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Profile of Executive and Memory Function Associated with Amphetamine and Opiate Dependence

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Cognitive function was assessed in chronic drug users on neurocognitive measures of executive and memory function. Current amphetamine users were contrasted with current opiate users, and these two groups were compared with former users of these substances (abstinent for at least one year). Four groups of participants were recruited: amphetamine-dependent individuals, opiate-dependent individuals, former users of amphetamines, and/or opiates and healthy non-drug taking controls. Participants were administered the Tower of London (TOL) planning task and the 3D-IDED attentional set-shifting task to assess executive function, and Paired Associates Learning and Delayed Pattern Recognition Memory tasks to assess visual memory function. The three groups of substance users showed significant impairments on TOL planning, Pattern Recognition Memory and Paired Associates Learning. Current amphetamine users displayed a greater degree of impairment than current opiate users. Consistent with previous research showing that healthy men are performing better on visuo-spatial tests than women, our male controls remembered significantly more paired associates than their female counterparts. This relationship was reversed in drug users. While performance of female drug users was normal, male drug users showed significant impairment compared to both their female counterparts and male controls. There was no difference in performance between current and former drug users. Neither years of drug abuse nor years of drug abstinence were associated with performance. Chronic drug users display pronounced neuropsychological impairment in the domains of executive and memory function. Impairment persists after several years of drug abstinence and may reflect neuropathology in frontal and temporal cortices.

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INTRODUCTION

Chronic use of psychoactive substances is associated with widespread deficits in neuropsychological function (Rogers and Robbins, 2001, 2003; Verdejo-Garcia *et al*, 2004). Deficits are pronounced in the executive domain including decision-making (Bechara *et al*, 2001, 2002; Bechara and Damasio, 2002; Grant *et al*, 2000), response inhibition (Fillmore, 2003; Kaufman *et al*, 2003; Hester and Garavan, 2004), planning (Ornstein *et al*, 2000), and working memory (Verdejo-Garcia *et al*, 2005; Mintzer and Stitzer, 2002). These deficits may be associated with prefrontal cortex dysfunction, and their extent and nature is likely to depend on the substance of abuse.

The present study compares executive function and memory in current users of amphetamines and opiates, both widely used substances (United Nations Office on Drugs and Crime, 2003) with distinctly different pharmacological actions. The acute pharmacological effects of amphetamines are to increase central monoamine neurotransmission by interaction with processes of transmitter release, uptake, and metabolism (for a review, see Seiden *et al*, 1993). Opiates, in contrast, exert their action mainly through μ-opioid receptors, indirectly increasing dopamine (DA), but decreasing noradrenaline (NA) levels (De Vries and Shippenberg, 2002; Maldonado, 1997). The chronic effects of prolonged substance abuse may differ between users of amphetamines and opiates. Examination of post-mortem brains indicates qualitatively more severe neuropathology in amphetamine users compared to opiate users (Kish *et al*, 2001; Wilson *et al*, 1996). While in opiate users, non-specific ventricular and cortical volume loss has been reported (Danos *et al*, 1998; Pezawas *et al*, 1998), structural

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abnormalities identified in brains of psychostimulant users (ie cocaine, methamphetamine) are more specific, encompassing particularly prefrontal and medial temporal lobe areas (Fein *et al*, 2002; Matochik *et al*, 2003; Thompson *et al*, 2004). Furthermore, alterations in brain function in psychostimulant users have shown direct associations with impaired working memory performance (Goldstein *et al*, 2004; Newton *et al*, 2004).

Despite growing evidence of the different neuropathology associated with chronic amphetamine and opiate use, respectively, neuropsychological research directly comparing cognitive performance in amphetamine and opiate users is still sparse. There is evidence that chronic amphetamine users display deficits in decision-making which are not evident in opiate users (Rogers *et al*, 1999b). Ornstein *et al* (2000) also found qualitative differences in attentional set-shifting between these two substance user groups, while on other measures of executive functions the two groups were equally impaired. The aim of the present study was to further investigate impairment of executive function subserved by dorsolateral prefrontal networks. We based our investigation on the Ornstein *et al* (2000) study, using a larger sample together with more sensitive task versions of visuo-spatial planning, attentional set-shifting, and pattern recognition. We also included a paired associate learning (PAL) task, which has shown sensitivity to mesiotemporal–frontal networks (Bullmore *et al*, 2003; Gould *et al*, 2003; Owen *et al*, 1995b; Sahakian *et al*, 1988). In addition, a group of former substance users was introduced to control for the direct pharmacological actions in the current drug user groups, and to assess the reversibility of any effect with prolonged abstinence. Urine screens prior to testing were carried out to confirm drug intake or abstinence. Since mood disorders are common in chronic substance users (Grant *et al*, 2004), we chose not to exclude participants who scored highly on the Beck Depression Inventory (BDI), but decided instead to statistically control for mood. We hypothesized that drug users compared to controls would show impairment on all neurocognitive tests administered, but chronic use of amphetamines would produce greater neurocognitive impairment than the use of opiates.

METHODS

Participants

The study received ethical approval from local research committees in Cambridge, Huntingdon, Fenland-Peterborough, and West-Suffolk. Substance users were recruited through local drug dependency units, charities providing services for drug users, and by word of mouth. Ex-drug users were recruited via Narcotics Anonymous and controls by advertisements in the local area. Prior to testing, all participants gave written informed consent. They underwent a screening process by a post-graduate psychologist using locally developed instruments concerning the history of drug use and diagnosis for substance dependence according to the DSM-IV (American Psychiatric Association, 1994), general health and demographic characteristics. Urine samples were analyzed for the following drugs: morphine, methadone, amphetamine, cocaine, and benzodiazepines using the SureStep Drug Screen Test (Euromed Limited, London, UK). All participants were compensated for their time. Criterion for inclusion for substance users was a minimum of 3 years dependence on either amphetamines or the opiates. Ex-drug users met criteria for past dependence on either opiates or amphetamines, but had been abstinent from all substances of abuse (except nicotine) for at least one year. Control participants were only included in the study if they had no drug-taking history. Exclusion criteria, which applied for all groups, were the following: color-blindness, a co-morbid psychiatric illness, a history of a head injury, a history of an overdose requiring resuscitation and overnight hospitalization. Dependence on another drug apart from the one falling under the inclusion criterion or nicotine led to exclusion from the study. Participants reporting a regular consumption of alcoholic beverage exceeding 21 U/week for men and 14 U/week for woman were also excluded from the study. Table 1 displays the drug-taking habits of other substances apart from their drug of choice, by current substance users.

