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Enduring Deficits in Sustained Visual Attention during Withdrawal of Intravenous Methylenedioxymethamphetamine Self-Administration in Rats: Results from a Comparative Study with *d*-Amphetamine and Methamphetamine

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Although amphetamine-derived stimulants are widely associated with neurotoxicity, it is poorly understood whether extended exposure to such drugs produces lasting effects on neurocognitive function. This study investigates whether chronically self-administered *d*-amphetamine, methamphetamine (MA), or methylenedioxymethamphetamine (MDMA) leads to residual deficits in a rodent test of sustained visual attention and impulsivity. Rats were trained on a five-choice serial reaction time task and subsequently trained to self-administer *d*-amphetamine, MA, or MDMA (all 50 μg/infusion), intravenously, for 3 weeks. Effects on performance were evaluated 24 h after drug discontinuation and for several weeks thereafter, including various challenge sessions to increase the attentional demands of the task. The results indicate divergent patterns of self-administration among the three drugs tested with increasing rates of intake evident in rats self-administering amphetamine, but not MA, and widely fluctuating rates in the MDMA group. Withdrawal of MA resulted in severe behavioral disturbances, with significant effects on accuracy, omissions, response latency, and impulsivity that lasted up to 2 weeks in some cases. Amphetamine and MDMA withdrawal were associated with similar, but shorter-lasting effects on performance. However, when challenged with a high event rate session 6 weeks after drug discontinuation, rats previously exposed to MDMA continued to show deficits in the accuracy and speed of responding. These findings show that amphetamine-derived stimulants have both short- and long-term consequences for psychomotor functioning. The demonstration of residual deficits in rats chronically exposed to MDMA raises some concern about the potential harm caused by this drug in human ecstasy users.
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INTRODUCTION

There has been a recent sharp rise in amphetamine abuse in humans and renewed efforts to determine whether psychostimulant drugs of abuse irretrievably harm the brain (McCann *et al*, 1998a; Ernst *et al*, 2000; Nordahl *et al*, 2003; Thompson *et al*, 2004; McCann and Ricaurte, 2004). Studies in human drug abusers support the existence of specific psychological deficits during acute drug withdrawal (Simon *et al*, 2000; Sim *et al*, 2002; Kalechstein *et al*, 2003), but there is a lack of reliable data on the long-term neurocognitive profile of abstinent stimulant abusers. Even more difficult is that drug abuse may coexist with other neuropathologies that may, in some circumstances, predate drug-taking behavior (Khantzian, 1985; Levin and Kleber, 1995; Sim *et al*, 2002). For these reasons, studies using animal models are especially important to establish the long-term effects on cognition of amphetamine and other drugs of abuse.

Substantial research in rodents and non-human primates indicates that amphetamine, methamphetamine (MA) and methylenedioxymethamphetamine (MDMA) are potentially toxic to the brain dopaminergic and serotonergic systems (Seiden *et al*, 1976; Lorez, 1981; Ricaurte *et al*, 1992; Woolverton *et al*, 1989; Melega *et al*, 1997; Semple *et al*, 1999; McCann *et al*, 1998b; Ernst *et al*, 2000; Cornish *et al*, 2003; Segal *et al*, 2005). Consistent with these findings post-mortem indices of striatal dopamine (DA) nerve terminal function, including levels of DA, tyrosine hydroxylase, and DA transporter, are reduced in recently deceased chronic

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MA users (Wilson *et al*, 1996). Structural and metabolic changes in the brain are also a reported consequence of chronic stimulant abuse that is evidently persistent in some cases (Ernst *et al*, 2000; Robinson and Kolb, 2004; Thompson *et al*, 2004; Wang *et al*, 2004; London *et al*, 2005).

However, increasingly, there have been reports of functional recovery following protracted abstinence from drugs such as MA, for example, especially of the striatal DA systems (Melega *et al*, 1997; Harvey *et al*, 2000; Volkow *et al*, 2001; Stefanski *et al*, 2002; but see Segal *et al*, 2005). Indeed, a recent brain imaging study in detoxified human MA addicts found that DA transporter levels in the striatum recover following protracted drug abstinence (Volkow *et al*, 2001). However, other deficits such as decreased cortical glucose metabolism persisted for periods up to 17 months (Wang *et al*, 2004), suggesting that chronic MA use may cause intractable cognitive impairment. To date, however, little is known about the nature, severity, and time course of such deficits in animals. Moreover, it is not known whether the approach of administering high, noncontingent doses of stimulants to animals, is relevant to the profile of cognitive impairment in animals trained to self-administer these same compounds.

Our aim in this study was to elucidate the effects of extended intravenous (i.v.) self-administration of *d*-amphetamine, MA, and MDMA on pretrained performance of a five-choice serial reaction time (5-CSRT) task, an automated operant procedure for assessing visual attention and impulsivity in rodents (Robbins, 2002). Performance on this task depends on the functional integrity of many of the same limbic cortical–striatal brain structures affected by chronic drug abuse, including dorsal and ventral prefrontal cortex, orbitofrontal cortex, and the nucleus accumbens (Volkow *et al*, 1993; Robbins, 2002; Chudasama *et al*, 2003; Hester and Garavan, 2004; Thompson *et al*, 2004; Wang *et al*, 2004). In addition, lesions of the primary neurochemical targets of stimulant drugs, namely the DA and serotonin (5-HT) systems, produce distinct deficits on the 5-CSRT task. Specifically, mesostriatal DA loss primarily affects the speed and vigor of responding, whereas selective 5-HT depletion impairs inhibitory response control leading to increased impulsivity (Harrison *et al*, 1999; Robbins, 2002; Winstanley *et al*, 2004). This study tests for the occurrence of residual deficits in performance on the 5-CSRT task following prolonged withdrawal from chronically self-administered amphetamine, MA, or MDMA. In particular, we have tested the hypothesis that chronic drug exposure leads to deficits in impulse control (Jentsch and Taylor, 1999), especially in the case of MDMA, a popular recreational drug widely recognized for its toxicity to the brain 5-HT systems (Ricaurte *et al*, 1992; McCann *et al*, 1998a; Fantegrossi *et al*, 2004).

MATERIALS AND METHODS

Subjects

The subjects were 33 male Lister Hooded rats (Charles River, UK), weighing 350–410 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). Animals were placed on a food-restricted diet (14 g laboratory chow/day, Purina, UK) to maintain body weight at roughly 85–90% of free-feeding weight during behavioral testing. Animals' weights were recorded every week and food provision adjusted accordingly to ensure uniform body weights throughout the study. All procedures complied with the requirements of the UK Animals (Scientific Procedures) Act of 1986 (Project number 80/1767).

Behavioral Training on the 5-CSRT Task

The apparatus consisted of eight nine-hole 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 of 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 microswitch. A PC using WhiskerServer software (version 2.8) and FiveChoice client (version 2.6) controlled the apparatus.

