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ORIGINAL INVESTIGATION

Chronic cocaine but not chronic amphetamine use is associated with perseverative responding in humans

Karen D. Ersche · Jonathan P. Roiser · Trevor W. Robbins · Barbara J. Sahakian

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Abstract
Rationale Chronic drug use has been associated with increased impulsivity and maladaptive behaviour, but the underlying mechanisms of this impairment remain unclear. We investigated the ability to adapt behaviour according to changes in reward contingencies, using a probabilistic reversal-learning task, in chronic drug users and controls.
Materials and methods Five groups were compared: chronic amphetamine users (n = 30); chronic cocaine users (n = 27); chronic opiate users (n = 42); former drug users of psychostimulants and opiates (n = 26); and healthy non-drug-taking control volunteers (n = 25). Participants had to make a forced choice between two alternative stimuli on each trial to acquire a stimulus–reward association on the basis of degraded feedback and subsequently to reverse their responses when the reward contingencies changed.
Results Chronic cocaine users demonstrated little behavioural change in response to the change in reward contingencies, as reflected by perseverative responding to the previously rewarded stimulus. Perseverative responding was observed in cocaine users regardless of whether they completed the reversal stage successfully. Task performance in chronic users of amphetamines and opiates, as well as in former drug users, was not measurably impaired.
Conclusion Our findings provide convincing evidence for response perseveration in cocaine users during probabilistic reversal-learning. Pharmacological differences between amphetamine and cocaine, in particular their respective effects on the 5-HT system, may account for the divergent task performance between the two psychostimulant user groups. The inability to reverse responses according to changes in reinforcement contingencies may underlie the maladaptive behaviour patterns observed in chronic cocaine users but not in chronic users of amphetamines or opiates.

Keywords Cocaine · Amphetamines · Opiates · Probabilistic reversal learning · Serotonin · Perseveration

K. D. Ersche (✉)
Department of Psychiatry, Brain Mapping Unit,
School of Clinical Medicine, University of Cambridge,
Box 255, Addenbrooke's Hospital,
Cambridge, UK
e-mail: ke220@cam.ac.uk

K. D. Ersche · J. P. Roiser · T. W. Robbins · B. J. Sahakian
Behavioural and Clinical Neurosciences Institute,
University of Cambridge,
Cambridge, UK

J. P. Roiser · B. J. Sahakian
Department of Psychiatry, School of Clinical Medicine,
University of Cambridge,
Box 189, Addenbrooke's Hospital,
Cambridge, UK

T. W. Robbins
Department of Experimental Psychology,
University of Cambridge,
Downing Street,
Cambridge, UK

J. P. Roiser
Institute of Cognitive Neuroscience,
17 Queen Square,
London WC1N 3AR, UK

Introduction

Response reversal has been defined as the ability to adapt behaviour according to changing reward contingencies (Rolls 2000). Impaired response reversal has been linked with

socially inappropriate conduct (Rolls et al. 1994) and impulsive behaviour (Jentsch and Taylor 1999). The behaviour of chronic drug users often appears impulsive and maladaptive, as exemplified by continued drug-taking, despite the negative consequences involved such as job loss or relationship breakdown. Deficits in adjusting one's actions according to changes in environmental contingencies may contribute to such maladaptive patterns of behaviour. Probabilistic response-reversal tasks have widely been used in research settings to investigate behavioural adaptation to changing reward contingencies in humans (Cools et al. 2002; Hornak et al. 2004). The probabilistic nature of the task has the advantage that performance is not attributable to the implementation of strategies or simple motor disinhibition (Hornak et al. 2004). Recently, Fillmore and Rush (2006) identified a significant impairment in response reversal in a group of 20 polydrug users on a probabilistic discrimination-reversal-learning task. The authors suggested that this impairment might be caused by chronic consumption of either alcohol or cocaine or could reflect the additive effect of both substances, as all participants consumed both drugs.

In light of evidence showing differential effects of individual drugs of abuse on executive functions in polydrug users (Verdejo-Garcia et al. 2005) and distinct performance profiles in cognitive function between amphetamine and opiate-dependent individuals (Ornstein et al. 2000), it is possible that reversal-learning impairments may differ between different drug-user groups. For example, response reversal requires the inhibition of a previously rewarded response, and recent data indicates that the behavioural impairment profile on response inhibition tasks such as the Go/Nogo task is different in psychostimulant users than in opiate users. Thus, although inhibition impairments have frequently been reported in chronic psychostimulant users (e.g. Hester and Garavan 2004; Kaufman et al. 2003), the majority of studies in opiate users do not find such a deficit (Forman et al. 2004; Lee et al. 2005; Verdejo-Garcia et al. 2007).

The aim of the present study was to investigate the impact of current and former drug use on probabilistic response-reversal performance. Five groups of drug users were compared: chronic amphetamine users; chronic cocaine users; chronic opiate users; former drug users of psychostimulants and opiates; and healthy non-drug-taking controls. On the basis of accumulating evidence of impaired response inhibition in psychostimulant users, we hypothesised that chronic amphetamine and cocaine users would make significantly more errors at the response-reversal stage than controls, while opiate users would not differ from controls on the task. A group of former drug users was included to control for the direct pharmacological actions in the current drug user groups and to explore possible reversibility of impairments with prolonged abstinence.

Materials and methods

Participants

The study received ethical approval from local ethics research committees in the East Anglia region of the UK. After complete description of the study, all participants provided written informed consent before testing. A total of 152 volunteers participated, grouped as follows: (a) 28 individuals with a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis of current substance dependence on amphetamine and two individuals with a DSM-IV diagnosis of amphetamine abuse; (b) 24 individuals with a DSM-IV diagnosis of current substance dependence on cocaine and three with a DSM-IV diagnosis of cocaine abuse; (c) 42 individuals with a DSM-IV diagnosis of current substance dependence on opiates; (d) 26 individuals with a DSM-IV diagnosis of past substance dependence on stimulants or opiates, who had been abstinent from all drugs of abuse for at least one year; and (e) 27 healthy controls with no drug-taking history. Exclusion criteria, which applied for all groups, were the following: colour blindness; a co-morbid psychiatric illness; a history of a head injury; or a history of an overdose requiring resuscitation and overnight hospitalisation. Dependence on another drug apart from the one falling under the inclusion criterion or nicotine also led to exclusion from the study. Adult attention-deficit/hyperactivity disorder was not part of the psychiatric assessment. Table 1 displays the drug-taking habits of other substances apart from their drug of choice by current drug users. Drug users were recruited through local drug-dependency units, by advertisement and word of mouth. Recovering drug users were recruited via Narcotics Anonymous and controls by advertisements in the local area.

