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Cognitive Sequelae of Intravenous Amphetamine Self-Administration in Rats: Evidence for Selective Effects on Attentional Performance

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Characterizing the nature and severity of cognitive deficits associated with chronic stimulant abuse may provide new insights into the neural substrates of drug addiction because such deficits may contribute to the chronic relapsing nature of compulsive drug use. This investigation examines in rats the long-term cognitive consequences of intravenously self-administered amphetamine, specifically on performance of a 5-choice serial reaction time task (5-CSRTT), which assesses visuo-spatial attention and impulsivity. Rats experienced 5 days of intravenous (i.v.) amphetamine self-administration and were then withdrawn for a period of 9 days, during which time testing on the 5-CSRTT took place. This was repeated on five consecutive occasions for a period of 10 weeks. Controls experienced identical training on the 5-CSRTT but during the self-administration sessions received yoked i.v. infusions of normal saline. The results reveal a selective and reproducible pattern of deficits on the 5-CSRTT following repeated withdrawal from amphetamine self-administration, with deleterious effects on the speed and accuracy of responding as well as increased omission errors. Premature (impulsive) responding, perseveration, and food consumption latencies were not significantly affected. Deficits in attentional performance fully recovered 4–5 days after amphetamine cessation and there was no evidence of any long-term disturbances, even when the attentional load was increased. However, following a 2-month abstinence period, abnormalities in the subsequent effects of acute noncontingent amphetamine were found, with increased omissions, slower response times, and reduced impulsivity. Thus, contingent i.v. amphetamine administration has both short- and long-term consequences, which may be relevant to the complex disturbances that accompany drug addiction.

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INTRODUCTION

It is becoming widely recognized that one of the major consequences of the long-term use of amphetamine and other psychomotor stimulants (eg, methamphetamine and cocaine) is impaired neuropsychological functioning, including effects on attentional control, decision-making, planning, and spatial working memory (O'Malley *et al*, 1992; Berry *et al*, 1993; Rosselli and Ardila, 1996; Bolla *et al*, 1999; Rogers *et al*, 1999; Ornstein *et al*, 2000). What is less clear, however, is whether such impairments persist over months of abstinence and whether they contribute in any direct way to the chronic relapsing nature of compulsive drug addiction. The issue of whether or not human addicts continue to display neurocognitive disturbances following acute abstinence is especially pertinent in light of research indicating persistent alterations in striatal D2 receptor function and metabolic activity in several regions of the frontal lobe, including the orbitofrontal cortex and cingulate gyri in detoxified cocaine addicts (Volkow *et al*, 1993, 1997). However, for a number of reasons, identifying a causal relationship between drug abuse and subsequent neuropsychological impairment has proved elusive. For example, research in human drug addicts is often hampered by variable drug histories, including amount and frequency of drug use, polydrug abuse, duration of abstinence, and the confounding effects of remediative drug treatment (Rogers and Robbins, 2001). Moreover, because most studies are conducted in long-term drug addicts, it is usually difficult to chart the development and progression of neurocognitive

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decline in experienced users, which also allows a consideration of their cognitive capabilities prior to drug abuse.

In this respect, animal models of drug addiction offer an attractive alternative because the drug experience and premorbid capabilities of each subject can be tightly controlled in relation to subsequent cognitive and behavioral assessment. Unfortunately, however, for studies of this type it is frequently the case that the experimenter, not the subject, controls the rate and pattern of drug administration. While there is ample evidence to suggest that the noncontingent (ie, experimenter delivered) administration of amphetamine impairs various attentional functions, including latent inhibition (Weiner *et al*, 1988), prepulse inhibition of the acoustic startle response (Mansbach *et al*, 1988), sustained (Deller and Sarter, 1998; Kondrad and Burk, 2004), and selective (Crider *et al*, 1982) attention, it is simply unknown whether these effects are relevant to the types of deficit that might follow the response-contingent self-administration of amphetamine. Indeed, similar problems arise with the notion of a causal relationship between psychostimulant use and increased impulsivity (Jentsch and Taylor, 1999; Paine *et al*, 2003), again because much of the supporting evidence is based on the noncontingent administration of addictive drugs.

It is also poorly understood whether the long-term self-administration of amphetamine and other drugs of abuse produces persistent alterations in cognitive and behavioral function that extend beyond the acute abstinence phase. In a recent investigation, Udo *et al* (2004) established that certain forms of learning are susceptible to disruption by prior intravenous (i.v.) cocaine self-administration, namely the acquisition of a conditioned cue preference task. However, because testing was carried out at a time when animals were still under the influence of cocaine, the inferences that can be drawn from these data on the longer-term effects of cocaine on learning and memory and other cognitive processes remain unclear. Moreover, it has not been established whether prolonged i.v. drug self-administration also affects behavior that has already been acquired.

In the present investigation, we addressed these issues by evaluating the cognitive and behavioral effects of i.v. amphetamine self-administration, both after acute withdrawal and again following a relatively prolonged period of abstinence, using a 5-choice serial reaction time task (5-CSRTT), which assesses visuo-spatial attention and impulsivity (Carli *et al*, 1983; Robbins, 2002). It is known that different aspects of performance on this task can be dissociated by selective excitotoxic lesions of the medial and orbitofrontal prefrontal cortices (Muir *et al*, 1996; Chudasama *et al*, 2003), as well as systemic and central manipulations of the ascending cholinergic and monoaminergic systems (for a review, see Robbins, 2002). Since the monoaminergic neuromodulatory systems are the primary targets of amphetamine (Wise, 1996), it was hypothesized that the 5-CSRTT would be a particularly appropriate task to investigate potential disturbances in cognitive functions that are known to be modulated by monoaminergic transmission in the prefrontal cortex (PFC) and associated striatal structures that underlie task performance (Robbins, 2002).

Subjects experienced five consecutive days of i.v. amphetamine self-administration before being withdrawn for 24 h and tested on the 5-CSRTT over the course of 9 days. Performance deficits on the 5-CSRTT were compared against a control group of animals that received 'yoked' infusions of normal saline. This pattern of i.v. self-administration followed by behavioral testing on the 5-CSRTT continued for 10 weeks. To examine whether longer-term deficits occurred after i.v. amphetamine self-administration, subjects were subsequently tested on the 5-CSRTT after a 2-month abstinence period with various behavioral manipulations being used to increase the attentional requirements of the task. Challenge sessions included reducing the stimulus duration, in addition to presenting the stimuli either more frequently over a large number of trials, or in a temporally unpredictable fashion (Parasuraman and Giambra, 1991). Finally, as a further challenge, noncontingent amphetamine was administered to determine whether prior amphetamine exposure affected the subsequent behavioral effects of this compound, which have been widely characterized on the 5-CSRTT after acute administration (Robbins, 2002).

MATERIALS AND METHODS

Subjects

The subjects were 41 male Lister Hooded rats (Charles River, UK), weighing 370–420 g at the time of i.v. surgery. Following surgery, animals were housed individually in a temperature- and humidity-controlled holding room under a 12 h light/dark cycle (lights off at 0730 hours). During behavioral testing, animals were placed on a food-restricted diet (14 g/day, Purina, UK) in order to maintain body weight at roughly 85% of free-feeding weight. All surgical procedures complied with the requirements of the UK Animals (Scientific Procedures) Act of 1986 (Project number 80/1767).