Subjects were trained on the 5-CSRT task over 45 daily sessions (5–6 sessions/week). Each session consisted of 100 discrete trials and lasted approximately 30 min. Trials were initiated by animals entering the food magazine. After an intertrial interval (ITI) of 5 s had elapsed, a brief visual stimulus of duration 0.5 s was presented in a single aperture, the location of which varied on a trial-by-trial basis. Rats were rewarded with a single food pellet if they correctly located the position of the target stimulus with a nose-poke response. A failure to respond within 5 s of the target presentation (deemed an 'omission') resulted in a time-out of 5 s where the house-light and tray-light were extinguished for 5 s and no food was made available. Responses made before the target stimulus or in an adjacent hole were deemed 'premature' and 'incorrect', respectively. Each of these trial types also resulted in a 5 s time-out. Omissions were expressed as a percentage of correct + incorrect + omission trials (maximum 100%). Premature or impulsive responses were expressed as a percentage of correct + incorrect + omission + premature trials. A premature response was considered an incomplete trial and had the effect of resetting the previous trial. Response accuracy was defined as the proportion of correct responses to incorrect responses expressed as a percentage. Two measures of the speed of responding were used. The first was latency to respond correctly, defined as the time between the onset of the target stimulus and the response. The second measure was latency to collect food reward from the magazine, defined as the time between the correct response and the first entry into the magazine. Animals were considered to have acquired the basic task when their accuracy of responding was at least 80% and omissions were stable and less than 20%.

I.V. Catheterization and 5-CSRT Task Baseline Assessment

Subjects were anesthetized with ketamine (Ketalar, 100 mg/kg, intraperitoneally (i.p.); Vet Drug, Bury St Edmunds, UK) and xylazine (Rompun, 12 mg/kg, i.p.; Vet Drug) and implanted with an i.v. catheter (CamCaths, Cambridge, UK) that exited dorsally between the scapulae as described previously (Caine *et al*, 1992). Catheters were maintained by flushing once weekly with 0.2–0.4 ml saline (0.9% sterile saline; CP Pharmaceuticals Ltd, Wrexham, UK). Subjects were given at least 7 days to recover from surgery before being re-tested on the 5-CSRTT over 7 daily sessions. The ITI was increased to 7 s on day 3 to increase the frequency of impulsive responding (Dalley *et al*, 2005a).

I.V. Drug Self-Administration

Detailed descriptions of the self-administration procedure can be found elsewhere (Dalley *et al*, 2005b). Briefly, the self-administration chambers (24 × 20 × 22 cm; Med Associates, UK) were equipped with two levers located 10 cm apart and 5 cm above the grid floor. One was designated the 'active' lever, responses on which resulted in drug delivery and the illumination of a white stimulus light (3 W, 24 V) positioned directly above the lever. Responses on the second 'inactive' lever were recorded but had no consequences. A software-operated pump delivered the drug infusions and a PC using WhiskerServer software (version 2.8) and a SecondOrder client (version 3.4) controlled the self-administration apparatus (Cardinal and Aitken, 2001).

Subjects were divided into four groups destined to receive either yoked infusions of sterile saline ($n=9$), self-administered *d*-amphetamine ($n=8$), (+)-MA ($n=10$), or (±)-MDMA ($n=6$). Self-administration was conducted over 21 consecutive days under a fixed ratio-1 schedule of reinforcement. Each infusion delivered 50 μg of the free drug base in 0.1 ml saline. The selection of doses for *d*-amphetamine, MA, and MDMA was based on recent studies showing these to reliably support i.v. self-administration in rats (Stefanski *et al*, 2002; Cornish *et al*, 2003; Dalley *et al*, 2005a; Shepard *et al*, 2006; Kitamura *et al*, 2006). It was assumed that rats would titrate drug intake to achieve relatively optimal levels of drug in the plasma. No attempt was made therefore to correct the unit dose of each drug based on relative differences in biopotency, elimination half-live or molecular weight. On the first 5 days, access was limited to 25 infusions a day. On days 6–21, access to each drug was increased by increasing the session duration to 8 h and the maximum number of infusions potentially achievable to 75.

Re-Testing on the 5-CSRT Task during Extended Drug Withdrawal

Subjects were re-tested on the 5-CSRT task 24 h after the last self-administration session. Attentional performance was assessed for 24 consecutive daily sessions, each 30 min in duration and consisting of 100 trials. The stimulus duration and ITI was 0.5 and 5 s, respectively. On days 5, 12, and 19, the ITI was increased to 7 s and the session duration increased to 60 min. These challenge sessions were used to encourage premature responding and so avoid any potential floor effects on this form of impulsivity (see Dalley *et al*, 2002).

Following this test phase, rats were left in their home cage for 6 weeks with free access to water and a restricted food diet (18 g/rat/day). They were then tested under different challenge conditions, specifically to increase the demand for attentional processing and inhibitory response control. Challenge sessions consisted of (in the following sequence) a reduced stimulus duration (0.125 s), variable ITI, white noise distractor, and a high event rate, which were each separated by 2 days of baseline testing (stimulus duration and ITI, 0.5 and 5 s, respectively). The variable ITI session consisted of four discrete ITIs (2, 4, 6, and 8 s), with trials presented uniformly across each ITI in a pseudorandom order. White noise (0.5 s in duration) was presented during the ITI 4.5, 3.5, 2.0, or 0.5 s before the onset of the visual target. The high event rate session consisted of a short fixed ITI of 2 s and was terminated after 200 trials.

Drugs

d-Amphetamine sulfate, (+)-MA hydrochloride, and (±)-MDMA hydrochloride were purchased from Sigma-Aldrich (UK) and dissolved in sterile saline (CP Pharmaceuticals, Wrexham, UK). Doses were determined from the combined weight of the free base and salt.

Statistical Analyses

All analyses were conducted using repeated measures analysis of variance (ANOVA; SPSS type III sum-of-squares method, version 12, SPSS Inc., Chicago, IL). Significant deviations from the requirement of 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). All tests of significance, including tests of sphericity of the covariance matrix, were performed at $\alpha=0.05$.

In a previous study, withdrawal from 5-day amphetamine self-administration resulted in increased omissions, which while high in magnitude (~50%), nevertheless permitted attentional accuracy to be reliably computed (Dalley *et al*, 2005a). In this study, however, withdrawal from *d*-amphetamine and MA self-administration greatly increased omissions (>80%) to the point that attentional accuracy provided a less robust measure of performance. Hence, in this study, the number of correct responses indexed the spatial accuracy of performance. Behavioral variables on the 5-CSRT task were first analyzed to ensure uniform matching of baseline behavioral data between future control and drug self-administering animals. Accuracy data were transformed using the formula $x' = 2\arcsin[\sqrt{x}]$ before ANOVA. Performance effects during stimulant withdrawal were computed across six bins, each consisting of four consecutive daily sessions described in the form $A_2 \times (B_4 \times C_6 \times S)$, where A is the between-subjects factor *group* with two levels (saline, drug), B is the within-subjects factor *session* with four levels (four consecutive daily test sessions), C is the within-subjects factor bin (six levels) and S represents subjects. Effects on performance of the various challenge sessions were

computed using two-way ANOVA with factors *group* (two levels) and *manipulation* (four levels) and independent *t*-tests where appropriate.