All participants were screened using a semi-structured interview to ascertain their history of drug use and diagnosis for substance dependence according to the DSM-IV, general health and demographic characteristics. Urine samples were analyzed for the following drugs: morphine, methadone, amphetamine, cocaine and benzodiazepines using the Sure-Step Drug Screen Test (Euromed Limited, London UK) or the Triage Drug Screen (Biosite, Belfast, UK). All participants were compensated for their time. Control participants were only included in the study if they had no drug-taking history.

Seven amphetamine users were prescribed *d*-amphetamine from a Consultant Psychiatrist (36.4mg, SD = 21.9, range = 15–70). Amphetamine users without a prescription consumed street amphetamine daily. One street-amphetamine user was HIV-positive. Three amphetamine users met the criteria of a DSM-IV diagnosis of alcohol abuse and one for alcohol dependence. Twenty-nine out of 30 urine screens tested positive for amphetamine (additional substances: six morphine, two benzodiazepines, four cocaine). The one sam-

Table 1 Percentage of participants per group using legal and illegal drugs at some point in their lives

Drugs	Usage	Amphetamine group	Cocaine group	Opiate group	Ex-drug user group
Amphetamine	Never	0	19	14	12
	Present	100	11	5	0
	Past	0	70	81	88
Cocaine	Never	17	0	12	8
	Present	33	100	33	0
	Past	50	0	55	92
Ecstasy	Never	33	4	48	54
	Present	7	26	0	0
	Past	60	70	52	46
Opiates	Never	53	74	0	12
	Present	0	4	100	0
	Past	47	22	0	88
Alcohol	Never abused	43	41	40	19
	Present	17	59	7	0
	Past	40	0	53	81
Cannabis	Never	23	0	2	12
	Present	43	41	50	0
	Past	33	59	48	88
Tobacco	Never	17	11	0	4
	Present	83	82	98	62
	Past	0	7	2	35
Benzodiazepines	Never	66	63	32	35
	Present	3	7	15	0
	Past	31	30	54	65
Hallucinogenic	Never	40	18	29	23
	Present	7	22	2	0
	Past	53	59	69	77

ple that was negative was provided by a chronic amphetamine user who had recently consumed a large quantity of non-alcoholic liquids, so his data were included in the study. Six out of the 24 cocaine-dependent individuals were using crack-cocaine. Thirteen cocaine users met the DSM-IV criteria for alcohol abuse and two for alcohol dependence. All urine screens tested positive for cocaine (additional substances: three morphine, four benzodiazepines, one amphetamine). Twenty-seven opiate abusers were on a methadone prescription (mean ± SD dose, 45.2 ± 17.9mg; dose range, 20–80mg). Two methadone-maintained participants also received benzodiazepines on prescription. One opiate user was on a prescription of 4mg buprenorphine, and another one received 4 × 60mg dihydrocodeine. A further opiate user had a prescription for 200mg diamorphine and 90mg morphine sulphate slow release. Twelve opiate users exclusively consumed street heroin on a daily basis. One methadone user received antidepressant medication (dothiepin) and another rabeprazole sodium for treatment of heartburn.

The 26 former drug users were abstinent from all drugs of abuse, except nicotine, for on average 8.2years (SD = 6.3, range 1–18), and urine analyses were negative for all substances. This group was included to control for the current effect of drugs and to explore possible recovery function with prolonged drug abstinence. Eight were ex-stimulant users, five were ex-opiate users, and 13 had been dependent upon both stimulants and opiates. One ex-drug user was on antidepressant medication (citalopram). Twelve of the past/current tobacco-smoking controls (71%) reported social experiences with cannabis but no regular use. The urine screens provided by former drug users and by control participants were negative for all substances.

Materials

Reversal-learning was examined using the Probabilistic Reversal-Learning (PROB) task (Swainson et al. 2000), which involves the simultaneous presentation of two stimuli that differ only in colour (one is green, the other red). One stimulus is correct, and the other is wrong, which is indicated by positive and negative feedback. The stimuli changed position after each trial to avoid the development of motor perseveration. Participants were told to select the stimulus that was usually reinforced as being correct; on 20% of the trials, the computer provided false feedback, i.e. selecting the correct stimulus was followed by false

negative feedback. Negative feedback was presented both acoustically (by a tone) and visually (by a red circle around the response box). After 40 trials (stage 1), the contingencies reversed for the subsequent 40 trials (stage 2), i.e. the stimulus that was previously correct became incorrect, and vice versa. Participants were told that at some time during the task, the other stimulus would become correct, and that when this happened, they should reverse their responses. Only participants who passed stage 1 (measured by eight consecutive correct responses, see Swainson et al. 2000) were included in the analysis. The ability to acquire the initial stimulus–reward association was measured by the *number of errors* on stage 1. The ability to reverse the acquired stimulus–reward association was measured by the number of c*onsecutive responses to the incorrect stimulus* immediately following the change in stimulus–reward contingencies and was only calculated for participants who passed stage 1. The ability to maintain response set in the face of misleading negative feedback was calculated for each stage (*maintenance error score*) by dividing the number of errors (i.e. responses to the incorrect stimulus) made following attainment of the criterion by the total number of trials that remained following attainment of criterion, provided there were at least ten trials remaining (see Murphy et al. 2003). We also calculated the *probability matching score*, which measures the likelihood that a participant inappropriately switched to the incorrect stimulus after being given misleading negative feedback that his or her correct response on the previous trial was wrong (see Murphy et al. 2003). The probability matching score was calculated by dividing the number of trials on which the participant chose the incorrect stimulus immediately following a negatively reinforced correct response by the total number of correct responses that were negatively reinforced. The probability matching score was calculated separately for each stage.