The amphetamine-dependent group was composed of 25 chronic amphetamine users. Seven amphetamine users were prescribed D-amphetamine (Dexedrine®) from a Consultant Psychiatrist (mean $\pm$ standard deviation (SD) dose: 36 ± 21.9 mg, dose range: 15–70 mg), a substitute treatment for amphetamine dependence in accordance with the UK Department of Health guidelines (UK Department of Health, 1999). One participant who received Dexedrine® on prescription was also prescribed benzodiazepines. Amphetamine users without a prescription consumed street amphetamine daily. In all, 88% of amphetamine users were tobacco smokers (mean $\pm$ SD 12 ± 8.1 cigarettes/day). One street amphetamine user was HIV positive. Out of 25 urine screens, 23 tested positive for amphetamine (additional substances: six morphine, two benzodiazepines, three cocaine). One sample, which was negative for amphetamine, was positive for cocaine. The other negative sample was provided by a chronic amphetamine user, who had consumed a very large amount of non-alcoholic liquids, and therefore was included in the study. The opiate dependency group was formed of 42 chronic opiate users. Twenty-seven opiate users were on a methadone prescription (mean $\pm$ SD dose: 45.2 ± 17.9 mg, dose range: 20–80 mg). Two methadone-maintained participants also received benzodiazepines on prescription. One opiate user was on a prescription of 4 mg buprenorphine (Subutex®), another one received 4×60 mg dihydrocodeine (Sonodor®). A further opiate user had a prescription for 200 mg diamorphine and 90 mg morphine sulphate slow release (MST Continous®). Twelve opiate users exclusively consumed street heroin on a daily basis. One methadone-maintained participant received antidepressant medication (Dothiepin) and another Rabeprazole Sodium for treatment of heartburn. In all, 98% of opiate users were current smokers (mean $\pm$ SD cigarettes/day 18.5 ± 11.5). All urine samples provided by our opiate users tested positive for methadone or morphine. Twenty also tested positive for cocaine, 18 for benzodiazepines, and one for amphetamine. The 26 ex-drug users, were abstinent from all drugs of abuse for on average 8.2 years (SD 6.3) and urine analyses were negative for all substances. Continuous abstinence was counted from the time of detoxification. Although no medical records were available to verify the reported length

Table 1 Percent of Participants per Group Using Legal and Illegal Drugs at Some Point in Their Lives

	Controls	Amphetamine	Opiate	Ex-drug
Amphetamines				
Never	100	0	14	12
Present	0	100	5	0
Past	0	0	81	88
Opiates				
Never	100	44	0	12
Present	0	0	100	0
Past	0	56	0	88
Ecstasy				
Never	100	40	48	54
Present	0	4	0	0
Past	0	56	52	46
Cocaine				
Never	100	16	12	8
Present	0	36	33	0
Past	0	48	55	92
Benzodiazepines				
Never	100	67	31	35
Present	0	4	15	0
Past	0	29	54	65
Hallucinogens				
Never	100	36	29	23
Present	0	8	2	0
Past	0	56	69	77
Alcohol				
Never	100	40	40	19
Present	0	16	7	0
Past	0	44	53	81
Cannabis				
Never	100	20	2	12
Present	0	52	50	0
Past	0	28	48	88
Nicotine				
Never	37	12	0	4
Present	22	88	98	62
Past	41	0	2	34

Both amphetamine and opiate users were meeting the DSM-IV criteria for amphetamine or opiate dependence, but they did not meet DSM-IV criteria for current abuse or dependence of another substance (except nicotine).

of abstinence, in combination with urine analysis and no fear of negative repercussions, self-reported drug use has been considered to be valid (Nelson *et al*, 1998). In particular, the fact that we recruited within self-support groups of recovering drug users who were highly motivated to participate in this research meant that they were likely to have reported the length of drug abstinence correctly. Eight ex-drug users were ex-stimulant (amphetamine and cocaine) users, five were ex-opiate users and 13 had been dependent on both stimulants and opiates. In all, 62% of ex-drug users were current tobacco smokers (mean $\pm$ SD 10 ± 10.4 cigarettes per day). One ex-drug user was on antidepressant medication (Cipramil). Also, 22% of controls were smoking tobacco currently (mean $\pm$ SD 3 ± 6.4 cigarettes/day). Altogether, 12 of the past/current tobacco-smoking controls (71%) reported social experiences with cannabis, but no regular use. One participant had diabetes, which was well controlled on insulin. The urine screens provided by control participants were negative for all substances.

Procedure

Prior to testing, participants filled out the *BDI-II* (Beck *et al*, 1996), which is an established self–rating measure of depression severity. The computerized tasks were run on an Advantech personal computer with a touch-sensitive screen.

One-Touch Tower of London (*TOL*) (Owen *et al*, 1995a) is a modified version of the TOL task of spatial planning (Owen *et al*, 1990). Two arrangements of colored balls are presented on a computer screen and participants are asked to mentally plan and work out the minimum number of moves necessary to make the bottom array look like the top array. At the bottom of the screen there are six squares numbered one to six that stand for the minimum number of moves necessary to solve a given planning problem. The participants are told to touch the square indicating the number of minimum moves necessary to match the bottom array to the top array of balls. The TOL is considered to be more difficult than previous versions of the task. To ensure that all participants understood the task, each was given a block of practice trials in which they had to move the balls around and copy the top arrangement.