RESULTS

Acquisition and Rate of i.v. Drug Self-Administration

As shown in Figure 1, subjects readily acquired i.v. *d*-amphetamine, MA, and MDMA self-administration. However, although active lever responses were significantly greater than inactive lever responses for all groups (amphetamine: $F_{1,7} = 556$; $p < 0.01$; MA: $F_{1,9} = 1203$; $p < 0.01$; MDMA: $F_{1,5} = 11.46$; $p = 0.02$), significant variations were encountered in the rate of self-administration for each of these drugs. Thus, rates increased progressively for *d*-amphetamine up to session 12 ($F_{20,140} = 2.49$; $p = 0.01$), but not for MA ($F_{20,180} = 1.68$; $HF(\varepsilon) = 0.34$; $p = 0.21$), whereas for MDMA, the rate of self-administration showed appreciable variation, with especially high rates during the first 5 days of exposure and lower rates thereafter ($F_{20\,100} = 10.54$; $p < 0.01$). Notably, following an initial decline in active lever responding from day 6 to day 11, responding on the drug lever increased with continued MDMA exposure, almost to levels approaching those of *d*-amphetamine and MA.

Behavioral Consequences of *d*-Amphetamine, MA, and MDMA Withdrawal

Before the withdrawal phase of the experiment, animals destined to receive *d*-amphetamine, MA, or MDMA were evenly matched for baseline performance compared with future control subjects destined for yoked infusions of saline (all F-values < 1, NS).

Figure 2 summarizes the effects on 5-CSRT task performance of amphetamine withdrawal. The main effects were a reduction in the number of correct responses, an increase in omissions, and a general slowing of responding to the visual targets; however, there were no significant effects on impulsivity. These deficits were apparent for at least 4 days with no obvious long-term effects during protracted withdrawal. Thus, ANOVA revealed significant bin × session × group interactions for correct responses ($F_{15,225} = 5.59$; $p < 0.01$), omissions ($F_{15,225} = 10.32$; $p < 0.01$), and correct response latencies ($F_{15,225} = 5.20$; $p < 0.01$), and significant main effects of group (corrects: $F_{1,15} = 173$; $p < 0.01$; omissions: $F_{1,15} = 129.6$; $p < 0.01$, correct latencies: $F_{1,15} = 48.9$; $p < 0.01$) and significant group × session interactions for all three behavioral variables during the first 4 days of amphetamine withdrawal only (ie, bin 1).

Withdrawal from 21-day i.v. MA self-administration resulted in more severe disturbances in attentional

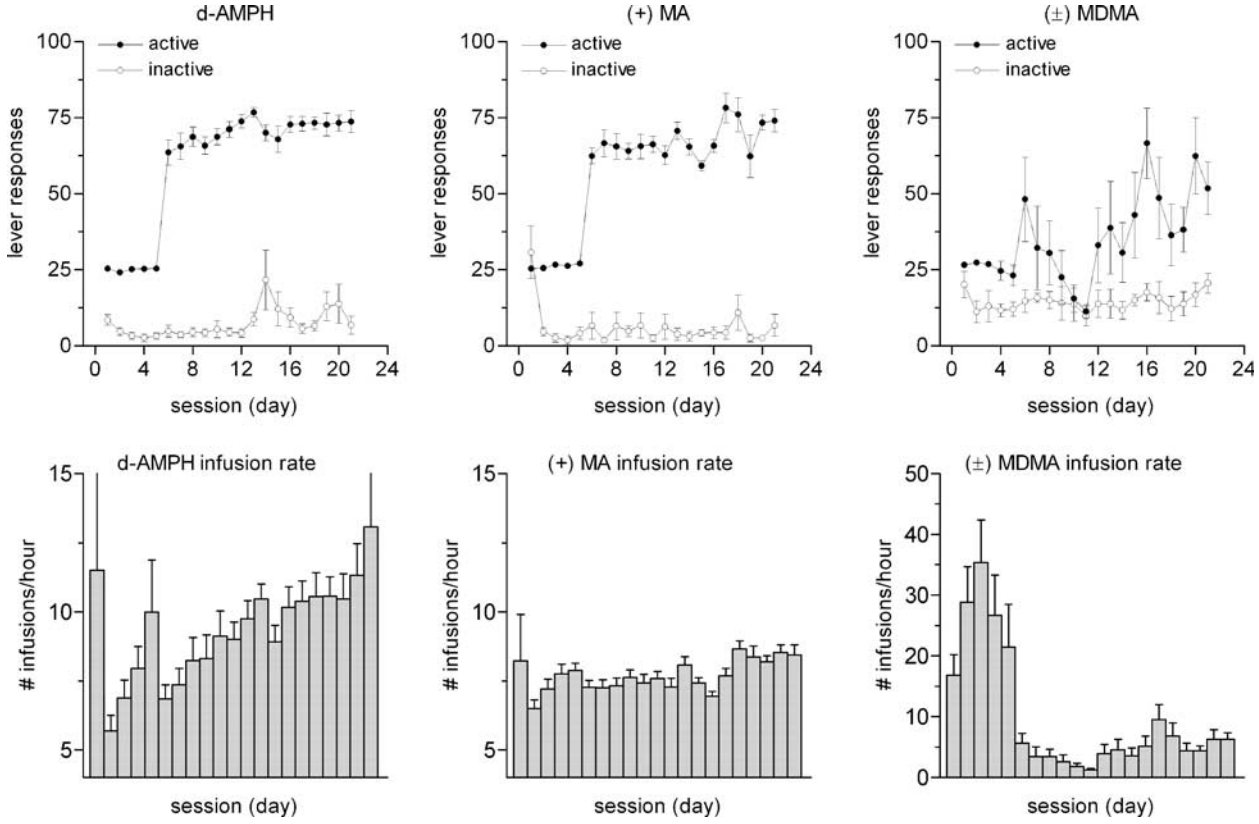

Figure 1 Number of active and inactive lever press responses during *d*-amphetamine, MA, and MDMA self-administration maintained under a fixed ratio (FR1) schedule of reinforcement (upper graphs). Access to drug was restricted on the first 5 days to 25 infusions. On days 6–21, access was increased to 75 infusions. Session limits of 5 and 8 h were imposed for the acquisition and maintenance stages, respectively. The lower graphs show the mean rate of *d*-amphetamine, MA, and MDMA self-administration (number of infusions/h). Error bars represent ± 1 SEM.