Participants were also administered Beck Depression Inventory (BDI-II; Beck et al. 1996), which measures the severity of depressive symptoms during the past week, and the Barratt Impulsiveness Scale 11 (BIS-11; Patton et al. 1995), as a measure of self-reported impulsiveness. The National Adult Reading Test (NART; Nelson 1982) was used to provide an estimate of premorbid IQ. Data were unavailable for five participants on the NART (three amphetamine, two ex-drug user) and for seven participants on the BIS-11 (four amphetamine, two opiates, one ex-drug user).

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 13 (SPSS, Ltd.). In preparation for parametric analyses, BDI total scores, BIS-11 scores, years of drug abuse and performance scores and latency data on the PROB task were square-root transformed before analysis to reduce skew (Howell 1997); however, for clarity, untransformed data are presented in the tables and figures. One-way analysis of variance (ANOVA) was used to explore group differences in age, verbal IQ, depression and impulsivity. Sub-scales of the BIS-11, attention, motor and non-planning impulsivity were analyzed using multivariate ANOVA. Handedness, gender and pass rates on the PROB task were analyzed using Fisher exact procedure. Perseverative response data were analyzed using univariate analysis of covariance (ANCOVA). Error, latency and probability matching score data were analyzed using repeated-measures ANCOVA with stage (two levels) as the within-subject factor and group (five levels) as the between-subjects factor. Post hoc comparisons were thresholded at level $p < 0.05$ and conducted using Tukey's test if variances were equivalent between groups or the Tamhane procedure if variances differed between groups. Post hoc analysis included covariates only where a main effect of the covariate was identified in the initial ANCOVA, in which case the least significant difference (LSD) test was used. Pearson correlations were two-tailed, and $p < 0.01$ was considered significant to correct for multiple comparisons.

Results

Group characteristics

Demographic characteristics are displayed in Table 2. The groups did not differ with regard to verbal IQ ($F_{4,142} = 1.64$, $p = 0.167$) or handedness (Fisher's exact: $p = 0.712$). The gender distribution differed significantly between the groups (Fisher's exact: $p = 0.031$). Since men made marginally more errors on stage 1 than women ($t_{142} = 1.93$, $p = 0.056$) and also significantly more errors on stage 2 ($t_{128.2} = 2.58$, $p = 0.011$), gender was entered as a covariate into the analysis of error data. The groups also differed with respect to age ($F_{4,147} = 2.68$, $p = 0.034$), which was due to a trend for ex-drug users to be older than current cocaine users ($p = 0.065$). Age correlated with response latency on stage 1 ($r = 0.030$, $p < 0.01$), and was included as a covariate in the analysis of latency data. The groups also differed with respect to BDI-II total scores ($F_{4,147} = 8.38$, $p < 0.001$). Current drug users scored higher than controls (amphetamine, $p = 0.002$; cocaine, $p = 0.010$; opiates, $p < 0.001$), but the drug-using groups did not differ from each other on the BDI-II. The BDI-II total score showed a trend towards correlating with errors on stage 1 ($r = 0.29$, $p < 0.05$), probability matching score on stage 1 ($r = 0.21$, $p < 0.05$) and maintenance error score on stage 2 ($r = 0.20$, $p < 0.05$) and was included as a covariate in the analysis of these variables. BIS-11 total scores also differed

Table 2 Means and mean total scores (±standard deviation) of descriptive group characteristics and ratio of participants' gender and handedness.

	Controls	Amphetamine	Cocaine	Opiates	Ex-drug
N	27	30	27	42	26
Age (years)	35.1 (8.9)	37.4 (7.4)	32.3 (7.9)	33.8 (7.8)	38.0 (6.5)
Age range (years)	25–56	26–56	20–47	25–49	25–53
Verbal IQ[a] (score)	114.4 (6.5)	111.0 (5.9)	110.7 (7.2)	113.0 (6.0)	113.5 (7.5)
Verbal IQ range	103–124	100–122	93–124	98–124	100–124
Gender (M:F)	14:13	18:12	22:5	33:9	14:12
Handedness (R:L)	25:2	28:2	27:0	40:2	24:2
BDI-II[b]	3.9 (2.9)	11.5 (8.6)	10.9 (10.9)	15.0 (9.9)	8.9 (10.2)
BIS-11[c]	61.5 (8.8)	74.0 (12.3)	76.3 (8.8)	68.1 (7.5)	69.4 (12.5)
Years of drug abuse	–	15.8 (8.9)	8.7 (7.2)	10.8 (8.6)	10.1 (5.3)

[a] Verbal IQ was estimated using the National Adult Reading Test (NART; Nelson 1982)
[b] Beck Depression Inventory II, total score (Beck et al. 1996)
[c] Barratt Impulsiveness Scale 11, total score (Patton et al. 1995)

between the groups ($F_{4,138}$ = 7.41, $p < 0.001$); all current drug users reported significantly higher levels of impulsivity compared with controls (amphetamine, $p = 0.001$; cocaine, $p < 0.001$; opiates, $p = 0.020$). Current cocaine users also rated themselves as being more impulsive than opiate users ($p = 0.002$). This group effect (Wilk's $\lambda = 0.69$, $p < 0.001$) was due to higher scores on the BIS subscales of attention ($F_{4,138}$ = 10.46, $p < 0.001$) and non-planning ($F_{4,138}$ = 5.48, $p < 0.001$). Since the BIS non-planning score correlated with perseverative errors ($r = 0.26$, $p = 0.002$) and BIS-11 total scores showed a trend towards correlating with total errors at stage 2 ($r = 0.17$, $p = 0.043$) and perseverative errors ($r = 0.22$, $p = 0.010$), these were included as covariates in the analysis of error data and perseverative responses, respectively. The drug users also differed with regard to the duration of their drug use ($F_{3,121}$ = 4.87, $p = 0.003$) such that current amphetamine users had taken drugs longer than cocaine users ($p = 0.002$) and opiate users ($p = 0.030$). However, since duration of drug use was not correlated with any outcome measure, it was not included as a covariate in the analysis.

Behavioural data

Although the majority of the participants passed the entire task (controls 96%, amphetamine 77%, opiates 79%, ex-drug users 92%), only 41% of cocaine users completed the task successfully; this difference was significant (Fisher's exact, $p < 0.001$). As shown in Table 3, there was no significant difference on pass rate at stage 1 (Fisher's exact, $p = 0.287$), but the groups differed significantly on pass rate at stage 2 (Fisher's exact, $p < 0.001$). In accordance with previous studies, only participants who passed stage 1 were included into subsequent analysis to ensure that the task's demands had been learned (Swainson et al. 2000).