Behavioral Training on the 5-CSRTT

The apparatus consisted of eight 5-choice chambers ($25 \times 25 \times 25$ cm) each housed within a ventilated wooden sound-attenuating box. The rear wall of the chamber was curved with nine contiguous 2.5×2.5 cm apertures, 4-cm deep and set 2 cm above a wire grid floor. A metal insert blocked every alternate hole (ie, holes 1, 3, 5, 7, and 9 were left open). A photocell beam was located at the entrance of each aperture to detect nose-poke responses. A 3 W stimulus light was located at the rear of each the five apertures. On the front of the chamber, a magazine connected to a food dispenser allowed the automatic delivery of 45-mg food pellets (Noyes dustless pellets, Research Diets, UK). Subjects gained access to the food magazine by pushing a hinged Perspex panel monitored by a micro-switch. The apparatus was controlled by software written in Arachnid (Paul Fray Ltd), a real-time extension to BBC Basic V running on an Acorn Archimedes computer.

Subjects were trained on the 5-CSRTT over approximately 10 weeks, with 5–6 daily 30-min sessions each week. In the initial training stage, consisting of two 20-min sessions, 5–10 pellets were placed in the magazine and in each of the

open apertures to encourage the subjects to enter these locations. In subsequent sessions, subjects were trained over approximately 45 sessions to detect the presence of a brief light stimulus (0.5 s in duration) presented at the rear of each aperture. Training was facilitated in the early stages by lengthening the duration of both the visual stimulus and the limited hold period (see Dalley *et al*, 2002 for further details). The limited-hold period marks the interval from the onset of the stimulus to the time available for the subject to respond. A failure to respond within the limited-hold period was deemed an 'omission' and was punished by the house light being extinguished for 5 s and no delivery of food reward. Each test session began with the illumination of the chamber by the house light and the delivery of a food pellet in the magazine. The collection of this pellet by pushing open the magazine panel started the first trial. After a fixed intertrial interval (ITI) of 5 s, a light at the rear of one of the response apertures was briefly illuminated. Responses in this aperture within a limited hold period (5 s) were reinforced by the delivery of a food pellet in the magazine. Responses in a nonilluminated hole were recorded as incorrect responses and were punished by a 5-s time-out period. During this time, the house light was extinguished and no food pellet was delivered. The 'accuracy' of target detection was computed as the percentage of correct responses to the total number of correct and incorrect responses. Additional responses in any aperture prior to food collection ('perseverative responses') were recorded but not punished. Responses made in any aperture before the onset of the target stimulus (ie, ITI responses) were deemed 'premature' and were punished by a 5-s time-out period. Two measures of speed of responding were used. The first measure was latency to respond correctly, defined as the time between the onset of the stimulus and the response. The second measure was latency to collect the food reward, defined as the time between the correct response and the first entry into the magazine. Subjects were considered to have acquired the basic version of the task (ie, stimulus duration of 0.5 s and an ITI of 5 s) when their accuracy was greater than 80% and omissions were fewer than 20%.

Intravenous Catheterization

Subjects were anaesthetized with ketamine (Ketalar, 90 mg/kg i.p.; Vet Drug, Bury St Edmunds, UK) and xylazine (Rompun, 6.7 mg/kg, i.p.; Vet Drug) and implanted with chronic i.v. jugular catheters (manufactured by Brian Fromant, St John's Innovation Centre, Cowley Road, Cambridge, UK), as described previously (Caine *et al*, 1992). The catheter was inserted in the right jugular vein and passed subcutaneously over the right shoulder to exit dorsally between the scapulae. Subjects were given at least 5 days to recover from surgery before being retested on the 5-CSRTT. Animals were run on the 5-CSRTT for 1 week before commencing i.v. self-administration. Catheter patency was maintained by flushing once weekly with 0.1–0.2 ml heparanized saline (30 U/ml 0.9% sterile saline; CP Pharmaceuticals Ltd, Wrexham, UK). I.V. patency was also assessed on a weekly basis by administering a small subanaesthetic dose of ketamine (Vet Drug, UK) via the i.v. line (0.05 ml; 0.5 mg/kg). This test was conducted on the final day of 5-CSRTT testing (ie, 3 days before the next i.v. session) and was deemed satisfactory if subjects exhibited a more-or-less immediate, but brief response to the ketamine challenge, specifically by a change in the respiration rate, a transient loss of the righting reflex and a temporary loss of the corneal blink reflex. Subjects failing this test were recatheterized with a new i.v. catheter in either the right (if viable) or left jugular and allowed a further week in which to recover. Subjects were rejected from the study if a catheter failed on two occasions. At 2 weeks after surgery, the subjects were anaesthetized for a brief period with 2% halothane, delivered via a self-scavenging snout mask (Fluovac, UK), to remove any remaining sutures.

Intravenous Amphetamine Self-Administration

Six operant chambers ($24 \times 20 \times 22$ cm; Med Associates, UK), each contained within a sound-attenuating box with a ventilating fan, were employed in the study. Each chamber contained on the right side wall two 4-cm-wide retractable levers, positioned equidistantly, 10-cm apart and 5-cm from the grid floor. A white stimulus lens was positioned directly above each lever, which was illuminated by a 3 W, 24 V bulb. The whole chamber was illuminated by a 3 W, 24 V house light positioned at the left top corner of the chamber. I.V. infusions of amphetamine or sterile 0.9% normal saline (see below) were delivered by a software-operated infusion pump (Semat Technical Ltd., St Albans, UK) placed outside the sound-attenuating box, through a counterbalanced single channel liquid swivel (Lomir Biomedical Inc., Canada) and flexible tubing (i.d. 0.5 mm, wall thickness 0.5 mm; Altec, Hampshire, UK) enclosed within a metal spring tether. On each day of i.v. self-administration, subjects were connected to the infusion system by clamping the tether to a pedestal mounting on the animal's back. A PC using Whisker Server software (Multimedia edition version 2.3.01) controlled the self-administration apparatus.

Rats were trained to self-administer i.v. amphetamine under a continuous reinforcement schedule (fixed ratio 1; FR1). Lever presses on the active lever resulted in a 0.1-ml infusion delivered over approximately 4 s, the retraction of both levers for 20 s, the extinction of the house light, and the simultaneous illumination of the drug stimulus light above the lever for 20 s. Subjects could make 2–3 additional active lever responses before the lever was retracted but only the first resulted in an i.v. infusion. On completion of the 20-s time-out period, the levers were re-extended into the chamber, the house light was illuminated, and the stimulus light was extinguished. Additional active lever responses resulted in the same sequence of events. Responses on the inactive lever were recorded but had no programmed consequences. Active and inactive levers were assigned randomly to subjects at the start of the study and once selected remained fixed throughout the investigation. The acquisition of i.v. amphetamine self-administration was conducted over five consecutive daily sessions. Each acquisition session consisted of 25 infusions (0.05 mg/infusion, equivalent to roughly 0.12 mg/kg) and a maximum time limit of 5 h. In subsequent postacquisition sessions, the maximum number of amphetamine infusions obtainable in an 8-h session was increased to 75 (0.05 mg/infusion).