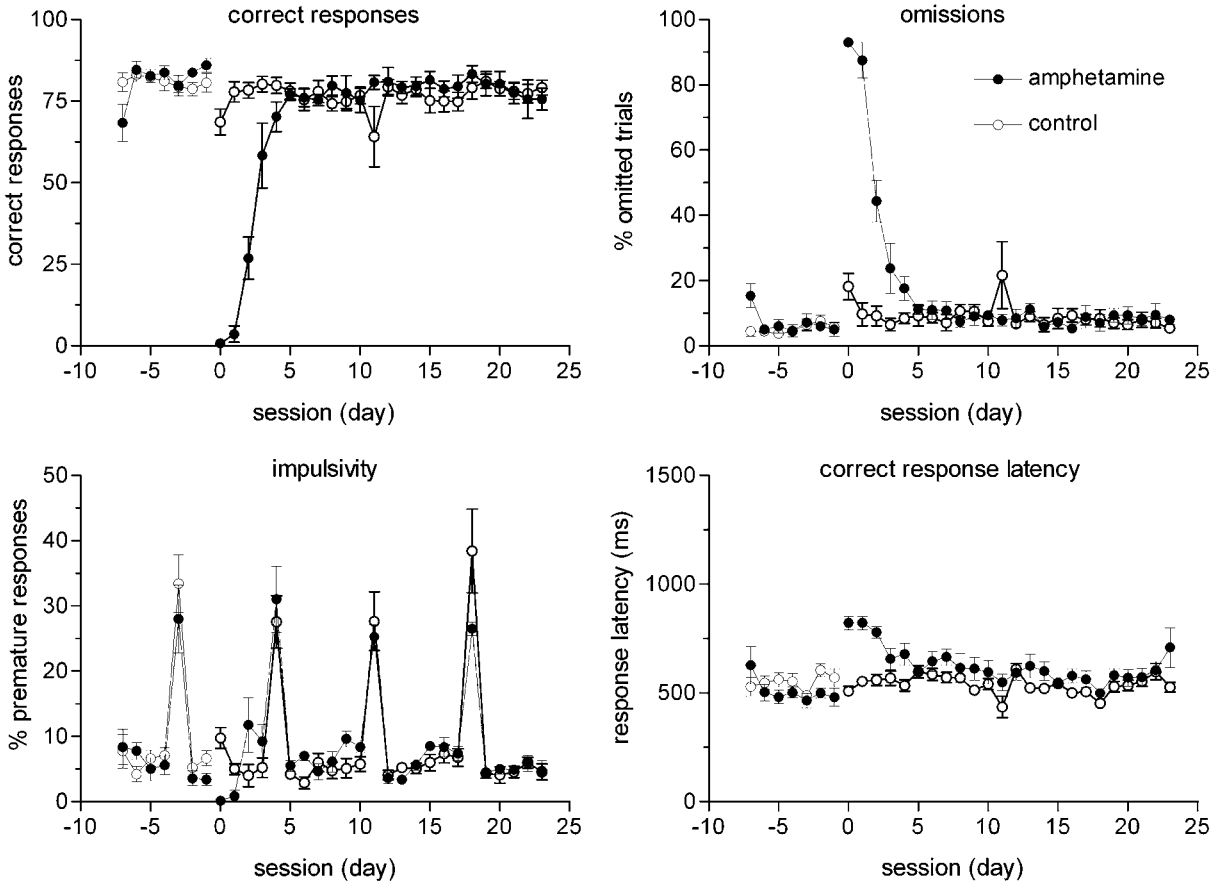

Figure 2 Transitory impairments in attentional performance in rats withdrawn from extended access to i.v. *d*-amphetamine self-administration. Shown are mean (± 1 SEM) correct responses, percentage omissions, percentage premature responses, and mean response latencies in active self-administering animals (closed symbols) and control subjects administered passive infusions of 0.9% saline (open symbols). Before i.v. self-administration, baseline performance on the 5-CSRT task was determined for 7 consecutive days. Postdrug performance was assessed 24 h after amphetamine discontinuation (shown as 'day 0').

performance that lasted up to 2 weeks in some animals (see Figure 3). In addition, and unlike amphetamine, MA withdrawal was associated with a significant increase in impulsive responding. Thus, our analysis revealed significant bin × session × group interactions for correct ($F_{15,255} = 2.89$; $p < 0.01$) and premature ($F_{15,255} = 2.90$; $p = 0.005$) responses, and significant bin × group interactions for omissions ($F_{5,85} = 46.6$; $p < 0.01$) and correct response latencies ($F_{5,85} = 9.93$; $p < 0.01$). Correct responding significantly decreased relative to controls during bin 1 (corrects: $F_{1,17} = 519$; $p < 0.01$) and bin 2 ($F_{1,17} = 13.77$; $p < 0.01$), but not during subsequent bins. Likewise, omissions decreased significantly during this period (bin 1: $F_{1,17} = 123.4$; $p < 0.01$; bin 2: $F_{1,17} = 8.05$; $p = 0.01$), whereas correct response latencies increased, but only during bin 1 ($F_{1,17} = 13.4$; $p < 0.01$). Finally, there was a delayed increase in premature responding that reached statistical significance during bin 3 relative to controls (ie, withdrawal days 9–12; $F_{1,17} = 8.29$; $p = 0.01$).

MDMA withdrawal was associated with qualitatively similar effects on performance, although of the three drugs tested, this compound produced the least disruptive effects during this phase of baseline testing (see Figure 4). During the acute period of withdrawal (ie, bin 1), correct responses significantly decreased ($F_{1,13} = 7.69$; $p = 0.016$), but there were no significant effects on omissions or correct response latencies. By contrast, MDMA withdrawal was associated with an overall increase in premature responding (group: $F_{1,13} = 7.71$; $p = 0.016$), which was significantly compared to controls during bin 2 (ie, withdrawal days 5–8, $F_{1,13} = 7.02$; $p = 0.02$).

The effects of discontinuing i.v. *d*-amphetamine, MA, and MDMA self-administration on magazine latencies on the 5-CSRT task are shown in Figure 5. Rats destined to receive either compound were evenly matched for baseline latencies compared with future control rats (all F-values < 1, NS). During the acute withdrawal period, magazine latencies were significantly slower in rats withdrawn from *d*-amphetamine (bin 1: $F_{1,15} = 8.83$; $p = 0.01$), MA (bin 1: $F_{1,17} = 7.41$; $p = 0.014$), and MDMA (bin 1: $F_{1,13} = 11.60$; $p = 0.005$). However, this was a transient phenomenon with latencies to collect food reward recovering to control levels by approximately the fourth day of withdrawal in the *d*-amphetamine and MA groups. Latencies in the MDMA group showed a slower pattern of recovery (bin 2: $F_{1,13} = 4.96$; $p = 0.044$; bin 3: $F < 1$, NS).