Three-dimensional IDED (Rogers *et al*, 1999a) is a cognitive rule-learning and set-shifting task adapted from the Wisconsin Cart Sorting Test (WCST) (Grant and Berg, 1948). Participants are required to learn a series of different visual dimensions involving stimuli that comprise three dimensions (number, shape, and color) and to shift attention between these dimensions. The task entails eight stages; proceeding to the next stage requires attaining the criterion of six consecutive correct responses. The task starts with a simple discrimination (SD) for stimuli varying in just one dimension. Then, a second alternative dimension to discriminate is introduced in a compound stimuli set (compound discrimination (CD)). This dimension is then tested in a novel set of stimuli (intradimensional shift (IDS)). Finally, participants need to learn a new dimension in a novel set of stimuli (extradimensional shift (EDS)). At each stage of the task, participants are required to inhibit the just learned stimulus–reinforcement association and reverse their responses (reversal shifts). The set-up of the 3D-IDED task is similar to 2D-IDED task, but the inclusion

of a further stimulus dimension is considered to increase task difficulty.

Paired Associate Learning (*PAL*) test (Robbins *et al*, 1997; Sahakian *et al*, 1988) from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition Ltd), assesses episodic memory and learning of geometric patterns and spatial locations. In the first six of the eight trials, six white boxes arranged in a circle on the screen automatically open up one at a time in a random order, each displaying a different geometric pattern. After the last box has disclosed its content, each pattern is displayed in succession in the center of the screen, and participants are asked to select the location where they remember the pattern was previously displayed. Feedback is provided after participants have located all of the patterns. If an error is made, the content of the six patterns is disclosed once again and participants are given another attempt at locating the patterns. Participants are given up to 10 attempts to locate all patterns correctly, and only when all patterns have been correctly located in the same trial can participants proceed to the next trial. In the final two trials, there are eight boxes on the screen with eight different patterns to remember their location. Response accuracy and latency are recorded for this task.

Delayed pattern recognition memory (*PRM*) (Sahakian *et al*, 1988), also taken from the CANTAB battery, is a test to assess short-term recognition memory for geometric patterns. Two sets of 12 geometric patterns are displayed consecutively in a box in the middle of the computer screen. Participants are instructed to memorize the patterns. After the presentation of the patterns, participants are given a two-choice test of two patterns, one which they have seen before together with a distractor pattern, and told to pick the pattern they remember having seen previously. The forced two-choice test is repeated after a 15-min delay. The pattern recognition task has shown to be sensitive to damage to temporal lobe structures, including the hippocampus (Owen *et al*, 1995b).

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 11 (SPSS Inc.). While untransformed values are displayed in figures and tables, some data were transformed in preparation for parametric analysis as described by Howell (1997). Thus, accuracy data, years of substance abuse, age of onset of amphetamine use and opiate use, as well as BDI depression scores were square root transformed and latency data were log-transformed. Pearson correlations were two-tailed and a significance level of 0.05 was assumed. The correlations for drug users and controls were calculated separately. One-way analyses of variance (ANOVA) were used to explore group differences in age, verbal IQ, and depression as measured by the BDI-II. Group differences regarding handedness, gender, and the results of the urine screens were analyzed via χ^2 or Fisher's exact procedures. The TOL and the PRM tasks were subject to repeated-measures ANOVA. If the Mauchly test showed violation of the sphericity assumption, Greenhouse–Geisser epsilon corrections were used. Univariate ANOVAs were conducted to further investigate significant results. The IDED and the PAL tasks were analyzed by multivariate analyses of variances (MANOVA). *Post-hoc* analyses of the effects of gender and positive urine samples of cocaine in opiate users and of opiates in amphetamine users were run on a single summary variable from each task to reduce the false-positive rate: TOL perfect solutions, IDED total errors, PRM delayed accuracy, and PAL first trial memory score.

Three planned orthogonal contrasts were conducted: (1) all three drug user groups compared to controls, (2) current drug users *vs* ex-drug users, and (3) current amphetamine users contrasted with current opiate users. In the event of group differences in the descriptive data, Tukey's *post-hoc* test was conducted if variances were equivalent between groups and Tamhane's test if variances differed between groups. *Post-hoc* procedures were thresholded at level $p<0.05$. Due to various computer problems data sets are not fully complete.

RESULTS

There were no significant group differences regarding age, verbal IQ, gender, or handedness, which are displayed in Table 2. Drug users also did not differ on years of drug abuse, showing that the groups were well matched. Neither was there a significant group difference regarding the age of onset of amphetamine use. However, the groups significantly differed regarding the age when they started using opiates ($F_{2,77}=9.17$; $p<0.001$). Not all ex-drug users had used opiates regularly, but those who did began using them significantly earlier than current amphetamine users (Tamhane's $p=0.008$) who reported taking opiates to calm down following an amphetamine binge. The ex-drug users also started using opiates earlier than the current opiate users, at trend level significance (Tamhane's $p=0.052$). The groups differed in regard to BDI depression scores ($F_{3,116}=14.22$, $p<0.001$). Drug users scored higher on the BDI than controls ($t_{116}=5.09$, $p<0.001$) and current drug users reported greater levels of depression symptoms than ex-drug users ($t_{116}=3.69$, $p<0.001$). Since depression has been shown to affect performance on the tasks administered (Murphy *et al*, 1999; Purcell *et al*, 1997; Sweeney *et al*, 2000), the BDI total score was included into the analysis as a covariate.