Analysis of total errors revealed a highly significant overall effect of group ($F_{4,128}$ = 6.46, $p < 0.001$) and a highly significant group × stage interaction ($F_{4,128}$ = 12.50, $p < 0.001$). The groups did not differ with respect to total errors during acquisition of the initial stimulus–reinforcement contingencies ($F_{4,128}$ = 0.971, $p = 0.426$), but cocaine users made significantly more errors at the reversal stage than all the other groups ($F_{4,129}$ = 19.08, $p < 0.001$; post hoc cocaine users vs all groups, $p < 0.001$). Analysis of consecutive responses immediately following the change in reinforcement contingencies (i.e. perseverative errors) revealed a highly significant effect of group ($F_{4,130}$ = 16.62, $p < 0.001$). As shown in Fig. 1, this effect arose from cocaine users making significantly more consecutive perseverative responses than all the other groups ($p < 0.001$ for all groups; effect sizes (Cohen's d) vs cocaine; controls, d = 1.82; amphetamine, d = 1.82; opiates, d = 1.80; ex-drug users, d = 1.79). By contrast, analysis of maintenance error scores revealed neither a main effect of group (F_{4106} = 0.50, $p = 0.461$) nor a group × stage interaction ($F_{4,106}$= 0.67, $p = 0.617$), suggesting that the inflated error rate on stage 2 was not caused by increased sensitivity to misleading negative feedback. Similarly, analysis of the probability matching scores revealed neither a main effect of group ($F_{4,126}$ = 0.60, $p = 0.661$) nor a group × stage interaction ($F_{4,126}$ = 0.86, $p = 0.489$), further supporting the finding that the elevated error rate on stage 2 in the cocaine users was caused by an inability to adapt to a change in reward contingencies. All effects of covariates were non-significant in the above analyses, suggesting that the elevated perseverative responding identified in the cocaine users was not confounded by depression, impulsivity or gender balance.

In view of the fact that only 41% of the cocaine users passed stage 2, we excluded all participants from the analysis

Table 3 Mean (±standard deviation) of main task measures per group

	Control	Amphetamine	Cocaine	Opiates	Ex-drug
Pass rate stage 1[a] (reward-association learning; %)	100	87	96	95	92
Pass rate stage 2[b] (reversal-learning; %)	96	89	41	83	100
Number of errors at stage 1	1.5 (2.8)	2.2 (2.2)	2.0 (2.7)	3.0 (4.2)	1.3 (2.1)
Number of errors at stage 2	6.0 (4.2)	7.7 (7.8)	22.4 (14.4)	8.4 (6.9)	5.3 (3.6)
Latency stage 1 (ms)	993.6 (436.4)	1,016.4 (436.3)	1,051.3 (490.3)	1,056.6 (414.5)	818.4 (287.1)
Latency stage 2 (ms)	890.3 (370.6)	971.5 (427.5)	1,030.9 (561.0)	1,101.1 (627.0)	790.1(351.6)
Probability matching score (stage 1)	0.07 (0.13)	0.10 (0.15)	0.03 (0.08)	0.11 (0.13)	0.07 (0.10)
Probability matching score (stage 2)	0.16 (0.11)	0.17 (0.17)	0.21 (0.30)	0.22 (0.26)	0.11 (0.10)
Maintenance error score (stage 1)	0.03 (0.06)	0.05 (0.07)	0.06 (0.08)	0.07 (0.13)	0.02 (0.05)
Maintenance error score (stage 2)	0.02 (0.06)	0.03 (0.06)	0.06 (0.08)	0.04 (0.08)	0.04 (0.09)
Number of consecutive perseverative responses (total)	3.2 (3.0)	4.0 (7.1)	17.8 (16.0)	3.6 (2.8)	3.2 (2.1)
Number of consecutive perseverative responses (pass stage 2 only)	3.3 (3.0)	2.6 (1.3)	5.7 (3.3)	3.2 (2.0)	3.2 (2.1)

Only participants who passed stage 1 were included in the analysis of task performance.
[a] All participants
[b] Provided that stage 1 was passed

who failed stage 2 to investigate whether cocaine users who eventually reached criterion at stage 2 also showed increased perseveration. Again, there was a significant effect of group on perseverative responses amongst volunteers who passed stage 2 ($F_{4,105} = 3.20$, $p = 0.016$). Post hoc analysis revealed a significantly higher number of perseverative errors, even in those cocaine users who passed on stage 2, compared to all the other groups (controls, $p = 0.043$, $d = 0.92$; ex-drug users, $p = 0.044$, $d = 0.89$; amphetamines, $p = 0.007$, $d = 1.27$; opiates, $p = 0.035$, $d = 1.06$).

Analysis of latency data revealed a main effect of group ($F_{4,136} = 2.77$, $p = 0.030$) but no significant group × stage interaction ($F_{4,135} = 0.96$, $p = 0.434$). There was also a significant main effect of age, which was entered as a covariate ($F_{1,136} = 9.00$, $p = 0.003$). The main effect of group was due to ex-drug users responding significantly faster than opiate users (LSD $p = 0.002$) and cocaine users (LSD $p = 0.010$).

To confirm that these findings were not confounded by current abuse of alcohol or use of other illicit substances, we performed supplementary analyses on perseveration scores excluding those individuals currently abusing alcohol and those currently using ecstasy and hallucinogens in separate ANOVAs. All contrasts remained significant, providing further support that the impairment observed on reversal-learning in cocaine users was specifically due to chronic cocaine use.