Attentional Challenges during Protracted Drug Withdrawal

Following baseline testing, animals were maintained in a drug-free state for a further 6 weeks and then re-tested

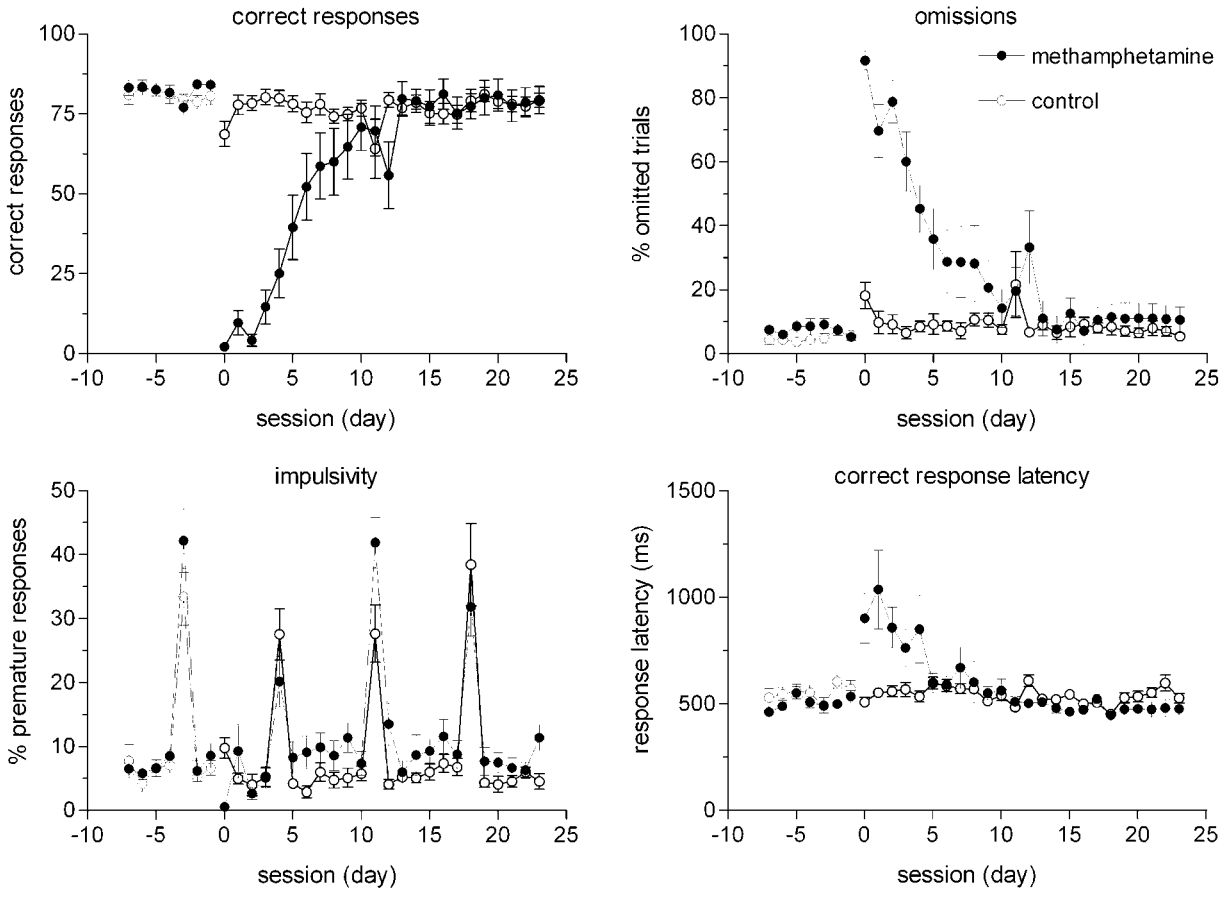

Figure 3 Long-lasting deficits in visual attentional performance in rats withdrawn from i.v. (+)-MA self-administration. Shown are mean (±1 SEM) correct responses, percentage omissions, percentage premature responses, and mean response latencies in active self-administering animals (closed symbols) and control subjects administered passive infusions of 0.9% saline (open symbols). Animals were tested on the 5-CSRT task 24 h after withdrawal of i.v. MA self-administration (shown as 'day 0'). Aside from obvious effects on correct responses, omissions, and response latency, MA withdrawal was also associated with a significant increase in impulsivity on the 5-CSRT task (see text for details).

under different conditions to tax various aspects of attentional performance. The findings are shown in Figure 6. MDMA-exposed rats showed a general deterioration in performance, mainly but not exclusively during the high event rate session when the target stimuli were presented frequently over many trials. Specifically, MDMA rats showed reduced accuracy (group: $F_{1,13} = 5.33$; $p = 0.038$; pair-wise *t*-test; $p = 0.033$), increased omissions (group × manipulation: $F_{3,39} = 6.75$; $p = 0.006$; pair-wise *t*-test; $p = 0.022$), slower correct response latencies (group × manipulation: $F_{3,39} = 2.97$; $p = 0.043$; pair-wise *t*-test; $p = 0.031$), and increased magazine latencies (group-manipulation: $F_{3,39} = 4.31$; $p = 0.01$; pair-wise *t*-test; $p < 0.01$). The MDMA group also showed slower response latencies ($p = 0.049$) and fewer premature responses (group × manipulation: $F_{3,39} = 4.97$; $p = 0.005$; pair-wise *t*-test; $p = 0.024$) during the variable ITI session and fewer premature responses ($p = 0.008$) and increased magazine latencies ($p = 0.006$) during the white noise distraction session. Magazine latencies also increased significantly in the MA group during both the white noise distraction session ($p = 0.02$) and the high event rate session ($p = 0.03$).