Tower of London

Univariate ANOVA on the percentage of correctly solved planning problems at first attempt revealed a main effect of group ($F_{3,113}=8.56$, $p<0.001$). Drug users solved fewer problems than controls ($t_{69.6}=-5.89$, $p<0.05$) and amphetamine users solved fewer problems than opiate users ($t_{42.7}=-2.34$, $p<0.05$). There was no difference between current and former drug users. Repeated-measures ANOVA on the different levels of difficulty revealed a significant main effect of difficulty ($F_{3.3,372.5}=10.97$, $p<0.001$) and a group × difficulty interaction at trend level ($F_{9.9,372.5}=1.66$, $p=0.088$). Univariate ANOVAs were then conducted to analyze the levels of difficulty separately. Performance on planning problems requiring one-move and two-moves did not differ between the groups ($F_{3,112}=1.44$, $p=0.236$; $F_{3,112}=1.333$, $p=0.268$). Significant differences emerged on three-moves ($F_{3,112}=6.39$, $p<0.001$), four-moves ($F_{3,112}=3.45$, $p=0.019$), and five-moves ($F_{3,112}=5.19$, $p=0.002$), and a

Table 2 Mean Total Scores (±Standard Deviation) of Descriptive Group Characteristics (Ratio of Participants' Gender, Handedness, and Percentage of Participants Who were Currently Employed)

	Controls	Amphetamine	Opiate	Ex-drug
N	**27**	**25**	**42**	**26**
BDI-II[a]	3.9 (2.9)	13.5 (8.5)	15.0 (9.9)	8.9 (10.2)
Verbal IQ[b]	114.4 (6.5)	111.2 (5.3)	113.0 (6.0)	113.5 (7.5)
Age (years)	35.1 (8.9)	37.0 (7.9)	33.8 (7.8)	38.0 (6.5)
Gender (M:F)	14:13	14:11	33:9	14:12
Handedness (R:L)	25:2	23:2	40:2	24:2
Years of drug abuse[c]	—	16.9 (9.1)	10.8 (8.6)	10.1 (5.3)
Age of onset:[d]				
Amphetamine use	—	18.4 (5.1)$^{n=25}$	18.1 (4.2)$^{n=15}$	16.8 (2.9)$^{n=23}$
Opiate use	—	27.1 (7.9)$^{n=14}$	22.1(4.7)$^{n=42}$	19.4 (4.2)$^{n=23}$

[a]BDI II, total score (Beck *et al*, 1996).
[b]Verbal IQ was estimated using the National Adult Reading Test (NART) (Nelson, 1982).
[c]Years of drug abuse were assessed from the time when the drug of choice was regularly used (defined as at least four times a week).
[d]Age of onset was assessed from the time when the drug was used frequently after it was first tried (as defined by at least once a week).

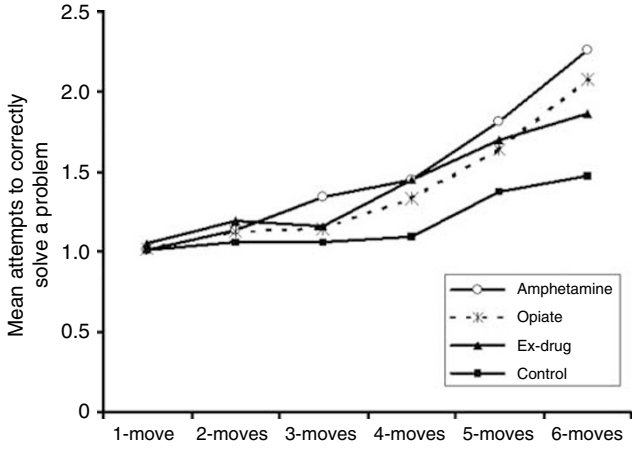

Figure 1 Mean attempts to success per group on 1–6-move planning problems on the one-touch TOL planning task. Planning performance for one-move and two-move problems was not different between the groups. For solving 3–6-move planning problems, all three drug user groups needed significantly more attempts than controls (all $p<0.001$). Performance did not differ between current and former drug users, but amphetamine users needed significantly more attempts on three-move problems relative to opiate users ($p<0.05$).

trend on six-move problems ($F_{3,112}=2.96$, $p=0.082$). As Figure 1 shows, the group differences were due to the fact that drug users needed more attempts to solve the planning problems than controls (three-moves: $t_{76.6}=4.09$; four-moves: $t_{83.6}=4.49$; five-moves: $t_{62.7}=4.30$ all $p<0.01$). There were no group differences in performance between current and former drug users at any stage. The contrast between amphetamine users and opiate users, however, revealed significantly more attempts in amphetamine users on three-move problems ($t_{37.8}=2.75$, $p<0.05$). Repeated-measures ANOVA was applied on latency at first response for the levels of difficulty (six levels) as the within-subject factor and group as the between-subject factor. There was a main effect of difficulty on latency at first attempt ($F_{2.1,161.1}=77.57$, $p<0.001$), but no group × difficulty interaction.

Three-Dimensional IDED Task

A total of 63% of the controls passed the entire task compared to 64% amphetamine users, 67% opiate users, and 65% of ex-drug users ($\chi^2=0.113$, $p=0.990$). Descriptive information on mean errors and latencies of the critical IDS and EDS stages are displayed in Table 3. Pass rates did not differ between the groups at any stage (data not shown). Performances in terms of errors made at each stage were analyzed by the use of MANOVA procedure. There was a significant group effect on the ID shift ($F_{3,77}=3.13$, $p=0.030$; Pillai's Trace $=0.38$, $p=0.171$), which was due to amphetamine users making significantly more errors than opiate users ($t_{46.4}=2.75$, $p<0.05$). The other two planned comparisons were not significant. Neither was there a significant group difference regarding the total number of errors made ($F_{3,77}=1.46$, $p=0.233$) nor on the total reversal errors ($F_{3,77}=0.32$, $p=0.809$). For response latencies, there was a group difference on the ED-reversal stage ($F_{3,77}=3.10$, $p=0.032$; Pillai's trace $=0.36$, $p=0.218$). Controls had longer ED-reversal latencies than the other groups (mean in seconds ± SD, controls: 1.75 ± 1.45, amphetamine: 1.37 ± 0.59, opiates: 1.22 ± 0.39, ex-drug: 1.15 ± 0.34), but this difference was not significant in the planned comparison. In addition, it is worth noting that, although the amphetamine users tended to have higher error rates throughout the test (see Table 3), none of the three planned comparisons was significant.