Behavioral Design

The basic design of the study involved alternating weeks of i.v. amphetamine self-administration interspersed with behavioral testing on the 5-CSRTT. Upon completion of training on the 5-CSRTT to criterion performance (see above), all subjects were subjected to a further 3 weeks of testing in order to establish a reliable behavioral baseline. In order to increase the sensitivity of the task to detect premature (impulsive) responses, the ITI was increased to 7 s on mid-week Wednesday sessions. Sessions on this day lasted 45 min and consisted of 100 trials. This pattern of testing continued throughout the remaining investigation. All other sessions consisted of 100 trails with stimuli duration and ITIs of 0.5 and 5 s, respectively. After 3 weeks of baseline testing, subjects were randomly assigned to one of two groups, either a control (drug-naïve) group or an amphetamine self-administration group. Baseline data from these two groups was statistically analyzed to ensure that their behavioral performance was evenly matched prior to i.v. surgery.

Control animals received noncontingent yoked infusions of normal 0.9% saline (0.1 ml/infusion), the frequency of which was determined by 'paired' amphetamine self-administering animals that were run at the same time. The number of left and right lever presses was recorded for this control group but their behavior had no programmed consequences. Behavioral testing on the 5-CSRTT commenced 24 h after amphetamine cessation and continued for 7 days. As before, sessions consisted of 100 trials with a stimulus duration and ITI of 0.5 and 5 s, respectively. The ITI was increased to 7 s on the mid-week Wednesday session in order to promote premature responding. Subjects were withdrawn from i.v. amphetamine self-administration on five separate occasions. Thus, the experimental observations were made over approximately 2–3 months.

Behavioral Testing after Prolonged Abstinence from I.V. Amphetamine

The same subjects were evaluated for any long-term deficits on the 5-CSRTT after a 2-month withdrawal period from i.v. amphetamine self-administration. Initially, rats were run on the task for five sessions using the standard training parameters (ie, stimulus duration 0.5 s, ITI 5 s) to re-establish baseline performance. Subsequent sessions involved three behavioral challenges, each separated by a standard baseline session. The challenges used included reduced stimulus duration (0.125 s, 100 trials), high event rate (ITI 2 s, 200 trials), and a variable ITI (ITIs of 2, 4, 6, and 8 s). Finally, animals were challenged with noncontingent systemic injections of amphetamine (saline, 0.2, 0.4, 0.8, and 1.6 mg/kg i.p.), dosed according to a Latin square design. Two washout baseline sessions separated each amphetamine test day. The stimulus duration and ITI of this component of the experiment was 0.5 and 5 s, respectively.

Plasma Analysis of Amphetamine

In a separate group of animals, levels of amphetamine were determined in blood plasma at varying time intervals following withdrawal from amphetamine i.v. self-administration. The purpose of this component of the investigation was to determine whether unmetabolized amphetamine could in any way account for the subsequent behavioral deficits on the 5-CSRTT. Subjects experienced three cycles of amphetamine i.v. self-administration; each separated by 1 week as before. Acquisition was conducted over five consecutive days (25 infusions/5 h, 0.05 mg/infusion), whereas on the subsequent two cycles the session length and maximum number of infusions (0.05 mg/infusion) was extended to 8 h and 75, respectively. Subjects were killed by anaesthetic overdose (sodium pentobarbitone, Euthatal®, 200 mg/ml, 1.5 ml/subject i.p.) and exsanguination via the dorsal aorta, either 24 or 48 h after the last amphetamine infusion. Blood samples were collected into standard fluoride/oxalate plastic tubes, centrifuged at 6000 rpm for 15 min, and aliquots of plasma decanted and stored at -80°C until further analysis. Plasma was also extracted from drug-naïve rats and used as blanks or spiked with amphetamine (2 mg/l) to validate the assay.

Plasma concentrations of amphetamine were determined by capillary gas chromatography (GC). Briefly, 400 µl of plasma was pipetted into a dreyer tube followed by 100 µl 0.88 M ammonia, and a small quantity of aqueous amylocaine (internal standard). *n*-Butyl acetate (50 µl) was then added and the tube vortex mixed for 30 s. After centrifuging to separate the solvent, the *n*-butyl acetete was transferred to an autosampler vial and 2 µl was injected into the GC. The chromatograph was a Hewlett-Packard 6890, fitted with a nitrogen detector, split/splitless injector, and Chemstation for system control and data capture. The column was a 25 m $\times$ 0.32 mm (0.52 µ) DB5 and injections were made in the splitless mode with the column at 100°C prior to ramping the temperature to 240°C. The carrier gas was helium delivered at constant pressure (30 psi). Samples are reported as the mean of duplicate results. The limit of detection was 0.01 mg/l.

Drugs

Amphetamine sulfate (Sigma, UK) was dissolved in 500-ml sterile bags of 0.9% saline and stored at room temperature for a maximum of 2 weeks. The dose of amphetamine was calculated from the combined weight of the free base and salt.

Data Analysis

Data for each dependent variable were subjected to analysis of variance (ANOVA) using SPSS (V9, Chicago, IL). Significant deviations from the requirement for homogeneity of variance were assessed by the Mauchly Sphericity test and corrected using the Huynh–Feldt (HF) epsilon (ε) to adjust degrees of freedom as recommended by Keppel (1991). Prior to ANOVA, accuracy data were transformed using the formula for angular transformation ($x' = 2\arcsin[\mathrm{SQRT}x]$), correct response and magazine latencies were subjected to logarithmic transformation. Separate ANOVA assessments were performed on the presurgical 5-CSRTT baseline data to ensure that future control and amphetamine self-administering animals were evenly matched. Main analyses of the 5-CSRTT data

included one between subject's factors, group (two levels) and two within subject's factors, cycle (five levels), and session (seven levels). Since one of the effects of withdrawal from i.v. amphetamine administration was an increase in omissions, accuracy was only computed if the percentage of omissions was equal to, or less than 60%. In the majority of cases, this condition held true (see Figure 3). Probabilities less than 0.05 were considered significant.

RESULTS

Intravenous Amphetamine Self-Administration

Figure 1a shows the number of active and inactive lever responses during the acquisition (cycle 1) and maintenance (cycles 2–5) phases of i.v. amphetamine self-administration. Taken as a whole, responses were greater on the active lever compared with the inactive lever (lever: $F_{(1,4)} = 7.22$; $p = 0.002$), indicating that the subjects had acquired discriminated lever responding for i.v. amphetamine. Lever responding also varied across the different cycles (cycle: $F_{(4,16)} = 8.59$; $p = 0.001$) and there was a significant three-way interaction between the factors lever, cycle, and session ($F_{(16,64)} = 4.43$; $p < 0.001$). To evaluate whether active lever responses, and hence the number of infusions, varied across session, a further ANOVA was conducted on the active response data. This revealed significant main effects of cycle ($F_{(4,16)} = 9.76$; $p < 0.001$) and session ($F_{(4,16)} = 5.59$; $p = 0.005$) and a significant interaction between cycle and session ($F_{(16,64)} = 2.25$; $p = 0.012$). Within each cycle, there were main effects of session for cycles 2 ($F_{(4,28)} = 10.61$; $p < 0.001$) and 3 ($F_{(4,28)} = 3.82$; $p = 0.013$), but not cycles 1, 4 and 5. Thus, the number of amphetamine infusions increased during the second and third cycles but not during acquisition or the final two cycles.

The rate of i.v. amphetamine self-administration (infusions/hour) during each session is shown in Figure 1b. Subjects self-administered approximately eight infusions an hour, this remaining constant across all cycles. However, infusion rates did vary as a function of session (session: $F_{(4,28)} = 9.20$; $p < 0.001$), specifically during cycle 1 ($F_{(4,28)} = 3.44$; $p = 0.0.21$), cycle 2 ($F_{(4,28)} = 4.80$; $p = 0.004$), and cycle 3 ($F_{(4,28)} = 2.93$; $p = 0.038$) but the not the last two cycles.

