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ORIGINAL INVESTIGATION

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Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users

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Abstract *Rationale:* Experimental evidence has shown that 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") can act as a serotonergic neurotoxin in laboratory animals. The serotonin system predominantly innervates frontal and limbic regions of the brain and has been associated with consolidatory learning and mnemonic processes in humans. *Objectives:* The aim of the present study was to investigate the cognitive neuropsychological profile of drug-free ecstasy users by employing a selection of tasks previously associated with lesion or neurodegenerative damage to the temporal lobe or fronto-striatal regions. *Methods:* The study comprised 40 participants: 20 ecstasy polydrug users and 20 polydrug users who had never taken ecstasy. *Results:* Ecstasy users were significantly impaired on a recognition task for complex visual patterns and spatial working memory, as a function of task difficulty rather than systematic search strategy. They also showed a trend towards impairment on several learning paradigms. Ecstasy users remained relatively unimpaired on most measures associated with prefrontal functioning, with the exception of verbal fluency "letter" generation. *Conclusions:* Initial cognitive deficits in ecstasy polydrug users may be more apparent in tasks known to be sensitive to temporal functioning.

Keywords Ecstasy · Memory · Learning · Temporal · Neurotoxicity · Serotonin

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Introduction

The "rave drug" MDMA ("ecstasy" 3,4-methylinedioxymethamphetamine) is a ring-substituted amphetamine derivative associated with persistent modulations of the serotonin (5-HT) system in both animals (Ricaurte 2000) and humans (McCann et al. 1998; Semple et al. 1999). Extensive pre-clinical evidence suggests that the integrity of the 5-HT system is vital to the successful acquisition of learning and mnemonic processes (Hunter 1988). In animals, deficits caused by either the destruction or chemical manipulation of 5-HT pathways have included induced inhibitory regulation of switching between behavioural states (AlRuwaitea et al. 1997) and disruption of spatial working memory (Santucci et al. 1995). In humans, clinical conditions associated with reductions in 5-HT, such as Alzheimer's disease (Freedman et al. 1989), obsessive compulsive disorder (Cavedini et al. 2001) and depression (Elliott et al. 1997), have been associated with selective temporal and fronto-striatal deficits, consistent with 5-HT distribution. These have included impairments of visual recognition (Sahakian 1990), planning (Elliott et al. 1997), set shifting (Veale et al. 1996) and associative learning (Sahakian et al. 1988).

Evidence from animal and human data shows ecstasy to be a 5-HT neurotoxin at certain doses (see Parrott 2000 for review). In view of previous clinical literature therefore, it may be suggested that the long-term consumption of the drug potentially exposes users to some risk of cognitive impairment. Extrapolation from extensive animal data further indicates that these impairments may reflect serotonergic modulation of frontal and hippocampal functioning (Aguirre et al. 1997). Data from non-human primates have shown decreases in striatal VMAT2 transporters (vesicular monoamine transporter type 2) and reductions in the anterograde transport of labelled material to forebrain areas in doses representative of those used recreationally by humans (Ricaurte 2000). In humans, imaging research has shown heavy recreational use to be linked with reductions in 5-HT

transporter binding within the frontal cortex, striatal regions (including the caudate and putamen) and hypothalamus (McCann et al. 1998).

The present study has therefore employed analogous versions of tasks that have previously demonstrated sensitivity to cognitive impairments in both ecstasy users and/or clinical patients suffering from neuropsychiatric disorders associated with serotonergic dysfunction. Some of the tasks have also shown sensitivity to frontal and temporal excision patients, representing regions of the brain consistent with 5-HT distribution and ecstasy-induced toxicity. All tasks have been extensively validated in neuroimaging studies with normal volunteers and/or within relevant clinical populations.

The cognitive tests used included a broad range of executive tasks in order to clarify the possible decrements in working memory processes. Selective impairments in short-term memory have been demonstrated with heavy ecstasy use (Bolla et al. 1998; Parrott et al. 1998; Morgan 1999); however, whether working memory is affected remains unclear. The present study, therefore, includes variants of the original CANTAB tasks, such as the one-touch Tower of London (TOL) task and the 3-D intra-dimensional extra-dimensional attentional set-shifting task (3-D IDED) as well as a decision-making task and a spatial working memory task with a separate strategy component. Increased planning times on manual versions of the TOL have been demonstrated in heavy ecstasy users (Milani and Schifano 2000; Fox et al. 2001b). Failure to shift set at the extra-dimensional stage of the 3-D IDED and sub-optimal quality of betting choice on the decision making task have also been associated with amphetamine use (Ornstein et al. 2000).

In addition a go/no go test was also included to assess response inhibition sensitive to both executive dysfunction and increased impulsivity implicated in ecstasy use (Morgan 1998).

Since most drugs of abuse and serotonergic depletion in normal individuals produce deficits in short-term memory, the CANTAB pattern recognition test was used to assess short-term memory function in ecstasy users. 5-HT depletion in both animals and humans has also been reported to result in the disruption of various learning processes (Hunter 1988). Furthermore, the paired associates learning (PAL) task has characterised deficits in healthy volunteers who have experienced artificially induced reduction of the 5-HT system via ingestion of a low-dose tryptophan drink (Park et al. 1994) as well as patients with localised frontal lesions (Petrides et al. 1993). Therefore the PAL test was used to assess visuospatial learning and memory (Swainson et al. 2001). Table 21.1 and Figure 21.2 published by Lee et al. (2000) provide a good summary of certain functions and brain regions targeted by many of the tasks used in the current study.

Methods

Participants

Ecstasy users

Twenty participants were recruited (10 females, 10 males) either through advertisements placed in magazines serving the London area or via the snowball technique (Solowij et al. 1992). