocaine access.

Neither cocaine nor heroin significantly affected impulsive responding on the 5-CSRTT. Similarly, no significant effect of a chronic intravenous administration of amphetamine was found previously on this measure of impulsivity (Dalley et al. 2005). One implication of these data is that executive dysfunction in human drug users, including impaired self-control, may be a pre-existing abnormality and not a consequence of chronic drug abuse. However, it is also possible that the low working memory load of the 5-CSRTT made the occurrence of impulsive responding less likely in the present study. Thus, using a Go/No-Go response inhibition test of working memory, it has recently been shown that human cocaine addicts find it more difficult to inhibit their actions when working memory demands are increased (Hester and Garavan 2004). Alternatively, or perhaps in addition, chronic drug use may affect other forms of impulsive behaviour, such as stop signal reaction time and delayed gratification (Evenden 1999; see also Petry et al. 1998; Fillmore et al. 2002).

An interesting finding of the present study was that heroin withdrawal, unlike cocaine or amphetamine withdrawal (see Dalley et al. 2005), was associated with a profound and selective increase in the latency to collect earned food from the magazine, an effect that persisted for at least 6 weeks. This effect was clearly unrelated to response vigour as latencies to respond correctly increased only transiently during acute heroin withdrawal, nor was it consistent with gross deficits in motivation because omissions did not increase in a corresponding manner. Rather, the origin of this deficit seems most parsimoniously related to the well-established involvement of the endogenous opioid system in feeding (Kelley et al. 2002). Specifically, it has been hypothesized that opiate agonists such as morphine and heroin augment food palatability or 'liking' whereas opiate antagonists such as naloxone have the opposite effect (Berridge 1996). Our findings suggest that withdrawal from chronic heroin may produce long-lasting adaptations in the endogenous opioid system, the consequence of which may be diminishment of the perceived value of food reward on the 5-CSRTT. These data are thus compatible with findings that rats previously exposed to morphine develop significantly less preference for food-associated cues than morphine-associated cues (Harris and Aston-Jones 2003) and that food-reinforced behaviour in monkeys can be suppressed by conditioned cues predictive

of morphine withdrawal (Goldberg and Schuster 1967). They also imply that the anhedonic effects of withdrawal from opiate and stimulant drugs as measured operationally by elevated ICSS (Intra-cranial self-stimulation) thresholds in rats (Markou and Koob 1991; Koob and Le Moal 1997) may be different from the anhedonic-like state of rats self-administering heroin in the present study.

In summary, the findings of this investigation indicate that, during acute withdrawal, generically different drugs of abuse transiently disrupt cognitive control functions such as attentional selection. Neither cocaine nor heroin withdrawal resulted in residual impairments in executive aspects of visual attention involving response inhibition. However, important distinctions were found between cocaine and heroin in their effects on food motivation during protracted abstinence. Further studies are needed to determine with greater precision the effects of chronic drug intake on other defined frontoexecutive functions, including working memory, and how these interact with premorbid cognitive capabilities.

Acknowledgements This study was supported by the Wellcome Trust within the Cambridge Medical Research Council Centre for Behavioural and Clinical Neuroscience.

References

Ahmed SH, Koob GF (1999) Long-lasting increase in the set point for cocaine self-administration after escalation in rats. Psychopharmacology 146:303–312

Ahmed SH, Walker JR, Koob GF (2000) Persistent increase in the motivation to take heroin in rats with a history of drug escalation. Neuropsychopharmacology 22:413–421

Ahmed SH, Kenny PJ, Koob GF, Markou A (2002) Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. Nat Neurosci 5:625–626

Beatty WW, Katzung VM, Moreland VJ, Nixon SJ (1995) Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. Drug Alcohol Depend 37:247–253

Ben-Shahar O, Ahmed SH, Koob GF, Ettenberg A (2004) The transition from controlled to compulsive drug use is associated with a loss of sensitization. Brain Res 995:46–54

Berridge KC (1996) Food reward: brain substrates of wanting and liking. Neurosci Biobehav Rev 20:1–25

Berry J, van Gorp W, Herzberg DS, Hinkin C, Boone K, Steinman L, Wilkins JN (1993) Neuropsychological deficits in abstinent cocaine abusers: preliminary findings after two weeks of abstinence. Drug Alcohol Depend 32:231–237

Bolla KI, Rothman R, Cadet JL (1999) Dose-related neurobehavioral effects of chronic cocaine use. J Neuropsychiatry Clin Neurosci 11:361–369

Caine SB, Lintz R, Koob GF (1992) Intravenous drug self-administration techniques in animals. In: Sahgal A (ed) Behavioral neuroscience, a practical approach, vol I. Oxford University Press, Oxford, pp 117–143

Cardinal RN, Aitken MRF (2001) Whisker, version 2.2, computer software. http://www.whisker.control.com

Dalley JW, Theobald DE, Eagle DM, Passetti F, Robbins TW (2002) Deficits in impulse control associated with tonically-elevated serotonergic function in rat prefrontal cortex. Neuropsychopharmacology 26:716–728

Dalley JW, Theobald DEH, Berry D, Milstein J, Laane K, Everitt BJ, Robbins TW (2005) Cognitive sequelae of intravenous amphetamine self-administration in rats: evidence for selective effects on attentional performance. Neuropsychopharmacology 30:525–537

Dawe S, Loxton NJ (2004) The role of impulsivity in the development of substance use and eating disorders. Neurosci Biobehav Rev 28:343–351