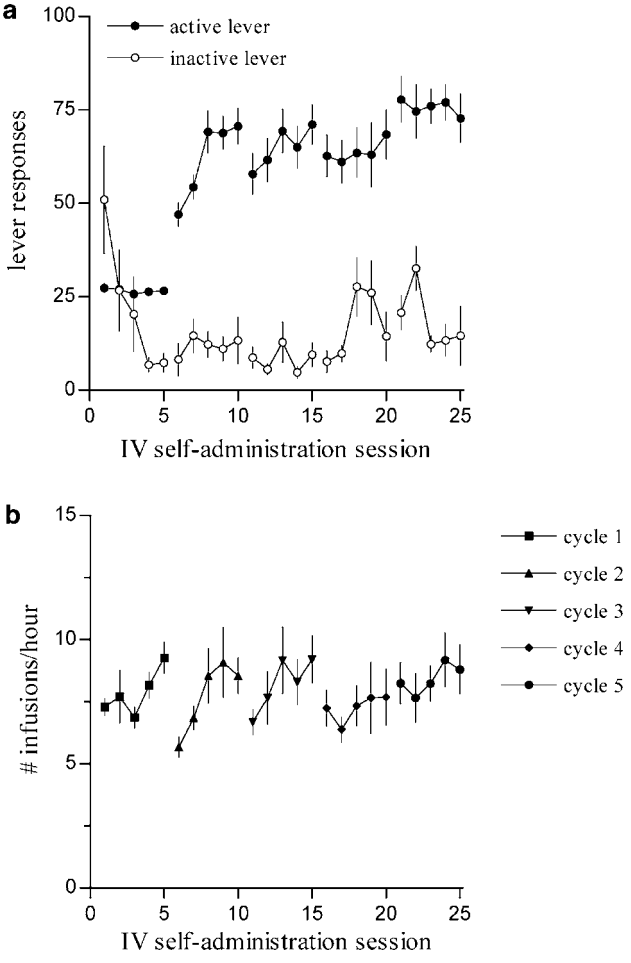

Figure 1 Mean (±SEM) number of active and inactive lever responses during the i.v. self-administration stages of the experiment (a). Self-administration of amphetamine was conducted over five cycles; each separated by 9 days, during which time testing on the 5-CSRTT took place. The maximum number of infusions (0.05 mg/infusion) was 25 for cycle 1 (acquisition) and 75 for cycles 2, 3, 4, and 5 (maintenance). The rate of amphetamine self-administration during each of the five cycles (mean infusions per hour±SEM) is shown in panel (b).

Attentional Accuracy

The effects of repeated acute withdrawal of i.v. amphetamine self-administration on the accuracy of performance on the 5-CSRTT are shown in Figure 2. Prior to surgery, the two groups (future yoked saline controls and amphetamine self-administering animals) were well matched in terms of discriminative accuracy (group: $F_{(1,14)} = 1.34$; $p = 0.267$; session: $F_{(9,126)} = 1.16$; $\varepsilon_{HF} = 0.72$; $p = 0.337$; group × session: $F_{(9,126)} = 2.11$; $\varepsilon_{HF} = 0.72$; $p = 0.091$). Following acute withdrawal of i.v. amphetamine, attentional accuracy decreased significantly in the amphetamine self-administering subjects compared with the control saline group (group: $F_{(1,14)} = 16.40$; $p = 0.001$). This deficit was independent of the cycle of i.v. self-administration indicating that there were no cumulative effects of the multiple self-administration sessions. Accuracy was most profoundly affected on the first day of abstinence but recovered to the performance levels of the control animals after 4–5 days (group × session: $F_{(6,84)} = 24.26$; $p < 0.001$; group × session × cycle: $F_{(24,336)} = 1.20$; $\varepsilon_{HF} = 0.72$; $p = 0.26$).

A breakdown of performance across the five cycles revealed a very similar pattern of effects, namely a significant main effect of session (all $p < 0.001$) and a significant group × session interaction (all $p < 0.002$). With the exception of the first cycle of testing that followed the acquisition of i.v. amphetamine self-administration, there were also significant main effects of group for the different cycles (all $p < 0.027$). This indicates that the degree of attentional impairment was somewhat less on the first cycle of testing, presumably because the number of amphetamine infusions was restricted to 25/session during the first week of self-administration acquisition.

Omissions

Figure 3 shows the corresponding effects of repeated acute withdrawal of i.v. amphetamine self-administration on the

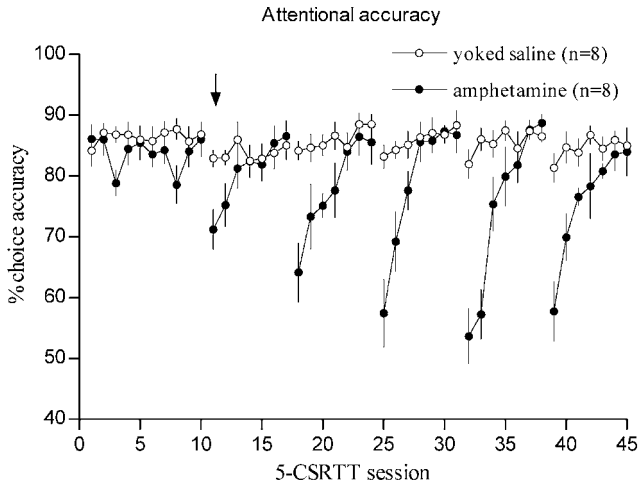

Figure 2 Effects of repeated acute withdrawal from i.v. amphetamine self-administration on attentional accuracy on the 5-CSRTT (percentage of total correct responses to total correct + incorrect responses ± SEM, ie, errors of commission). Sessions 1–10 are presurgical baseline days of future control and amphetamine self-administering animals. The arrow marks the first postsurgical test day on the 5-CSRTT, 24 h after the last self-administration session of cycle 1 (ie, acquisition). Performance on the 5-CSRTT was evaluated for the next 6 days, after which the subject's received a further 5 days of i.v. amphetamine self-administration (cycle 2), before being withdrawn again and retested on the 5-CSRTT for 9 days. This pattern of alternating amphetamine exposure and 5-CSRTT testing continued for five complete cycles. Control animals received noncontingent 'yoked' infusions of normal saline during the i.v. amphetamine self-administration sessions.