DISCUSSION

This investigation was motivated by the paucity of data on the consequences of stimulant drug self-administration on defined cognitive and behavioral functions assessed before, and following, drug self-administration. The 5-CSRT task provides an automated assessment of visuospatial attention and impulsivity in rodents and depends in particular on the functional integrity of the prefrontal cortex and striatum, as well as the cortically projecting DA, NA, ACh, and 5-HT systems of the brain (Robbins, 2002). Previous work has shown that diverse drugs of abuse, including self-administered heroin, cocaine, and *d*-amphetamine, similarly impair attentional performance on this task and that these deficits, in the main, recover fully with protracted abstinence (Dalley *et al*, 2005a, b). This study extends these findings by showing that MA and MDMA also disrupt performance during the acute withdrawal period, with especially long-lasting deficits induced by prior MA exposure. The results also show that impulsivity, as defined operationally by increased levels of responding before the onset of the target stimulus, is one short-term consequence of MA and MDMA withdrawal, not seen with *d*-amphetamine, cocaine, or

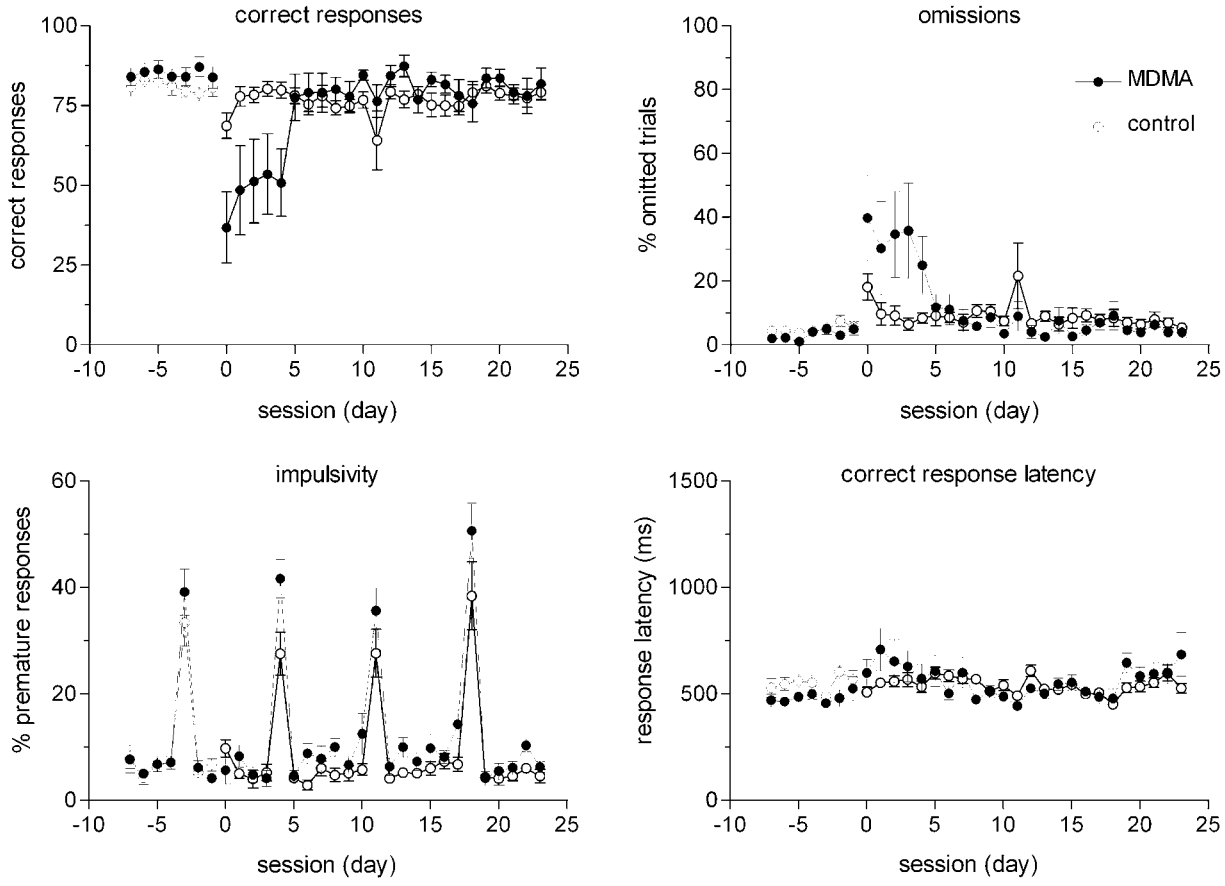

Figure 4 Effects of acute withdrawal of i.v. MDMA self-administration on attentional performance on the 5-CSRT task. Shown are mean (± 1 SEM) correct responses, percentage omissions, percentage premature responses, and mean response latencies in active self-administering animals (closed symbols) and control subjects administered passive infusions of 0.9% saline (open symbols). Similar to MA, MDMA was also associated with significant elevations in impulsive responding that was evident approximately 1 week after withdrawal.

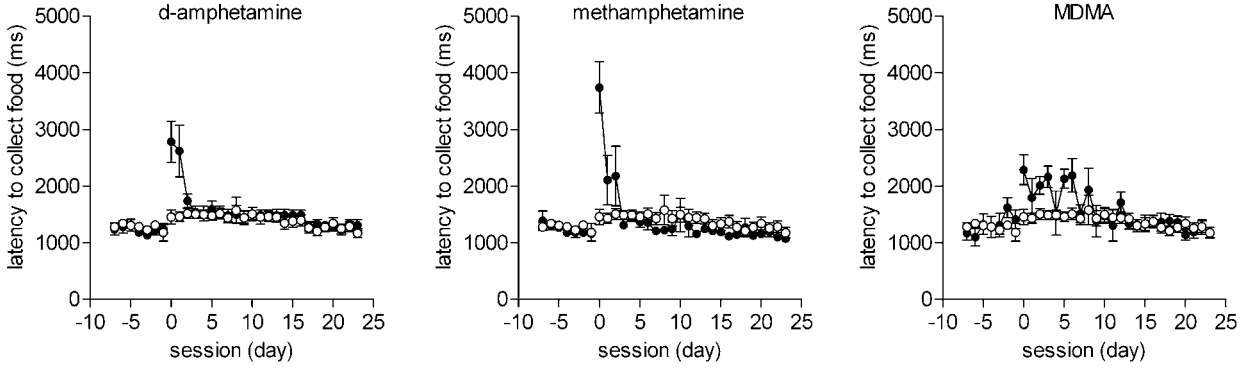

Figure 5 Effect of acute withdrawal of i.v. *d*-amphetamine, MA, and MDMA self-administration on magazine latencies on the 5-CSRT task. Shown are mean (± 1 SEM) latencies (expressed in ms) in active self-administering animals (closed symbols) and control rats administered passive infusions of 0.9% saline (open symbols).

heroin (see Dalley *et al*, 2005a, b). Finally, this study demonstrated the presence of residual deficits in rats withdrawn from MDMA self-administration for a period of 2 months, including a vigilance decrement, a *reduction* in impulsivity, increased omissions, and slower latencies to respond correctly and to collect food reward from the magazine. Deficits were also found in MA-exposed rats with residual effects mainly on motivational indices of performance under certain conditions. The discussion that follows considers the significance of the observed differences in the effects of withdrawal from i.v. *d*-amphetamine, MA, and MDMA self-administration and the relevance of the present behavioral findings to the cognitive and affective sequelae of chronic stimulant abuse in humans.