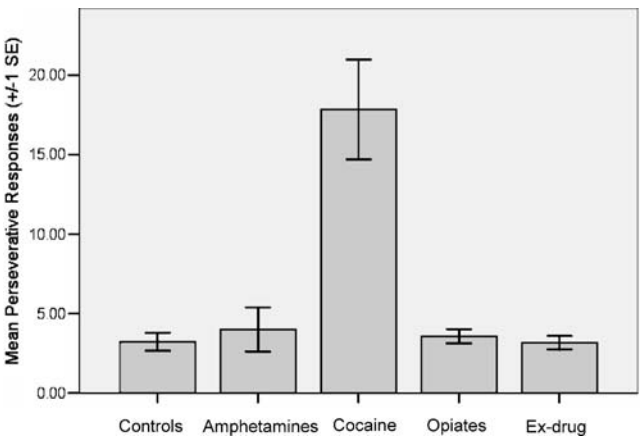

Fig. 1 Consecutive incorrect responses immediately following the change in reward contingencies, regardless whether stage 2 was completed successfully. Chronic cocaine users were relatively insensitive to changes in reward contingencies, showing significantly elevated perseverative responding to the previously rewarded stimulus when the reinforcement contingencies changed (compared with all the groups $p<0.001$)

Discussion

We investigated probabilistic reversal-learning in chronic amphetamine users, chronic cocaine users, chronic opiate users, former drug users of stimulants and opiates and healthy, non-drug using controls volunteers. As hypothesised and in keeping with findings in experimental animals chronically treated with cocaine (Jentsch et al. 2002; Schoenbaum et al. 2004), our sample of chronic cocaine users was severely impaired in probabilistic reversal learning due to significant perseverative responding to the previously rewarded stimulus (see Fig. 1). This perseveration of cocaine users appeared to be related to the motivational properties of the stimuli; since the location of the stimuli changed on every trial, we can rule out the possibility that it was related to motor perseveration. Elevated response perseveration was also observed in cocaine users who passed the reversal stage, suggesting that this response pattern is not restricted to a subgroup of chronic users of cocaine. We also assessed whether participants inappropriately switched to the incorrect stimu-

lus after being given misleading negative feedback, but the incorrect negative feedback had little effect on participants' choices. Furthermore, the acquisition of the initial reward association was not impaired in cocaine users, and all participants demonstrated the ability to maintain an acquired response in the presence of degraded feedback. This detailed analysis of error pattern suggests that the poor performance by cocaine users during the reversal stage was due to an inability to adjust responses to changes in reward contingencies, leading to perseverative responding.

Although amphetamine and cocaine both belong to the class of psychostimulant drugs and their reinforcing effects have been considered as similar (Peltier et al. 1996), task performance on the PROB task was strikingly divergent between the two stimulant user groups. This seems particularly surprising in light of accumulating evidence from experimental animal studies, indicating that stimulant drugs such as *d*-amphetamine can induce perseverative responses and response-reversal impairment (e.g. Ridley et al. 1981a). The reasons why task performance in the two stimulant user groups was so different in the present study may lie in the distinct pharmacological profiles of these two substances.

Both cocaine and amphetamine enhance monoaminergic neurotransmission, either by blockade of re-uptake or by directly releasing monoamines (Johanson and Fischman 1989; Seiden et al. 1993). However, the two substances differ in their affinity for the individual monoaminergic transporters. Thus, amphetamine has the highest affinity for dopamine (DA) and noradrenaline (NA) transporters (White and Kalivas 1998), and acute administration results in a tenfold increase in extracellular DA concentration in the nucleus accumbens (Di Chiara and Imperato 1988). However, amphetamine has a relatively low affinity for the serotonin (5-HT) transporter (White and Kalivas 1998), and acute administration only increases extracellular levels of 5-HT when administered in very high doses (Kuczenski and Segal 1997). Indeed, it has been questioned whether the high dose regimens of amphetamine treatment that are frequently used in experimental animal research to elicit neurotoxic effects actually reflect the pattern of use in humans (Segal et al. 2003). Cocaine, by contrast, has a fivefold lower affinity for the DA transporter than for the 5-HT transporter (White and Kalivas 1998), and its affinity for the NA transporter is lower still (White and Kalivas 1998). Furthermore, blockade of the 5-HT transporter abolishes cocaine-induced increases in regional cerebral blood flow (Howell et al. 2002). It has also been suggested that chronic cocaine exposure significantly dysregulates the 5-HT system (Filip et al. 2005). In light of the selective impairment in response reversal identified in experimental monkeys following 5-HT depletion in the prefrontal cortex (Clarke et al. 2004), one may speculate whether the specific action of cocaine on the 5-HT system might account for the observed response perseveration in chronic cocaine users. However, despite the convincing evidence from animal experiments, the effect of 5-HT depletion on response reversal requires further investigation in humans, given the inconsistent findings from studies employing the acute tryptophan-depletion technique, an experimental procedure that reduces central 5-HT levels (Evers et al. 2005).

Our findings are consistent with those of Fillmore and Rush (2006) in polydrug users consuming mainly cocaine and alcohol, who also showed significant impairments in reversal learning and elevated perseverative responding. In fact, our findings demonstrate that chronic cocaine consumption alone, and not only in combination with alcohol, can produce this pattern of deficit on reversal-learning tasks. Fillmore and colleagues suggested that an impairment in reversal-learning might reflect an impairment in the suppression of prepotent responses. Impairments on tests tapping response inhibition have previously been demonstrated in both chronic amphetamine and cocaine users, for example, the stop-signal task (Fillmore and Rush 2002; Monterosso et al. 2005) which is modulated by noradrenergic but not serotonergic neurotransmission (Chamberlain et al. 2006; Clark et al. 2005). Behaviour on the PROB task, by contrast, is sensitive to serotonergic modulation (Chamberlain et al. 2006; Evers et al. 2005). We therefore hypothesise that the different pharmacological actions of cocaine and amphetamine on the central 5-HT system account for the divergent task performance between the two stimulant user groups on probabilistic reversal learning. However, further research that includes either assessment or modulation of serotoninergic function in cocaine users during reversal learning is needed to further investigate this possibility.

Our findings are also consistent with contemporary theoretical models of the role of 5-HT in reinforcement learning. It has been suggested that 5-HT complements the role of DA during learning (Daw et al. 2002), such that DA is implicated in generating a prediction error for reward (Schultz et al. 1997) and 5-HT for punishment (Daw et al. 2002). In the context of this theory, assuming that 5-HT function was significantly dysregulated in the cocaine users, it is possible that our cocaine users were unable to develop a prediction error for punishment and therefore failed in adjusting their behaviour to a change in reinforcement contingencies. However, since reward and punishment are not independent in the PROB task, it is not possible to unequivocally conclude that the deficit we observed was due to impaired punishment signalling.