Ettenberg A, Petit HO, Bloom FE, Koob GF (1982) Heroin and cocaine intravenous self-administration in rats: mediation by separate neural systems. Psychopharmacology 78:204–209

Evenden JL (1999) Impulsivity: a discussion of clinical and experimental findings. J Psychopharmacol 13(2):180–192

Fillmore MT, Rush CR, Hays L (2002) Acute effects of oral cocaine on inhibitory control of behavior in humans. Drug Alcohol Depend 67:157–167

Gawin FH, Kleber HD (1986) Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Arch Gen Psychiatry 43:107–113

Goldberg SR, Schuster CR (1967) Conditioned suppression by a stimulus associated with nalorphine in morphine-dependent monkeys. J Exp Anal Behav 10:235–242

Grant I, Adams KM, Carlin AS, Rennick PM, Judd LL, Schoof K (1978) Collaborative neuropsychological study of polydrug users. Arch Gen Psychiatry 35:1063–1074

Harris GC, Aston-Jones G (2003) Altered motivation and learning following opiate withdrawal: evidence for prolonged dysregulation of reward processing. Neuropsychopharmacology 28:865–871

Hester R, Garavan H (2004) Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. J Neurosci 24:11017–11022

Jentsch JD, Taylor JR (1999) Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. Psychopharmacology 146:373–390

Kelley AE, Bakshi VP, Haber SN, Steininger TL, Will MJ, Zhang M (2002) Opioid modulation of taste hedonics within the ventral striatum. Physiol Behav 76:365–377

Keppel G (1991) Design and analysis. Prentice Hall, Englewood Cliffs, NJ

Khantzian EJ (1985) The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. Am J Psychiatry 142:1259–1264

Koob GF, Le Moal M (1997) Drug abuse: hedonic homeostatic dysregulation. Science 278:52–58

Kuhar MJ, Pilotte NS (1996) Neurochemical changes in cocaine withdrawal. Trends Pharmacol Sci 17:260–264

Levin FR, Kleber HD (1995) Attention-deficit hyperactivity disorder and substance abuse: relationships and implications for treatment. Harv Rev Psychiatry 2:246–258

Lyvers M (2000) 'Loss of control' in alcoholism and drug addiction: a neuroscientific interpretation. Exp Clin Psychopharmacol 8:225–249

Maisonneuve IM, Ho A, Kreek MJ (1995) Chronic administration of a cocaine 'binge' alters basal extracellular levels in male rats: an in-vivo microdialysis study. J Pharmacol Exp Ther 272:652–657

Markou A, Koob GF (1991) Postcocaine anhedonia. An animal model of cocaine withdrawal. Neuropsychopharmacology 4:17–26

O'Malley S, Adamse M, Heaton RK, Gawin FH (1992) Neuropsychological impairments in chronic cocaine abusers. Am J Drug Alcohol Abuse 18:131–144

Ornstein TJ, Iddon JL, Baldacchino AM, Sahakian BJ, London M, Everitt BJ, Robbins TW (2000) Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. Neuropsychopharmacology 23:113–126

Parsons LH, Smith AD, Justice JB (1991) Basal extracellular dopamine is decreased in the rat nucleus accumbens during abstinence from chronic cocaine. Synapse 9:60–65

Petry NM, Bickel WK, Arnett M (1998) Shortened time horizons and insensitivity to future consequences in heroin addicts. Addiction 93:729–738

Pettit HO, Ettenberg A, Bloom FE, Koob GF (1984) Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology 84:167–173

Pothos E, Rada P, Mark GP, Hoebel BG (1991) Dopamine microdialysis in the nucleus accumbens during acute and chronic morphine, naloxone-precipitated withdrawal and clonidine treatment. Brain Res 566:348–350

Robbins TW (2002) The 5-choice serial reaction time task: behavioral pharmacology and functional neurochemistry. Psychopharmacology 163:363–380

Rogers RD, Robbins TW (2001) Investigating the neurocognitive deficits associated with chronic drug misuse. Curr Opin Neurobiol 11:250–257

Rogers RD, Everitt BJ, Baldacchino A, Blackshaw AJ, Swainson R, Wynne K, Baker NM, Hunter J, Carthy T, Booker E, London M, Deakin JFW, Sahakian BJ, Robbins TW (1999) Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with frontal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: evidence for monoaminergic mechanisms. Neuropsychopharmacology 20:322–339

Rosselli M, Ardila A (1996) Cognitive effects of cocaine and polydrug abuse. J Clin Exp Neuropsychol 18:122–135

Rossetti ZL, Hmaidan Y, Gessa GL (1992) Marked inhibition of mesolimbic dopamine release: a common feature of ethanol, morphine, cocaine and amphetamine abstinence in rats. Eur J Pharmacol 221:227–234

Shoaib M, Bizarro L (2005) Deficits in a sustained attention task following nicotine withdrawal in rats. Psychopharmacology 178:211–222

Sim T, Simon SL, Domier CP, Richardson K, Rawson RA, Ling W (2002) Cognitive deficits among methamphetamine users with attention deficit hyperactivity disorder symptomatology. J Addict Dis 21:75–89

Volkow ND, Fowler JS, Wang G-J, Hitzemann R, Logan J, Schlyer DJ, Dewey SL, Wolf AP (1993) Decreased dopamine D2 receptor availability is associated with reduced frontal metabolisms in cocaine abusers. Synapse 14:169–177

Zacny JP (1995) A review of the effects of opioids on psychomotor and cognitive functioning in humans. Exp Clin Psychopharmacol 3:432–466