Paired Associate Learning

All control participants successfully completed the entire task compared to 88% of amphetamine users, 88% of opiate users, and 89% of ex-drug users. Pass rates did not differ significantly between the groups (Fisher's exact

Table 3 Mean (±Standard Deviation) of Main Task Measures per Group

Task	Main measures	Controls	Amphetamine	Opiate	Ex-drug	*p*-values
TOL	Perfect solutions at first attempt (%)	86.11 (9.32)	67.21 (13.84)	75.40 (12.88)	71.83 (18.88)	**<0.001**
	Mean attempts (1–3 moves)	1.04 (0.14)	1.16 (0.12)	1.10 (0.12)	1.13 (0.06)	**0.002**
	Mean attempts (4–6 moves)	1.31 (0.63)	1.90 (0.47)	1.68 (0.52)	1.67 (0.28)	**<0.001**
	Mean latency (s) (1–3 moves)	8.20 (1.77)	7.52 (1.66)	8.13 (2.19)	7.80 (1.95)	0.580
	Mean latency (s) (4–6 moves)	33.38 (13.354)	34.66 (17.28)	31.08 (17.47)	30.07 (17.57)	0.752
3D-ID/ED	SD mean errors	0.41 (1.08)	0.72 (1.57)	0.26 (0.66)	0.46 (0.81)	0.073
	CD mean errors	2.56 (5.71)	3.04 (5.94)	2.93 (6.64)	2.08 (3.11)	0.585
	IDS mean errors	1.65 (3.47)	2.52 (3.36)	1.26 (2.58)	1.83 (4.82)	**0.030**
	EDS mean errors	7.85 (8.67)	12.17 (9.88)	9.89 (9.19)	8.82 (8.16)	0.420
	Total reversal errors (sum of the 4 stages)	7.00 (5.24)	9.63 (4.51)	7.82 (5.40)	9.39 (7.68)	0.809
	Total errors on the task (sum of 8 stages)	18.53 (12.37)	23.00 (9.30)	17.45 (11.22)	18.11 (10.10)	0.233
	IDS mean latency (s)	1.86 (0.82)	1.48 (0.65)	1.58 (0.52)	1.49 (0.53)	0.446
	EDS mean latency (s)	1.84 (0.67)	1.50 (0.57)	1.52 (0.47)	1.49 (0.52)	0.261
	Reversal latencies (s) (mean of the 4 stages)	1.25 (0.41)	1.21 (0.49)	1.27 (0.70)	1.13 (0.43)	0.627
PAL	Percent of stages passed on first trial	71.11 (21.72)	57.60 (21.07)	60.00 (20.24)	65.38 (14.49)	0.070
	first trial memory score (mean)	16.96 (3.37)	12.84 (4.20)	13.81 (3.68)	14.46 (3.74)	**0.011**
	Total trials to success (mean)	7.52 (2.58)	11.04 (3.61)	10.29 (3.79)	9.81 (2.98)	**0.005**
PRM	Percent of correctly recognized patterns (immediate)	93.21 (8.81)	80.00 (11.72)	86.41 (12.14)	87.34 (10.24)	**0.001**
	Percent of correctly recognized patterns (delay)	92.75 (7.89)	82.00 (14.86)	83.33 (11.16)	84.29 (12.49)	**0.025**
	Latency (s) (immediate)	2.06 (0.45)	2.22 (0.65)	2.28 (0.56)	2.08 (0.50)	0.404
	Latency (s) (delay)	2.17 (0.54)	2.14 (0.61)	2.21 (0.51)	2.06 (0.52)	0.682

Bold indicates values with $p<0.05$.

test, $p=0.263$). However, there were significant differences on the three main measures: the first trial memory score, total errors, and total trials. As revealed by MANOVA procedures, there was a group effect on the number of stimuli correctly located after first presentation ($F_{3,115}=3.89$, $p=0.011$, Pillai's trace $=0.15$, $p=0.045$) such that drug users had a significantly lower first trial memory score than controls ($t_{116}=-3.96$, $p<0.05$). As displayed in Figure 2, the group effect on total errors ($F_{3,115}=4.26$, $p=0.007$, Pillai's trace $=0.15$, $p=0.045$) was due to a significantly greater number of errors made by drug users relative to controls ($t_{116}=4.52$, $p<0.05$). The groups significantly differed in the number of trials needed to learn the paired associates ($F_{3,115}=4.52$, $p=0.005$, Pillai's trace $=0.15$, $p=0.045$), with drug users needing significantly more trials than controls ($t_{116}=4.17$, $p<0.05$). On all three measures, the other two planned comparisons did not reveal significant group differences.

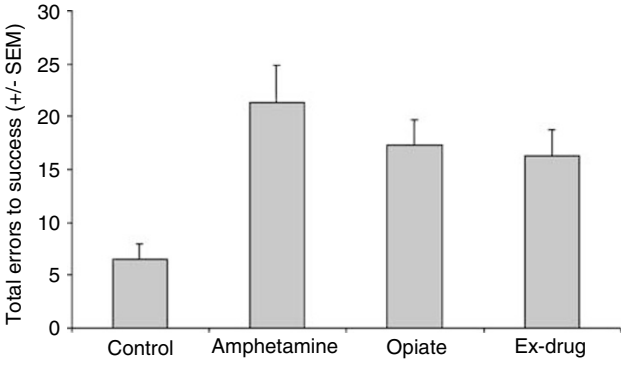

Figure 2 Total errors made to successfully complete the PAL task. All three drug user groups made a significantly greater number of errors compared to controls in learning the correct associations between the patterns and their spatial locations ($p=0.007$).