Although we have argued that the deficit we observed on response reversal was mediated by 5-HT dysfunction, we have to acknowledge that there is also evidence from experimental animal studies showing impairment in reversal following experimental modulation of DA (Lee et al. 2007; Ridley et al. 1981b). However, the experimental conditions in which the animals were tested are different from the

present study. Thus, D2-receptor blockade only impairs response reversal reliably when performance is tested *with* a retention session just before the reversal trial (Lee et al. 2007), which might plausibly be related to the important role of DA in working memory (Arnsten 1998). By contrast, response reversal in the PROB task is required immediately after the change in response contingencies, and therefore, task performance may be less susceptible to dopaminergic modulation. However, it must be acknowledged that the performance profile in our cocaine user group was remarkably similar to impairments previously observed on the PROB task in patients with Huntington's disease (Lawrence et al. 1999), a neurological disorder characterised by pronounced atrophy of the putamen and caudate nucleus (Graveland et al. 1985). In light of the different striato-cortical dopaminergic projections of the dorsal and ventral part of the striatum to the dorsolateral prefrontal and orbitofrontal cortex, respectively, it has been suggested that the dorsal-to-ventral progression of cell loss in the striatum may account for the reversal impairment observed in patients with Huntington's disease at a relatively late stage of the disease (Lange et al. 1995). In this regard, it is of note that progressive alteration in the structure of the striatum is also thought to play an important role in the development of drug addiction, albeit in the opposite direction to that in Huntington's disease. It has been suggested that the transition from recreational drug use, motivated by the anticipation of the pleasurable effects of the drug, to habitual drug-taking and finally to compulsive drug-seeking behaviour is reflected in a progression from ventral-to-dorsal striatal involvement (see, for review, Everitt and Robbins 2005). In light of evidence from experimental animals showing that the initial cocaine exposure leads to a decrease in glucose metabolism in the ventral striatum and in the orbitofrontal cortex (OFC; Lyons et al. 1996; Porrino and Lyons 2000; Porrino et al. 2007), future studies should investigate whether perseverative responding during reversal learning can be identified in cocaine users who have not yet entered the cocaine-addiction cycle.

The absence of reversal deficits in amphetamine users may seem surprising, in particular in light of evidence suggesting lower relative regional metabolism in the OFC in recently abstinent methamphetamine users (London et al. 2004). Therefore, it is important to bear in mind that our participants were abusing *d*-amphetamine, which is widely abused in Europe, while in America and Asia, the abuse of methamphetamine is more prominent (United Nations Office on Drugs and Crime 2007). This structural difference of amphetamine is potentially important, given the evidence indicating that methamphetamine is more potent than *d*-amphetamine in releasing 5-HT (Kuczenski et al. 1995; Peat et al. 1985). It has even been suggested that large doses of methamphetamine may result in long-term depletion of 5-HT levels, an effect not seen, however, following *d*-amphetamine administration (Ricaurte et al. 1983). Recent neuroimaging research in humans supports this view, as the density of serotonin transporters in various brain areas, including the orbitofrontal cortex, is significantly reduced in recreational methamphetamine users (Sekine et al. 2006). However, a systematic investigation of whether these differences between *d*-amphetamine and methamphetamine in effects on 5-HT neurotransmission found in experimental animals are generalisable to humans is nevertheless warranted. Despite the fact that polydrug use across the groups was reasonably balanced and the exclusion of individuals currently abusing alcohol, ecstasy and hallucinogens did not alter the results, we cannot rule out any long-term effects on the 5-HT system of past drug abuse. This may particularly be relevant in light of the ongoing discussion of ecstasy-induced serotonergic neurotoxicity in humans (Gouzoulis-Mayfrank and Daumann 2006; Lyvers 2006) and evidence suggesting that even recreational use of ecstasy may entail prolonged effects on brain function (De Win et al. 2007).

Although the deficit in reversal-learning that we identified in cocaine users is striking, some limitations of our study must be acknowledged. Firstly, although we assessed substance dependence according to the DSM-IV criteria, we did not specifically evaluate the severity of dependence either by structured interview (McLellan et al. 1992) or by self-report measures (Gossop et al. 1995). Therefore, we cannot rule out the possibility that our groups differed in the severity of their substance abuse. Secondly, details about last drug intake were not recorded, which could have provided us with information of whether participants were performing the PROB under the current effect of the drug. Accumulating evidence from experimental animal studies suggests that acute administration of cocaine impairs reversal learning (Jentsch et al. 2002) as does amphetamine when injected into the ventral striatum (Annett et al. 1983). However, recent studies in human cocaine users have shown some intriguing exceptions for effects on response inhibition paradigms, as cocaine users' performance may improve under the acute influence of cocaine (Fillmore et al. 2006; Garavan et al. 2005 and personal communication). Although we did not record the time of last drug intake, we did analyse urine samples for evidence of undeclared drugs before testing. Except for one urine sample, all current drug users tested positive for their drug of dependence; indicating that cocaine or amphetamine had been consumed within the last 72h (U.K.Department of Health 1999). The relatively short half-life of cocaine of 40–60min (Johanson and Fischman 1989) compared with the half-life of amphetamines of 6–12h (de la Torre et al. 2004) may raise the question whether cocaine users were undergoing early withdrawal during the testing session which might have affected their task performance. Stimulant withdrawal is

characterized by a cluster of depression-related symptoms, particularly during the first days of abstinence (McGregor et al. 2005; Sofuoglu et al. 2005). Although we did not specifically examine stimulant withdrawal symptoms before testing, we however assessed depressed mood using the BDI-II, and we did not find significant differences in depression scores between the three current drug-using groups. This suggests that depressed mood, which could reflect symptoms of stimulant withdrawal, is unlikely to have accounted for differences in performance.

Finally, since we did not include tests other than the PROB in this study, we were unable to assess to what extent deficits on different cognitive processes, for example working memory, procedural memory or inhibitory control, might have impacted on the profound deficits apparent in the cocaine users. Future studies of reversal-learning in cocaine users should employ such measures to help elucidate the cognitive mechanisms underpinning the deficit in reversal-learning we identified.