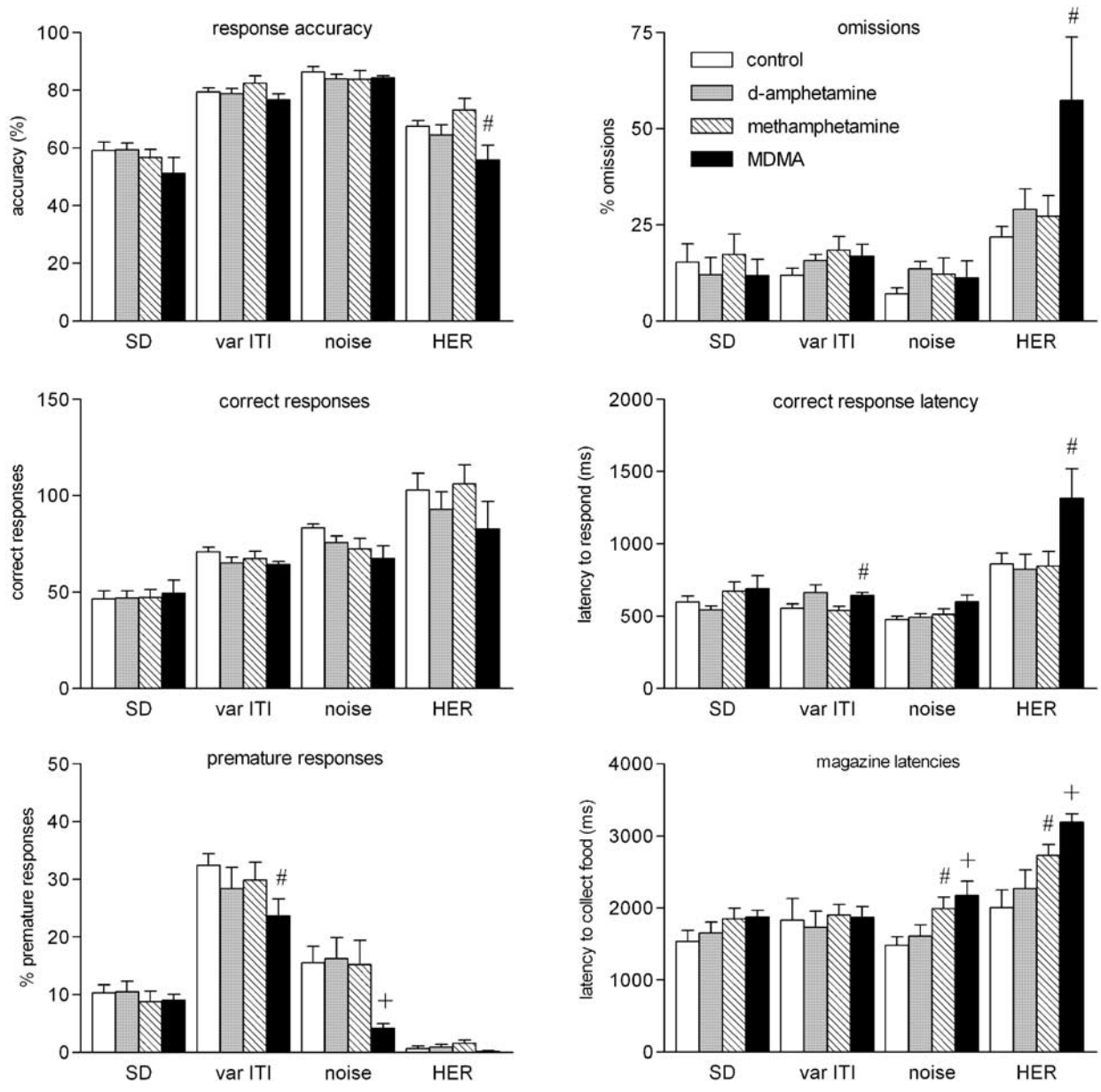

Figure 6 Residual psychomotor deficits in rats previously exposed to i.v. MDMA self-administration. Subjects were withdrawn for a 6-week period and subsequently tested under different challenge conditions, including a reduced stimulus duration ('SD') of 0.125 s, a variable ITI ('var ITI'), white noise distractor ('noise'), and a high event rate ('HER'). Deficits in the accuracy and speed of correct responding as well as food collection latencies were most evident during the high event rate session where target stimuli were presented with high frequency over a large number of trials. $^{\#}p<0.05$; $^{+}p<0.01$ (*vs* control group). Data are means ± 1 SEM.

Chronic Self-Administration of *d*-Amphetamine, MA, and MDMA

A large corpus of data indicate that, following increased availability of opiate and stimulant drugs, rats typically show escalating rates of self-administration that normally develop within the first 7–10 days of drug exposure (Ahmed and Koob, 1999; Ahmed *et al*, 2000; Kitamura *et al*, 2006). It is unclear, therefore, why we were unable to demonstrate an escalation of MA self-administration, as seen in other studies in rats (Kitamura *et al*, 2006; Shepard *et al*, 2006). Although, in this study, sessions were limited both by time and by the number of infusions, it is unlikely that our results were affected by inadequate drug access because doses and session times were employed that were comparable to the above studies. Moreover, we did observe a progressive increase in *d*-amphetamine self-administration, similar to a previous study (Dalley *et al*, 2005a). This discrepancy suggests that variables in addition to drug availability may contribute to escalating rates of self-administration (eg, rat strain). Nevertheless, it is clear that escalation *per se* is not an important determinant of cognitive outcome during the acute withdrawal period. Thus, of the three drugs tested, MA withdrawal was

associated with the most severe behavioral deficits despite its lowered propensity to produce escalation in our hands.

A further finding meriting comment was the wide fluctuation in i.v. MDMA self-administration. Recent studies have shown that MDMA is self-administered by mice (Trigo *et al*, 2006), rats (Ratzenboeck *et al*, 2001; Cornish *et al*, 2003; Schenk *et al*, 2003), and monkeys (Fantegrossi *et al*, 2002, 2004), but supports lower rates of self-administration than cocaine (Ratzenboeck *et al*, 2001). Serotonergic mechanisms have been implicated in the reinforcing properties of MDMA, as MDMA self-administration is attenuated by 5-HT2 receptor antagonists such as ketanserin (Fantegrossi *et al*, 2002). MDMA also activates the DA system via inhibition of the DA transporter (Metzger *et al*, 1998) as well as indirectly via the activation of certain 5-HT receptor subtypes (eg, Schmidt *et al*, 1994). In a recent study, high rates of responding for MDMA were also reported during the initial phase of MDMA self-administration, which too decreased over subsequent exposure (Schenk *et al*, 2003). Here, it was speculated that the decrease in responding might reflect the long elimination half-life of MDMA and/or the accumulation of an active metabolite. However, influences such as these would likely affect the loading phase of MDMA self-administration and not the between-sessions rise and fall in MDMA self-administration apparent in this study.