Immediate and Delayed Pattern Recognition (PRM)

Repeated-measures ANOVA was conducted on accuracy and latency of the recognized patterns with delay as a within-subject factor (two levels) and group as a between-subject factor. The ANOVA revealed a significant main effect of delay for latency ($F_{1,115}=857.75$, $p<0.001$) and a significant delay × group interaction on accuracy ($F_{3,115}=5.72$, $p=0.001$). Univariate ANOVA on the percentage of correctly recognized patterns after immediate presentation showed a group difference ($F_{3,115}=6.26$, $p=0.001$). Drug users recognized fewer patterns relative to controls ($t_{116}=-3.78$, $p<0.05$) and amphetamine users recognized fewer patterns relative to opiate users ($t_{116}=-2.41$, $p<0.05$). There was also a significant group difference on patterns recognized after a 15-min delay ($F_{3,115}=3.24$, $p=0.025$) such that drug users recognized fewer patterns relative to controls ($t_{116}=-3.87$, $p<0.05$). Recognition memory did not differ between current and

Table 4 Mean (±Standard Deviation) per Group in Respect to Gender of the Number of Patterns Correctly Located after First Presentation (First Trial Memory Score) and the Number of Patterns Correctly Recognized Following Presentation and Following a 15-min Delay

		Controls		Amphetamine		Opiate		Ex-drug	
Task	**Measures**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
PAL	Mean 1st trial memory score	18.29 (2.61)	15.54 (3.60)	11.50 (3.84)	14.55 (4.18)	13.21 (3.54)	16.00 (3.54)	14.29 (4.32)	14.67 (3.11)
PRM	Percent of correctly recognized patterns (delay)	95.24 (6.51)	90.06 (8.60)	77.08 (16.49)	88.26 (10.00)	83.21 (11.29)	83.80 (11.30)	82.44 (12.14)	86.46 (13.7)

former drug users, but amphetamine users tended to recognize more patterns after the delay than after immediate presentation (see Table 3). According to the univariate ANOVA on the difference score, the number of recognized patterns after the delay minus number of immediately recognized patterns was not significant.

Correlational Analyses

Neither years of drug use nor years of drug abstinence were associated with any outcome measure. To assess the influence of current tobacco smoking on task performance in all participants, correlational analyses were carried out on the number of cigarettes smoked per day and a summary measure of each task, with no significant effects found.

Gender Effects

Although the groups were matched for gender, nonetheless the data were analyzed in order to explore gender differences. Results of these analyses showed that neither in controls nor in drug users did male and female participants differ regarding BDI scores, age, or verbal IQ. Male and female drug users also did not differ in respect to duration of drug use. Univariate ANOVA was applied to the summary measures of each task with both group and gender as independent variables. A significant group × gender interaction on the first trial memory score ($F_{3,112} = 3.70$, $p = 0.014$) and a marginal significant group × gender interaction on PRM delayed accuracy ($F_{3,112} = 2.26$, $p = 0.085$) were found. The means and SD of the performance measures are displayed in Table 4. To explore the nature of the effects, univariate ANOVAs were carried out for controls and drug users separately using gender as independent variable. Figure 3 shows that in controls, men remembered more paired associates following first presentation than their female counterparts ($F_{1,25} = 5.21$, $p = 0.031$). In drug users the relationship was reversed: women had a significantly higher first trial memory score than the male drug users ($F_{1,91} = 5.56$, $p = 0.021$). While there was no significant difference in performance between female controls and female drug users on the memory score, male drug users performed significantly worse than male controls ($F_{1,73} = 23.10$; $p < 0.001$). The PRM delayed accuracy, shown in Table 4, illustrates that the gender effect was of a similar nature to the first trial memory score.

In summary, drug users showed marked impairments on the TOL, PAL, and PRM compared to controls, while performance on the 3D-IDED task did not significantly differ from controls. No significant differences between current and former drug users were found on any of the tasks. Compared to opiate users, amphetamine users showed more pronounced deficits on tasks of executive function including attentional set-shifting, PRM and visuo-spatial planning in the TOL task. Subsequent analyses regarding the positive urine screens for opiates in amphetamine users and for cocaine in opiate users were non-significant.

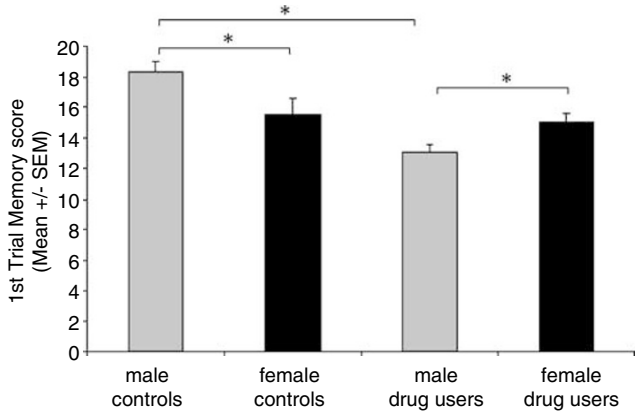

Figure 3 Gender differences regarding how many paired associates (PAL) had been remembered following first presentation. In controls, men remembered significantly more paired associates than women ($p = 0.031$). In drug users, the performance profile was reversed: women remembered more paired associates than men ($p = 0.021$). While there was no significant difference between drug using women and female controls, male drug users performed significantly worse than male controls ($p < 0.001$). Note: Neither in the control group nor in the drug user group did male and female participants differ regarding BDI scores, age, or verbal IQ. Male and female drug users did not differ with respect to duration of drug use. *$p < 0.05$

DISCUSSION

Consistent with our hypothesis, drug users showed marked impairments in spatial planning, PAL, and visual pattern recognition relative to controls. Performance of former drug users was not significantly different from current drug users on any task measure, suggesting that the neurocognitive impairment does not simply reflect the current effects of the substances abused. As hypothesized, current amphetamine users showed more profound impairments than opiate users on spatial planning, pattern recognition memory, and attentional set-shifting.

Comparison of Cognitive Performance of Chronic Drug Users with Controls

On the TOL spatial planning task, all three drug user groups solved significantly fewer problems correctly, and therefore needed more attempts relative to controls. However, on the easy stage of the task, performance was intact. Despite having problems with spatial planning, drug users did not deliberate longer on the problems. This stands in contrast to other patient groups with a fronto-striatal pathology, such as patients with Parkinson's Disease or with schizophrenia, who also perform poorly on the TOL (Owen *et al*, 1992, 1995a; Pantelis *et al*, 1997). The fact that our drug users and controls did not differ on response latency may indicate that drug users did not reflect sufficiently long to solve the problems accurately. The significantly higher number of errors on the TOL in our drug user groups compared to controls is in keeping with evidence for prefrontal dysfunction in chronic drug users (Ersche *et al*, 2005; Hester and Garavan, 2004; Paulus *et al*, 2002) since the right DLPFC has shown to be critically involved in spatial planning on the TOL (Baker *et al*, 1996; Manes *et al*, 2002).

Drug users' performance on the 3D-IDED task did not significantly differ from controls, although it has been reported that the right DLPFC is implicated in the critical EDS stage (relative to IDS) (Rogers *et al*, 2000). It is possible that group differences in performance on the 3D-IDED task did not emerge because only 78% of our controls, who were specifically selected to match the drug user groups, passed the EDS stage. The relatively high number of controls failing the EDS stage led to an overall pass rate of the task of 63%. Previous research with this task indicates a pass rate around 80% in healthy volunteers, albeit in participants with a high level of education (Mehta *et al*, 1999). On the other hand, unimpaired performance of substance users in comparison to healthy controls has been found on the WCST (Grant and Berg, 1948), which contains a similar set-shifting component to the 3D-IDED task (Simon *et al*, 2002, in cocaine users; Rotheram-Fuller *et al*, 2004, in methadone-maintained opiate users; Pau *et al*, 2002, in former heroin users). Our results, however, contrast with the impaired performance on a related but different test of attentional set-shifting in chronic substance users relative to healthy controls reported by Ornstein *et al* (2000). There are a number of possible explanations for the differing findings. One possibility may be due to the fact that we used a different task, which includes three stimulus dimensions similar to the WCST. Using a two-dimension task, Ornstein *et al* (2000) reported an overall pass rate of 90% in controls, which may assist the detection of deficits in attentional set-shifting. It is thus likely that, due to the poor performance of our controls on the EDS stage, the high number of EDS errors in amphetamine users, as shown in Table 3, did not reach significance. In addition, sample size, demographic, and clinical characteristics of the groups differed between the two studies. However, in accordance with Ornstein *et al* (2000), we did not find significant group differences on reversal errors, which are considered to reflect orbitofrontal dysfunction (Hornak *et al*, 2004).

Severe impairments in drug users relative to controls were evident in the PAL task, which requires forming associations between a stimulus (*what*) and a spatial location (*where*). Drug users not only performed poorly at locating patterns correctly after first presentation, but they also made significantly more errors and needed more trials to learn the correct associations (*what goes where*). Experimental research in animals has found that the encoding and retrieval of object–spatial paired associations (*what is where*) requires the hippocampal formation in the temporal lobe (Day *et al*, 2003; Parkinson *et al*, 1988); areas which are not only involved in learning and memory but also undergo structural changes in the course of drug addiction (Everitt *et al*, 1999; Nestler, 2002; Robbins and Everitt, 2002; Vorel *et al*, 2001). Recent evidence also suggests that mesiotemporal areas are the most affected by the metabolic changes following chronic cocaine use (Porrino *et al*, 2004). In particular, neural changes in the hippocampus associated with chronic drug use are considered to be long-lasting (Nestler, 2001, 2002). It should also be noted that the hippocampi are among the first brain regions that are affected by Alzheimer's Disease (Ball, 1977; Hyman *et al*, 1984), and the PAL task has recently demonstrated a high sensitivity to the early memory decline in Alzheimer's disease (Blackwell *et al*, 2004). Moreover, early signs of memory impairment and associate learning are also detectable with the PAL task in patients with schizophrenia following the first psychotic episode (Barnett *et al*, 2005). For recognition memory, impairments in both conditions, immediately and after a 15-min delay, were obvious in drug users. Drug users recognized significantly fewer patterns than our drug-naive controls in both conditions, thereby extending the findings by Ornstein *et al* (2000), who only investigated immediate recognition memory performance. The poor performance of our drug users on the PAL and the PRM task provides further evidence that substance dependence is associated with deficient learning and memory of the declarative type (Nestler, 2001, 2002; Robbins and Everitt, 2002).

In view of the accumulating evidence that indicates that chronic drug use has more adverse effects on the male than on the female human brain (Chang *et al*, 1999; Kaufman *et al*, 2001; Kim *et al*, 2005; King *et al*, 2000; Levin *et al*, 1994; Lyoo *et al*, 2004), we matched our groups for gender. We took the opportunity to explore gender differences *post hoc* and confirmed findings from previous research that healthy male volunteers perform better on visuo-spatial tests than their female counterparts (Delgado and Prieto, 1996; Weiss *et al*, 2003). This relationship, however, was reversed in drug users. Figure 3 shows that male drug users showed significantly greater impairment in remembering paired associates than female drug users, whose performance was not significantly different from female controls. At trend level the same gender effects were also evident on accuracy in delayed PRM (Table 4). Our finding therefore suggests that visual memory impairment associated with chronic drug use is limited to the male gender. Given that findings from experimental animal studies show greater neurotoxic effects in male compared to female brains (Heller *et al*, 2001; Wagner *et al*, 1993), it seems unlikely that the more severe impairment seen in our male drug users is simply due to more heavy drug use in men. Recently, it has been suggested that the gonadal steroid hormone estrogen, in contrast to testosterone, has a neuroprotective effect on drug toxicity (Dluzen *et al*, 2002;

Dluzen and Horstink, 2003; Dluzen and McDermott, 2004; Myers *et al*, 2003; Yu and Liao, 2000). Our study extends previous research that has reported greater neurocognitive impairment in male drug users compared to male controls (Kim *et al*, 2005; Stout *et al*, 2005) and has, to the best of our knowledge, provided new evidence suggesting the dramatic decline in visuo-spatial memory in male drug users via the reversed gender effect between drug-naive controls and chronic drug users.