In summary, we investigated the ability to adapt behaviour according to changes in reward contingencies using a probabilistic reversal-learning task. We found that chronic cocaine users were insensitive to changes in reward contingencies, showing marked perseveration to the previously rewarded stimulus. The size of this effect is striking given that these findings were not confounded by depression, impulsivity, duration of drug use, co-morbid alcohol abuse, current use of other illicit substances or gender balance. Task performance in amphetamine, opiate users and former drug users was not measurably impaired. These data suggest that chronic cocaine use specifically results in a significant impairment in adjusting behaviour during changing reinforcement contingencies, which may partly account for maladaptive behaviour seen in chronic cocaine users.

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References

Annett LE, Ridley RM, Gamble SJ, Baker HF (1983) Behavioral effects of intracerebral amphetamine in the marmoset. Psychopharmacology 81:18–23

Arnsten AFT (1998) Catecholamine modulation of prefrontal cortical cognitive function. Trends Cogn Sci 2:436–447

Beck AT, Steer RA, Brown GK (1996) Manual for Beck Depression Inventory-II. Psychological Corporation, San Antonio, TX, USA

Chamberlain SR, Muller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ (2006) Neurochemical modulation of response inhibition and probabilistic learning in humans. Science 311:861–863

Clark L, Roiser JP, Cools R, Rubinsztein DC, Sahakian BJ, Robbins TW (2005) Stop signal response inhibition is not modulated by tryptophan depletion or the serotonin transporter polymorphism in healthy volunteers: implications for the 5-HT theory of impulsivity. Psychopharmacology 182:570–578

Clarke HF, Dalley JW, Crofts HS, Robbins TW, Roberts AC (2004) Cognitive inflexibility after prefrontal serotonin depletion. Science 304:878–880

Cools R, Clark L, Owen AM, Robbins TW (2002) Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. J Neurosci 22:4563–4567

Daw ND, Kakade S, Dayan P (2002) Opponent interactions between serotonin and dopamine. Neural netw 15:603–616

de la Torre R, Farre M, Navarro M, Pacifici R, Zuccaro P, Pichini S (2004) Clinical pharmacokinetics of amfetamine and related substances—monitoring in conventional and non-conventional matrices. Clin pharmacokinet 43:157–185

De Win MML, Reneman L, Jager G, Vlieger EJP, Olabarriaga SD, Lavini C, Bisschops I, Majoie CBLM, Booij J, den Heeten GJ, Van den Brink W (2007) A prospective cohort study on sustained effects of low-dose ecstasy use on the brain in new ecstasy users. Neuropsychopharmacology 32:458–470

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

Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci 8:1481–1489

Evers EAT, Cools R, Clark L, van der Veen FM, Jolles J, Sahakian BJ, Robbins TW (2005) Serotonergic modulation of prefrontal cortex during negative feedback in probabilistic reversal learning. Neuropsychopharmacology 30:1138–1147

Filip M, Frankowska M, Zaniewska M, Golda A, Przegalinski E (2005) The serotonergic system and its role in cocaine addiction. Pharmacol Rep 57:685–700

Fillmore MT, Rush CR (2002) Impaired inhibitory control of behavior in chronic cocaine users. Drug Alcohol Depend 66:265–273

Fillmore MT, Rush CR (2006) Polydrug abusers display impaired discrimination-reversal learning in a model of behavioural control. J Psychopharmacol 20:24–32

Fillmore MT, Rush CR, Hays L (2006) Acute effects of cocaine in two models of inihibitory control: implications of non-linear dose effects. Addiction 101:1323–1332

Forman SD, Dougherty GG, Casey BJ, Siegle GJ, Braver TS, Barch DM, Stenger VA, Wick-Hull C, Pisarov LA, Lorensen E (2004) Opiate addicts lack error-dependent activation of rostral anterior cingulate. Biol Psychiat 55:531–537

Garavan H, Lingford-Hughes A, Jones T, Morris P, Rothwell J, Williams S (2005) Overview of the application of functional neuroimaging to studying addiction: with particular reference to cognitive neuroscience investigations. UK Government Foresight Report.

Gossop M, Darke S, Griffiths P, Hando J, Powis B, Hall W, Strang J (1995) The severity of dependence scale (SDS): Psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. Addiction 90:607–614

Gouzoulis-Mayfrank E, Daumann J (2006) Neurotoxicity of methylenedioxyamphetamines (MDMA; ecstasy) in humans: how strong is the evidence for persistent brain damage. Addiction 101:348–361

Graveland GA, Williams RS, Difiglia M (1985) Evidence for degenerative and regenerative changes in neostriatal spiny neurons in Huntingtons-disease. Science 227:770–773

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

Hornak J, O'Doherty J, Bramham J, Rolls ET, Morris RG, Bullock PR, Polkey CE (2004) Reward-related reversal learning after surgical excisions in orbito-frontal or dorsolateral prefrontal cortex in humans. J cogn neurosci 16:463–478

Howell DC (1997) Statistical methods for psychology. Duxbury, London

Howell LL, Hoffman JM, Votaw JR, Landrum AM, Wilcox KM, Lindsey KP (2002) Cocaine-induced brain activation determined by positron emission tomography neuroimaging in conscious rhesus monkeys. Psychopharmacology 159:154–160

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

Jentsch JD, Olausson P, De La Garza IR, Taylor JR (2002) Impairments of reversal learning and response perseveration after repeated, intermittent cocaine administrations to monkeys. Neuropsychopharmacology 26:183–190

Johanson CE, Fischman MW (1989) The pharmacology of cocaine related to its abuse. Pharmacol Rev 41:3–52

Kaufman JN, Ross TJ, Stein EA, Garavan H (2003) Cingulate hypoactivity in cocaine users during a GO–NOGO task as revealed by event-related functional magnetic resonance imaging. J Neurosci 23:7839–7843

Kuczenski R, Segal DS, Cho AK, Melega W (1995) Hippocampus norepinephrine, caudate dopamine and serotonin, and behavioral responses to the stereoisomers of amphetamine and methamphetamine. J Neurosci 15:1308–1317

Kuczenski R, Segal DS (1997) Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. J Neurochem 68:2032–2037

Lange KW, Sahakian BJ, Quinn NP, Marsden CD, Robbins TW (1995) Comparison of executive and visuospatial memory function in Huntington's disease and dementia of Alzheimer type matched for degree of dementia. J Neurol Neurosurg Psychiatry 8:598–606

Lawrence AD, Sahakian BJ, Rogers RD, Hodges JR, Robbins TW (1999) Discrimination, reversal, and shift learning in Huntington's disease: mechanisms of impaired response selection. Neuropsychologia 37:1359–1374