The initial rapid increase in MDMA self-administration in this study may be related to the emergence of tolerance, perhaps similar to that observed with serotonergic hallucinogens such as lysergic acid diethylamide (Winter, 1971) mediated by a downregulation in 5-HT2a receptor function (Gresch *et al*, 2005). As the reinforcing effects of MDMA depend, in part, on 5-HT2a receptor activity (Fantegrossi *et al*, 2002), putatively via increased DA release (Gobert and Millan, 1999; Yan *et al*, 2000), our present findings suggest that tolerance to the reinforcing effects of MDMA may be the result of diminished 5-HT2a receptor function. Thus, the sharp decline and subsequent lowering of responding for MDMA may reflect the inadequacy of 5-HT2a receptor function to support high rates of responding in the face of increasing tolerance. This may be relevant to reports that the subjective effects of ecstasy lessen with repeated use in humans (Beck and Rosenbaum, 1994) as well as to findings that spontaneous abstinence is high in adolescent and adult ecstasy users (von Sydow *et al*, 2002).

Behavioral Consequences of *d*-Amphetamine, MA, and MDMA Self-Administration

The main focus of this study was to elucidate whether long-access, response-contingent administration of *d*-amphetamine and its analogs MA and MDMA results in long-term deficits in visuospatial attention and impulsivity. Previously, we found that withdrawal from 5-day cycles of i.v. *d*-amphetamine resulted in significant impairments in performance on the 5-CSRT task that persisted for up to 6 days (Dalley *et al*, 2005a). Surprisingly, although longer access to amphetamine in this study produced a more severe decline in performance, rats still recovered by the sixth day of withdrawal. Indeed, even when tested under more demanding conditions, rats previously exposed to amphetamine all showed a full recovery in attentional functioning. This would suggest that the neuronal plasticity that accompanies this history of chronic self-administration (see Robinson and Kolb, 2004) does not interfere permanently with executive functions of selection and inhibitory control. Thus, cognitive impairment in human amphetamine abusers may be limited to the acute withdrawal period only. However, it is important to point out that there are many forms of impulsivity (Evenden, 1999) and that the particular form of impulsivity measured in the 5-CSRT task may not necessarily be relevant to the forms of impulsivity underlying drug addiction. Clearly, additional studies will be needed to resolve this issue.

Chronic MA self-administration produced more disruptive effects on 5-CSRT performance during withdrawal than *d*-amphetamine, with deficits in baseline performance still evident 2 weeks after MA discontinuation. MA also produced residual effects on performance, specifically when an auditory distractor was presented and when the target stimuli were presented more frequently over many trials. In both cases, MA rats exhibited a selective increase in their latency to collect food reward from the magazine, a deficit perhaps suggestive of mild anhedonia (see Lin *et al*, 1999). As well as affecting general aspects of performance, similar to cocaine, heroin, and *d*-amphetamine (Dalley *et al*, 2005a, b), MA withdrawal also produced a short-lasting increase in impulsivity. Consistent with this finding, MA has been reported to increase other forms of impulsivity in rats, including choice for a large but delayed reward (Richards *et al*, 1999), a finding attributed by the authors to diminished DA transmission. It is unlikely though that a similar mechanism operated in this study, because reduced DA function is not normally associated with impulsiveness on the 5-CSRT task (Robbins, 2002). Clearly, further studies are needed to address this issue, including an investigation of altered 5-HT function.

Intriguingly, MDMA exposure led to a number of enduring deficits on the 5-CSRT task with a general slowing of responding and a reduced overall tendency to respond under certain conditions. MDMA-exposed rats were particularly sensitive to the high event rate manipulation, a test that probes the capacity of subjects to maintain attentional resources on a continuous basis. Notably, MDMA rats showed a decrement in attentional accuracy (or 'vigilance') and increased omissions and response latencies when the event rate was increased. They were also impaired when the target stimuli were made temporally unpredictable (variable ITI) and when distracting bursts of white noise were presented. The nature of these deficits implies that MDMA rats show lasting abnormalities in attentional functions related to selection, monitoring (eg, of readiness to respond) and maintenance. Interestingly, rather than showing increased impulsivity, as hypothesized to occur via MDMA-induced depletion of 5-HT, chronically withdrawn MDMA rats were actually *less* impulsive under certain conditions. A possible explanation is that the MDMA rats showed a general retardation in affective arousal (see below), evident by a slower overall speed of responding and increased omissions. Such effects may be different to those during the early stages of MDMA withdrawal where, like the MA group, impulsive responding on the 5-CSRT task increased significantly. The change from initially

increased then to reduced impulsive responding in the MDMA group suggests dynamic neurochemical changes throughout the period of self-administration and withdrawal, which need to be characterized further.

Implications for Cognitive Sequelae of Human Drug Abuse

There is currently much controversy about the cognitive and mood-altering effects of stimulant drugs, including MDMA (Krystal *et al*, 1992; McKetin and Mattick, 1997; Bolla *et al*, 1998; Parrot *et al*, 1998; Gouzoulis-Mayfrank *et al*, 2000; Kalechstein *et al*, 2003; Nordahl *et al*, 2003; Thomasius *et al*, 2003; London *et al*, 2005). It is difficult, however, to be sure that long-term effects are necessarily limited to abuse of a particular drug in polydrug abusers, or to take into account confounding effects of comorbidity for other forms of psychiatric disorder (eg, see Sim *et al*, 2002). In this study, we have shown clear, persistent effects of MDMA withdrawal to impair attentional performance under challenge, and actually to reduce the vigor of behavioral output in terms of long-term reductions in impulsive responding (see also Montgomery *et al*, 2006), lengthening of magazine latency (to collect earned food pellets), and increased omissions. These data indicate persistent motivational and attentional impairments that may be relevant to reports of enhanced signs of depression in chronic MDMA users (Sumnall and Cole, 2005), in particular, in individuals carrying the short allele form of the 5-HT transporter (Roiser *et al*, 2006). Similar effects on magazine latency and reduction of impulsivity have been associated with changes in central 5-HT function in rats (Carli and Samanin, 1992; Dalley *et al*, 2002), although such behavior, as well as the control of attentional accuracy, is also affected by other monoaminergic and cholinergic systems (Robbins, 2002).

The findings are also be relevant to reports that human MA and MDMA abuse leads to cognitive impairment, especially on tests of verbal learning and memory, vigilance, and psychomotor speed (McKetin and Mattick, 1997; Bolla *et al*, 1998; Parrot *et al*, 1998; Gouzoulis-Mayfrank *et al*, 2000; Kalechstein *et al*, 2003; Nordahl *et al*, 2003; London *et al*, 2005), and to a recent report that abstinent MA abusers are impaired on an analogous rapid visual information processing task, which too assesses attentional function and distractibility (Johanson *et al*, 2006). Importantly, this study shows that related cognitive disturbances can be demonstrated in animals with a controlled history of MA and MDMA intake. The findings thus raise concerns about the frequent use of MA and especially ecstasy in otherwise normal healthy individuals.

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