Cognitive Function in Chronic Amphetamine Users Relative to Opiate Users

Consistent with our hypothesis, amphetamine users showed more marked impairments compared to opiate users, which reached significance on spatial planning (three-move problems) and PRM. The deficits exhibited at these easy task stages may either reflect an overconfident approach towards the solution or inefficiency in concentrating on the task demands. The current user groups further differed in performance on the 3D-IDED task. Amphetamine users, relative to opiate users, made significantly more errors when required to generalize an already learned attentional set to a novel set of stimuli (IDS stage) and numerically more errors when they needed to learn a new dimension in a novel set of stimuli (EDS stage). It is interesting to note that, in patients with schizophrenia, errors on the IDS stage are associated with disorganized symptom characteristics of the disorder (Pantelis *et al*, 2004), while impairment on the EDS stage is considered to reflect the progressive deterioration of the illness (Pantelis *et al*, 1999, 2003, 2004). Chronic use of amphetamines can induce psychotic states similar to the psychosis seen in patients with schizophrenia (Curran *et al*, 2004; Robinson and Becker, 1986), in contrast to morphine which has been regarded as having antipsychotic properties (Comfort, 1977; Aguilar *et al*, 2004). This difference in the effects of the two substances seems to be mirrored in the performance of chronic users of these substances on this attentional set-shifting task.

Our findings, however, contrast with the double dissociation reported by Ornstein *et al* (2000), that opiate users fail on the IDS and amphetamine users on the EDS stage. Our amphetamine users did show a marked tendency toward increased errors on the EDS stage, but our opiate users did not display signs of impairment on the IDS stage. At first glance, these differing findings may be surprising, but performance on the WCST (Grant and Berg, 1948) has also been shown to fluctuate in chronic drug users. There is some indication that performance may depend upon whether participants are 'on the drug' during time of testing. For example, Lyvers and Yakimoff (2003) found that methadone-maintained opiate users in early withdrawal made more mistakes on the WCST than opiate users who were on a sufficient dose of methadone at the time of testing. Correspondingly, methamphetamine users on the drug performed worse than controls (Simon *et al*, 2002), whereas 25-day abstinent crack-cocaine users showed an even better performance on the WCST than controls (Hoff *et al*, 1996). This suggests that not only the difference in the task version but also group characteristics regarding demographic as well as clinical variables (ie dependency on more than one substance), type of substances currently used, and the state of drug intoxication need to be taken into consideration when explaining differing findings between these two studies. In line with Ornstein *et al* (2000), our findings show clear deficits in executive function in chronic opiate users at normal response latency, whereas previous research has found qualitatively unimpaired performance at the expense of increased response time in this patient group (Mintzer and Stitzer, 2002, re psychomotor speed Rogers *et al*, 1999b, re decision-making; Specka *et al*, 2000, re visual structuring). Future studies could address the question of whether specific encouragement of opiate users to increase deliberation time can reduce the level of impaired executive function.

Cognitive Function in Current Drug Users Relative to Former Drug Users

Performance in the former drug user group was not significantly different from current user groups, suggesting that impairments probably do not simply reflect current effects of the drug. Urine analyses prior to testing confirmed current drug taking in the amphetamine and opiate groups and drug abstinence in the former drug users. Retrospective reports indicated at least 1 year abstinence (on average over 8 years) in the former drug users. As such, we argue that the neuropsychological impairments are probably the result of chronic drug exposure. Particularly the fact that 50% of the former drug users had been dependent on both stimulants and opiates, using both together intravenously, may have exacerbated negative consequences of chronic drug use (Leri *et al*, 2003). Recovery of cognitive function may therefore be limited despite the prolonged abstinence. The length of drug abstinence was not associated with improved cognitive performance, in keeping with previous research (Hoff *et al*, 1996; Medina *et al*, 2004). The similarities between the current and former drug users are also consistent with the notion of pre-existing neurocognitive impairments in drug users, which predate drug taking and may represent vulnerability markers. There is evidence for executive dysfunction in adolescent groups at high risk for substance abuse (Nigg *et al*, 2004; Tarter *et al*, 2003).

General Comments and Summary

One limitation of the present study was an inevitable degree of polydrug use in the current users. However, the amphetamine and opiate groups both met the DSM-IV criteria for dependence, respectively, for those different drug classes. We also excluded participants who met DSM-IV criteria for dependence on substances other than amphetamines/opiates, although the current drug users reported recreational use of several drugs including ecstasy, cocaine, and cannabis unlike the controls. This polydrug use was reasonably balanced across the current amphetamine and opiate groups, and seems unlikely to have confounded the exaggerated cognitive deficits in the current amphetamine users. Although we included the BDI total score as a covariate in the analyses, the patterns of cognitive impairment displayed by our current drug users were different from the performance of patients suffering from major depression (Purcell *et al*, 1997; Sweeney *et al*, 2000), but did not differ from the non-depressed ex-drug users.

Our findings may therefore suggest that the substantial cognitive impairments associated with dependence on amphetamines and opiates are independent of depression. Our findings may further explain why treatment approaches which make use of a cognitive visual representation technique or which include cognitive training modules targeting strategies to improve memory and planning have shown to be very effective (Czuchry and Dansereau, 1999, 2003; Dansereau and Dees, 2002; Joe *et al*, 1997; Peel *et al*, 1996; Pitre *et al*, 1997). In summary, we found that participants engaged in current or previous drug use showed marked impairment in spatial planning, paired associates learning, and pattern recognition memory.

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