Lee B, Groman S, London ED, Jentsch JD (2007) Dopamine D2/D3 dopamine receptors play a specific role in reversal of a learned visual discrimination in monkeys. Neuropsychopharmacology 32 (10):2125–2134

Lee TMC, Zhou WH, Luo XJ, Yuen KSL, Ruan XZ, Weng XC (2005) Neural activity associated with cognitive regulation in heroin users: a fMRI study. Neurosci lett 382:211–216

London ED, Simon SL, Berman SM, Mandelkern MA, Lichtman AM, Bramen J, Shinn AK, Miotto K, Learn J, Dong Y, Matochik JA, Kurian V, Newton T, Woods R, Rawson R, Ling W (2004) Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. Arch Gen Psychiatry 61:73–84

Lyons D, Friedman DP, Nader MA, Porrino LJ (1996) Cocaine alters cerebral metabolism within the ventral striatum and limbic cortex of monkeys. J Neurosci 16:1230–1238

Lyvers M (2006) Recreational ecstasy use and the neurotoxic potential of MDMA: current status of the controversy and methodological issues. Drug Alcohol Rev 25:269–276

McGregor C, Srisurapanont M, Jittiwutikarn J, Laobhripatr S, Wongtan T, White JM (2005) The nature, time course and severity of methamphetamine withdrawal. Addiction 100:1320–1329

McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M (1992) The fifth edition of the addiction severity index. J Subst Abuse Treat 9:199–213

Monterosso JR, Aron AR, Cordova X, Xu J, London ED (2005) Deficits in response inhibition associated with chronic methamphetamine abuse. Drug Alcohol Depend 79:273–277

Murphy FC, Michael A, Robbins TW, Sahakian BJ (2003) Neuropsychological impairment in patients with major depressive disorder: the effects of feedback on task performance. Psychol Med 33:455–467

Nelson HE (1982) National adult reading test manual. NFER-Nelson, Windsor (UK)

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

Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt Impulsiveness Scale. J Clin Psychol 51:768–774

Peat MA, Warren PF, Bakhit C, Gibb JW (1985) The acute effects of methamphetamine, amphetamine and *p*-chloroamphetamine on the cortical serotonergic system of the rat brain: evidence for differences in the effects of methamphetamine and amphetamine. Eur j pharmacol 116:11–16

Peltier RL, Li DH, Lytle D, Taylor CM, Emmett-Oglesby MW (1996) Chronic *d*-amphetamine or methamphetamine produces cross-tolerance to the discriminative and reinforcing stimulus effects of cocaine. J Pharmacol Exp Ther 277:212–218

Porrino LJ, Lyons D (2000) Orbital and medial prefrontal cortex and psychostimulant abuse: studies in animal models. Cereb Cortex 10:326–333

Porrino LJ, Smith HR, Nader MA, Beveridge TJR (2007) The effects of cocaine: a shifting target over the course of addiction. Prog neuro-psychopharmacol biol psychiatry 31:1593–1600

Ricaurte GA, Fuller RW, Perry KW, Seiden LS, Schuster CR (1983) Fluoxetine increases long-lasting neostriatal dopamine depletion after administration of *d*-methamphetamine and *d*-amphetamine. Neuropharmacology 22:1165–1169

Ridley RM, Haystead TAJ, Baker HF (1981a) An analysis of visual object reversal-learning in the marmoset after amphetamine and haloperidol. Pharmacol Biochem Behav 14:345–351

Ridley RM, Haystead TAJ, Baker HF (1981b) An analysis of visual object reversal learning in the marmoset after amphetamine and haloperidol. Pharmacol Biochem Behav 14:345–351

Rolls ET (2000) The orbitofrontal cortex and reward. Cereb Cortex 10:284–294

Rolls ET, Hornak J, Wade D, Mcgrath J (1994) Emotion-related learning in patients with social and emotional changes associated with frontal-lobe damage. J Neurol Neurosurg Psychiatry 57:1518–1524

Schoenbaum G, Saddoris MP, Ramus SJ, Shaham Y, Setlow B (2004) Cocaine-experienced rats exhibit learning deficits in a task sensitive to orbitofrontal cortex lesions. Eur J Neurosci 19:1997–2002

Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. Science 275:1593–1599

Segal DS, Kuczenski R, O'Neil ML, Melega WP, Cho AK (2003) Escalating dose methamphetamine pretreatment alters the behavioral and neurochemical profiles associated with exposure to a high-dose methamphetamine binge. Neuropsychopharmacology 28:1730–1740

Seiden LS, Sabol KE, Ricaurte GA (1993) Amphetamine: effects on catecholamine systems and behavior. Annu Rev Pharmacol Toxicol 33:639–676

Sekine Y, Ouchi Y, Takei N, Yoshikawa E, Nakamura K, Futatsubashi M, Okada H, Minabe Y, Suzuki K, Iwata Y, Tsuchiya KJ, Tsukada H,

Iyo M, Mori N (2006) Brain serotonin transporter density and aggression in abstinent methamphetamine abusers. Arch Gen Psychiatry 63:90–100

Sofuoglu M, Dudish-Poulsen S, Poling J, Mooney M, Hatsukami DK (2005) The effect of individual cocaine withdrawal symptoms on outcomes in cocaine users. Addict Behav 30:1125–1134

Swainson R, Rogers RD, Sahakian BJ, Summers BA, Polkey CE, Robbins TW (2000) Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. Neuropsychologia 38:596–612

U.K.Department of Health (1999) Drug misuse and dependence—guidelines on clinical management. The Stationery Office, Norwich,UK

United Nations Office on Drugs and Crime (2007) World drug report 2007. United Nations Office on Drugs and Crime (UNODC), New York, NY, USA

Verdejo-Garcia AJ, Lopez-Torrecillas F, Aguilar de Arcos F, Perez-Garcia M (2005) Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: A multiple regression analysis. Addict Behav 30:89–101

Verdejo-Garcia AJ, Perales JC, Perez-Garcia M (2007) Cognitive impulsivity in cocaine and heroin polysubstance abusers. Addict Behav 32:950–966

White FJ, Kalivas PW (1998) Neuroadaptations involved in amphetamine and cocaine addiction. Drug Alcohol Depend 51:141–153