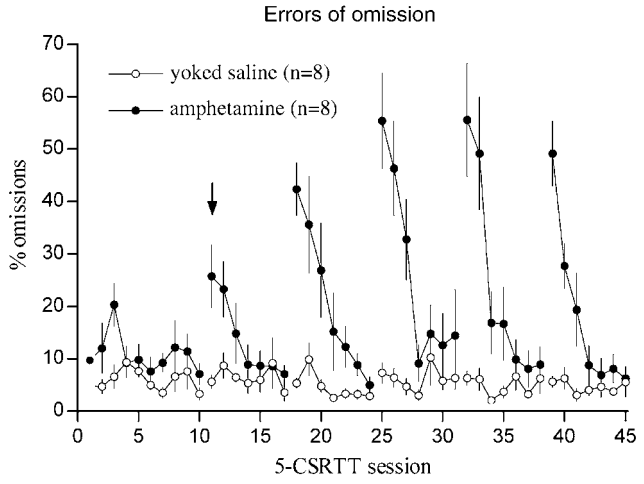

Figure 3 Increased errors of omission on the 5-CSRTT in animals acutely withdrawn from i.v. amphetamine self-administration compared to yoked control subjects. The arrow depicts the first 5-CSRTT session 24 h after the last i.v. amphetamine self-administration session of cycle 1. The data are percentage omissions (±SEM) expressed as a function of total trials. An omission was recorded when no response was made within a 5-s period from the onset of the target stimulus (ie, the limited hold period).

proportion of omitted trials on the 5-CSRTT. Presurgically, omissions were generally less than 10%, and although varying across the 10 baseline sessions (session: $F_{(9,126)} = 2.24$; $\varepsilon_{HF} = 0.76$; $p = 0.039$), were not statistically different between future control and amphetamine self-administering animals. Pronounced increases in omissions were observed in rats acutely withdrawn from i.v. amphetamine self-administration (group: $F_{(1,14)} = 54.4$; $p < 0.001$), which varied as a function of session (session: $F_{(6,84)} = 46.43$; $\varepsilon_{HF} = 0.68$; $p < 0.001$; group × session: $F_{(6,84)} = 34.97$; $\varepsilon_{HF} = 0.68$; $p < 0.001$) but not cycle. Therefore, omissions increased by more or less the same extent during each abstinence period but recovered to control levels over subsequent testing on the 5-CSRTT. The exception to this was the first cycle where the maximum increase in omissions was some 10–30% lower than subsequent cycles. Analysis of omission data for each cycle confirmed this interpretation, with significant interactions between session and group (all $p < 0.002$) and main effects of session (all $p < 0.004$) and group (all $p < 0.005$, except cycle 1 where $p = 0.075$).

Response Latencies and Inhibitory Response Control

Figure 4 summarizes the effects of acute withdrawal from i.v. amphetamine self-administration on ancillary measures of 5-CSRTT performance. There were no significant differences between the two groups during the presurgical baseline sessions with respect to correct response latencies, magazine latencies, perseverative responses, or premature responses.

Latencies to respond correctly increased differentially in animals withdrawn from i.v. amphetamine self-administration (see Figure 4a). Thus, overall, latencies to respond correctly were elevated in the amphetamine group (group: $F_{(1,14)} = 10.53$; $p = 0.006$), an effect which interacted significantly with session ($F_{(6,84)} = 16.58$; $p < 0.001$) but not cycle. Therefore, these data reveal a further, but nevertheless, reversible deficit in attentional performance following withdrawal from i.v. amphetamine self-administration, namely slower response times. This deficit was specific to responses directed at the target stimuli. Thus, latencies to collect food after a correct trial were not significantly affected (group: $F_{(1,14)} = 1.14$; $p = 0.331$; group × session: $F_{(6,84)} = 2.72$; $\varepsilon_{HF} = 0.35$; $p = 0.081$; group × cycle: $F_{(4,56)} = 0.272$; $\varepsilon_{HF} = 0.89$; $p = 0.895$). Although visual inspection of the data suggests that magazine latencies were somewhat slower on the first withdrawal day, this effect was not reliable across all subjects, and if anything, virtually disappeared after the fifth cycle.

Withdrawal from i.v. amphetamine self-administration produced no significant effects on inhibitory response control, as indexed by 'compulsive' perseverative responses (see Figure 4c) and 'impulsive' premature responses (see Figure 4d).

Plasma Levels of Amphetamine during Acute Abstinence

The limit of the assay for detecting amphetamine in blood plasma was 0.01 mg/l. Analysis of plasma samples taken from i.v. amphetamine self-administering animals that had not been trained on the 5-CSRTT revealed that there was no detectable presence of amphetamine 24 or 48 h after the cessation of i.v. amphetamine self-administration (see Figure 5a). Figure 5b shows the rate of i.v. amphetamine self-administration in animals included in this part of the study in comparison with the original set of trained animals

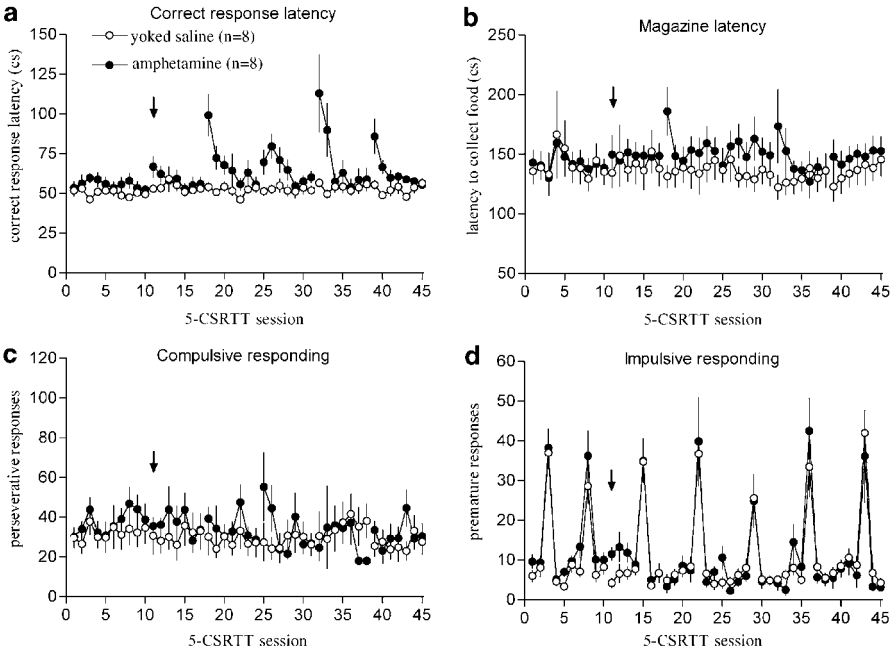

Figure 4 Effect of repeated acute withdrawal from i.v. amphetamine self-administration on the speed of responding for visual targets on the 5-CSRTT (a), the latency to collect food reward from the magazine following a correct response (b), perseverative (compulsive) responding (c), and premature (impulsive) responding. The data are means ± SEM, expressed in centi-seconds ('cs' response and magazine latencies) or number of responses for each session (perseverative and premature responses). The ITI was lengthened to 7 s (from 5 s) on the fifth day of behavioral testing to increase the frequency of premature responding.

on the 5-CSRTT (data reproduced from Figure 1). The results indicate that there were no significant differences in the rate of i.v. amphetamine self-administration between trained and untrained animals (session: $F_{(4,56)} = 26.36$; $p < 0.001$; group: $F_{(1,14)} = 0.13$; $p = 0.723$; group × cycle: $F_{(2,28)} = 1.74$; $p = 0.19$; group × session: $F_{(4,58)} = 0.87$; $p = 0.49$). Furthermore, as shown in Figure 5c, the two groups were well matched in terms of the number of active lever responses (and hence number of amphetamine infusions) over the three cycles (group: $F_{(1,14)} = 0.09$; $p = 0.765$; group × cycle: $F_{(2,28)} = 0.81$; $p = 0.455$; group × session × cycle: $F_{(8,112)} = 1.43$; $p = 0.192$). These data thus indicate that the behavioral effects during acute withdrawal from i.v. amphetamine self-administration were probably not due to the direct presence of amphetamine itself.

Behavioral Challenges after a 2-Month Abstinence

Although the behavioral deficits observed after acute amphetamine withdrawal were apparently reversible under standard test conditions, it is possible, nevertheless, that longer-term deficits still exist, and that such deficits only manifest under increased attentional load. However, as shown in Figure 6, there appears to be little direct support for this possibility 2 months after the cessation of i.v. amphetamine self-administration. Thus, there were no significant differences between the groups when the stimulus duration was reduced to 12.5 cs, in terms of accuracy, omissions, correct response latency, and premature responding. In addition, there were no significant differences between the two groups when the ITI was made variable (ie, temporally unpredictable stimuli; data not shown), or when the stimuli were presented more frequently.

Noncontingent Amphetamine Administration

Figure 7 summarizes the main effects of noncontingent amphetamine administration on 5-CSRTT performance following a 2-month abstinence period from i.v. amphetamine self-administration. Neither amphetamine preexposure (group: $F_{(1,7)} = 0.34$; $p = 0.58$; group × dose: $F_{(4,28)} = 0.46$; $p = 0.77$) nor acute noncontingent amphetamine administration ($F_{(4,28)} = 2.43$; $p = 0.072$) significantly affected attentional accuracy (see Figure 7a). However, errors of omission (Figure 7b) increased differentially in the amphetamine self-administration group ($F_{(1,7)} = 6.36$; $p = 0.04$), which was significant compared to control animals at 0.8 mg/kg ($F_{(1,7)} = 9.42$; $p = 0.018$). Correct response latencies were not significantly affected (group: $F_{(1,7)} = 2.61$; $p = 0.15$; group × dose: $F_{(4,28)} = 0.641$; $p = 0.638$), although the data suggest that response latencies were somewhat slower in the amphetamine group (see Figure 7c). The increase in premature responses produced by acute noncontingent amphetamine administration (Figure 7d; $F_{(4,28)} = 7.17$; $p < 0.001$) was attenuated in amphetamine animals (group: $F_{(1,7)} = 5.97$; $p = 0.045$; group × dose: $F_{(4,28)} = 1.28$; $p = 0.30$); this effect being significant at the 0.8 mg/kg dose ($F_{(1,7)} = 6.32$; $p = 0.04$). No other behavioral variables were affected by amphetamine, including latencies to collect food reward and perseverative responding.

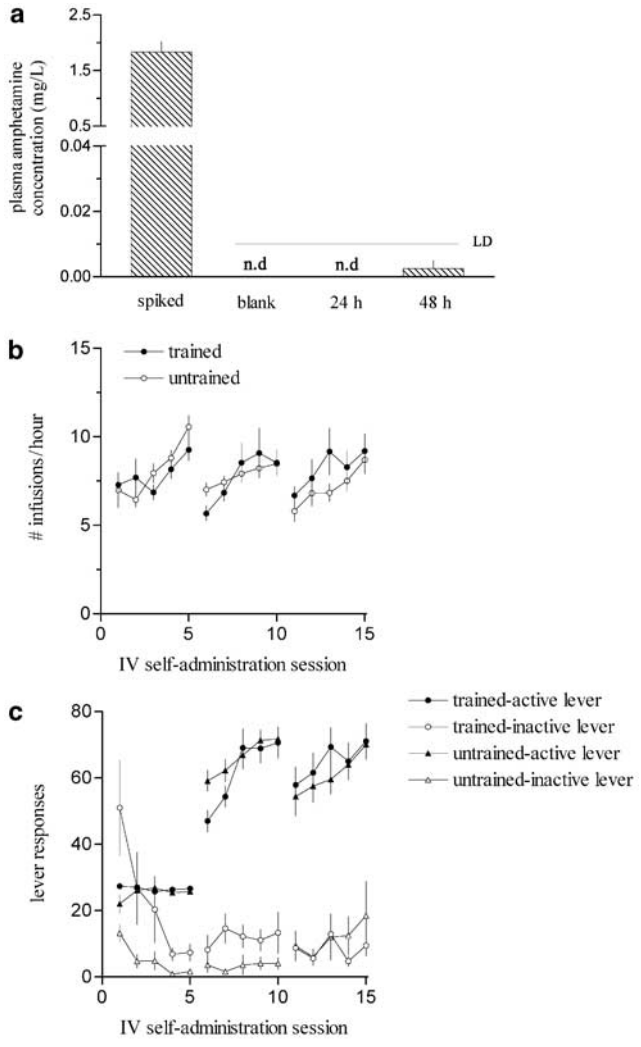

Figure 5 Levels of amphetamine in blood plasma 24 h ($n = 6$) and 48 h ($n = 5$) after cessation of i.v. amphetamine self-administration (a). The data were derived from a cohort of animals that were not trained on the 5-CSRTT, but nevertheless experienced the same parameters of i.v. self-administration as animals that were trained on the 5-CSRTT. Samples were taken after *three* complete cycles of i.v. amphetamine self-administration. The dashed line depicts the limit of detection (LD) of the gas chromatographic assay (0.01 mg/l). n.d. not detected. Levels from samples spiked with amphetamine (2 mg/l), in addition to blank samples taken from drug-naïve animals, are also shown. The corresponding rates of amphetamine self-administration (number of infusions per hour) for subjects trained and not trained on the 5-CSRTT as well as the mean ($\pm$SEM) number of active and inactive lever responses over three complete cycles i.v. self-administration is shown in panels (b) and (c), respectively.

DISCUSSION

The current study investigated the long-term neurocognitive effects of i.v. amphetamine self-administration in rats on a task assessing sustained visuo-spatial attention and impulsivity. This investigation was motivated firstly by the growing recognition that amphetamine and other drugs of abuse produce a variety of neuropsychological disturbances that are yet to be fully characterized, secondly by the controversy surrounding the persistence of such deficits during long-term abstinence, and thirdly by the paucity of preclinical studies adopting response-contingent self-administration protocols in this field of research. Our findings reveal a selective and profound pattern of deficits on the 5-CSRTT following repeated withdrawal from i.v. amphetamine self-administration, with impairments in the speed and accuracy of responding as well as increased omissions. There were no disproportionate changes in premature and perseverative responding between control and amphetamine self-administering animals, nor were there significant differences in the latency to collect food reward following a correct trial. Crucially, attentional performance in the amphetamine self-administering animals recovered 4–5 days after the withdrawal of the drug, and there was no evidence of any lasting impairment in visual attentional function following a 2-month abstinence period. However, when subsequently challenged with noncontingent amphetamine, subjects exhibited an altered response to the drug, with increased omissions, slower response times, and reduced impulsivity. These data indicate that i.v. amphetamine self-administration produces a marked, but reversible impairment in visuo-spatial attention when evaluated in withdrawal. The findings also indicate that prior contingent amphetamine administration alters the subsequent effects of acute noncontingent amphetamine, in a way that is relatively persistent and possibly related to neuroadaptive alterations.

The robust impairments in attentional accuracy were unlikely to have been due to any nonspecific effects on motor performance because on average the same motoric demands are required for both correct and incorrect responses. In addition, although latencies to respond correctly increased during the acute withdrawal phase, there was no evidence to suggest that other response latencies were adversely affected, including the time to collect food reward following the successful completion of a trial. The failure to detect amphetamine in blood plasma 24 h after the cessation of i.v. amphetamine self-administration implies that our behavioral observations were not confounded by the direct presence of amphetamine itself, and thus reflect a true withdrawal phenomenon. Although amphetamine is concentrated in the brain after its systemic administration, with a brain : blood ratio approaching 8 : 1 (Yokel and Pickens, 1974), a conservative estimate of blood amphetamine levels in the present study 24 h after withdrawal suggests that they were at least 20-fold less than the mean blood level reported in rats actively self-administering amphetamine (Yokel and Pickens, 1974). Furthermore, the acute effects of amphetamine on the 5-CSRTT are well established and bear little relationship to the effects seen here, with increased impulsiveness and faster, not slower response latencies (Robbins, 2002). Finally, it is unlikely that motivational variables affected the results because the increases in omissions were never accompanied by changes in food magazine latency. Therefore, our data strongly argue that the withdrawal of i.v. amphetamine results in gross impairments in executive attentional processes, such as response selection, known to depend on the PFC. The findings add to previous conclusions concerning elevations in brain reward thresholds following acute stimulant withdrawal (Lin *et al*, 1999; Koob *et al*, 2004), and suggests that such behavioral sequelae are both profound and wide-ranging.

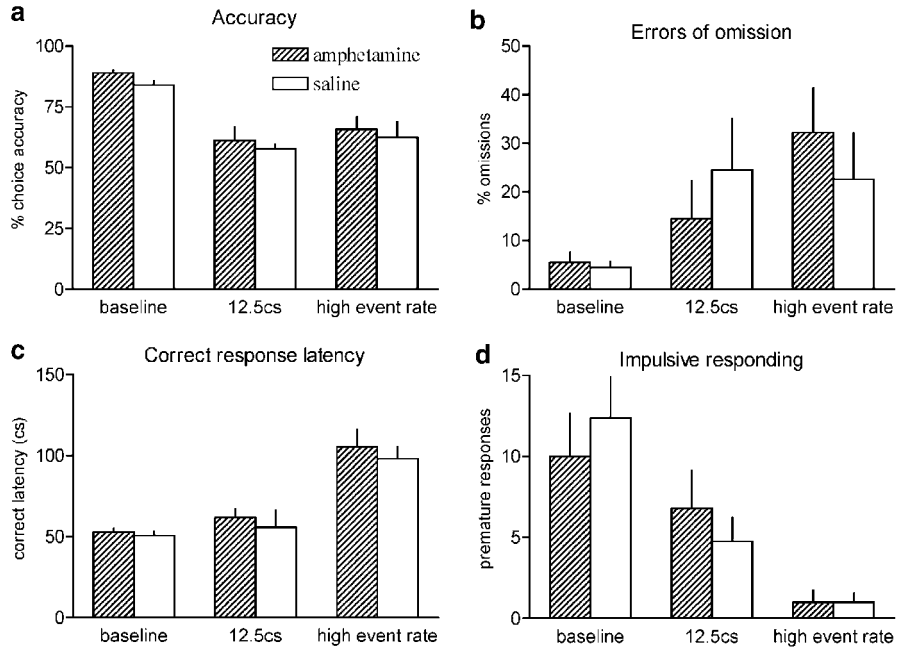

Figure 6 Lack of effect of increasing the attentional demands of the 5-CSRTT on the performance of control (saline) and amphetamine abstinent rats. Behavioral testing was conducted 2 months after the last self-administration session. The manipulations shown include reducing the stimulus duration from the normal baseline duration of 50 to 12.5 cs, and a high event rate where the frequency of the target stimuli was increased over a large number of trials.

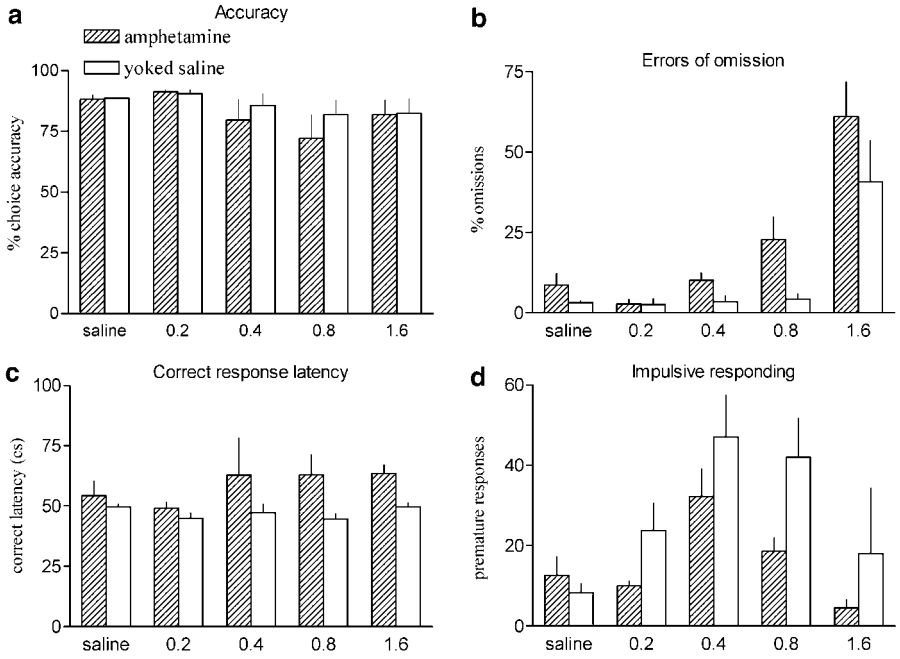

Figure 7 Differential effects of noncontingent amphetamine administration (0.2–1.6 mg/kg i.p.) on behavioral performance of the 5-CSRTT in animals previously exposed to either i.v. amphetamine self-administration or yoked infusions of normal saline. The time between behavioral testing and the last self-administered infusion of either amphetamine or saline was 2 months.

Psychostimulants and Cognitive Dysfunction

There is a growing consensus in humans that chronic cocaine and amphetamine use results in specific neuropsychological impairments during abstinence (O'Malley *et al*, 1992; Berry *et al*, 1993; Rosselli and Ardila, 1996; Bolla *et al*, 1999; McKetin and Solowij, 1999; Rogers *et al*, 1999; Ornstein *et al*, 2000). It remains unresolved, however, whether neuropsychological disturbances in chronic stimulant abusers persist for many weeks or even months after abstinence. Enduring deficits in abstraction and motor-perceptual integration have been described in a group of

polydrug users, with a history of amphetamine abuse, following several relatively drug-free months (Grant and Judd, 1976), and cocaine users continue to show deficits in learning and memory, problem solving, abstraction, and psychomotor speed for several weeks at least during abstinence (Berry *et al*, 1993; Beatty *et al*, 1995). Adverse effects on memory and concentration are also a reported consequence of long-term amphetamine use (McKetin and Mattick, 1997), with additional impairments in the quality of decision making (Rogers *et al*, 1999), extradimensional attentional set shifting (Ornstein *et al*, 2000), and other attentional capabilities (McKetin and Solowij, 1999).

Studies in animals confirm the notion that amphetamine produces specific disturbances in attentional processing. For example, amphetamine-treated rats appear unable to ignore irrelevant stimuli in the latent inhibition and blocking paradigms (Crider *et al*, 1982; Weiner *et al*, 1988), analogous to the selective attention deficits seen among schizophrenic patients. In addition, impairments in sustained visual attention have recently been reported in animals treated with amphetamine (Deller and Sarter, 1998; Kondrad and Burk, 2004). At this stage, the nature of the psychological processes that underlie the disruptive effects of amphetamine withdrawal on 5-CSRTT performance remains unclear. The steep rise in omissions that accompanied the decline in attentional accuracy implies an inability actively to deploy attentional resources between interoceptive and exteroceptive processing demands. It is also possible, but as yet untested under these conditions, that the amphetamine subjects were more distractible or impaired in their ability to filter out irrelevant information (Robbins and Sahakian, 1983; Crider *et al*, 1982). In addition, based on substantial clinical evidence (Berry *et al*, 1993; Beatty *et al*, 1995; Ornstein *et al*, 2000), it is possible that deficits in working memory contributed to the behavioral effects; for example, by a failure to hold representations of the visual cues 'on-line'. As well as exhibiting reduced accuracy and increased omissions, subjects were slower to respond correctly to the visual target stimuli, a finding that is compatible with slower reaction times and psychomotor speed reported in abstinent human cocaine and amphetamine users (Beatty *et al*, 1995; Bolla *et al*, 1999; McKetin and Solowij, 1999). The basis of this impairment is unknown but could potentially reflect disturbances in decision-making processes, analogous to those seen in chronic amphetamine abusers (Rogers *et al*, 1999). However, it is unlikely that the subjects were sedated or exhibited any gross impairment in motor performance because latencies to collect food reward were unaffected. This latter finding is somewhat at odds with observations of anhedonia (raised ICSS thresholds) following stimulant withdrawal (Markou and Koob, 1991; Koob *et al*, 2004), which would perhaps predict a general reduction in motivation for food reward during abstinence. However, it is also possible that distinct neuropsychological processes contribute to ICSS measures of anhedonia and consumption latencies on the 5-CSRTT and that these are affected differentially by stimulant withdrawal.

An important finding of the present study was the failure to demonstrate any significant effects of i.v. amphetamine self-administration on impulsive responding on the 5-CSRTT. The main effects of acute systemically administered *d*-amphetamine on 5-CSRTT performance are to *reduce* the latency to respond correctly and to *increase* premature responding, generally at doses having no significant effects on response accuracy (Cole and Robbins, 1987; Robbins, 2002). Although there has been a long-standing interest in the apparent relationship between drug addiction and impulsivity (Levin and Kleber, 1995; Jentsch and Taylor, 1999), it is not at all clear from this evidence how the two disorders might be causally related. Impulsive behavior in experimental animals can be defined in a number of ways, such as the failure to inhibit a prepotent motor response, an intolerance to delayed rewards, and overly rapid decision-making due to a lack of 'reflection' (Evenden, 1999). Emerging evidence suggests that these may be independent behavioral processes, each with distinct neural substrates (Winstanley *et al*, 2004). Previously, it has been demonstrated that withdrawal from 14 days of noncontingent cocaine (Paine *et al*, 2003) or methamphetamine (Richards *et al*, 1999) administration increases impulsivity in the delayed reward paradigm. By contrast, chronic intermittent cocaine injections had no effect on a Go/No-go visual discrimination task requiring inhibition of a primed motor response (Paine *et al*, 2003). The present data provide an important extension of these findings by showing that at least one form of impulsive behavior is impervious to prior *contingent* stimulant administration when assessed in withdrawal. In theoretical terms, it will be important in future studies to establish whether this lack of effect can be generalized to other forms of impulsive behavior and whether trait impulsiveness influences the subsequent cognitive effects of i.v. stimulant administration.

Neural Basis of Amphetamine-Induced Attentional Dysfunction

Optimal performance on the 5-CSRTT is known to depend on fronto-striatal circuitry, including distinct subregions of the PFC and interconnected structures within striato-pallidal circuitry (Muir *et al*, 1996; Robbins, 2002; Chudasama *et al*, 2003). It is likely therefore that drug-induced alterations in PFC and striatal functioning contributed to the behavioral deficits on this task. The results are perhaps best understood in terms of neuroadaptations in mesostriatal dopamine (DA) function, which are a widely reported consequence of repeated stimulant administration in humans and experimental animals (Ricaurte *et al*, 1984; Wilson *et al*, 1996; Rossetti *et al*, 1992; Stefanski *et al*, 1999). Indeed, the main behavioral impairments of acute amphetamine withdrawal in this study are entirely reminiscent of the effects of DA-depleting lesions of the dorsal striatum on this task (Baunez and Robbins, 1999), and in other reaction time procedures (Amalric and Koob, 1987), implying that reduced DA neurotransmission in the striatum probably contributed to the observed attentional impairments. The findings are also compatible with additional effects of DA on the regulation of basal forebrain cholinergic neurons (Sarter and Bruno, 1999), possibly in a way that diminishes the well-established influence of cortically projecting cholinergic neurons on visual attentional processing (Voytko *et al*, 1994; Himmelheber *et al*, 2001; McGaughy *et al*, 2002; Risbrough *et al*, 2002; Dalley *et al*, 2001, 2004). Indeed, it is noteworthy that the main effects of selective

lesions of the basal forebrain cortical cholinergic system on the 5-CSRTT are reduced response accuracy and increased omissions (McGaughy *et al*, 2002; Risbrough *et al*, 2002; Lehmann *et al*, 2003; Dalley *et al*, 2004), effects that bear close resemblance to the present study.

Long-Term Behavioral Effects of I.V. Amphetamine Self-Administration

Our results show very clearly that attentional dysfunction is a relatively temporary outcome of amphetamine withdrawal. The time course of recovery is suggestive of an underlying reversal of specific drug-induced neuroadaptations, possibly involving DA-related functions. Furthermore, our findings show that there is no deterioration in executive attentional performance during a prolonged abstinence period, even with systematic increases in attentional load, for example with a high target frequency sustained over many trials, a manipulation that requires attentional resources to be maintained on a continuous basis (Parasuraman and Giambra, 1991). However, it was significant that when subsequently challenged with acute noncontingent amphetamine, subjects exhibited an altered drug response, with increased omissions, slower response times, and *reduced* impulsivity. In theoretical terms, these data are relevant to the long-standing view that amphetamine and other drugs of abuse produce lasting effects on drug-related neurobehavioral processes (Robinson and Berridge, 1993; Koob and Le Moal, 1997), as well as previous speculations concerning impulsivity as a consequence of repeated drug use (Jentsch and Taylor, 1999). A germane point to consider is whether rats in the present study were sensitized to amphetamine following contingent amphetamine administration. Sensitized attentional impairments have been observed in other settings, namely as a consequence of intermittent noncontingent amphetamine administration (Deller and Sarter, 1998), and there is evidence that repeated noncontingent amphetamine sensitizes the ability of amphetamine to stimulate cortical acetylcholine efflux (Nelson *et al*, 2000). However, in the present study, similar attentional disturbances were not observed—indeed, subjects appeared to be less responsive to amphetamine, as measured by the latency to respond correctly and premature responding. These findings may therefore be compatible with evidence that prolonged access to i.v. cocaine self-administration apparently diminishes behavioral sensitization (Ben-Shahar *et al*, 2004).

In summary, this study provides important new insights into the effects of i.v. amphetamine self-administration on cognitive capabilities in rats. Our findings demonstrate that executive attentional processes known to depend on the PFC and associated circuitry are especially impaired during acute withdrawal from amphetamine. Such deficits, while severe, appear to be relatively short lasting and dependent, in part, on specific neuroadaptive changes in the dopamine and cholinergic neuromodulatory systems. These data are compatible with growing evidence of executive dysfunction in human stimulant abusers (Bolla *et al*, 1999; Ornstein *et al*, 2000; Rogers and Robbins, 2001), and therefore confirm the potential utility of this approach as a way of evaluating the complex neurochemical and neuropsychological dysfunctions that accompany drug addiction.

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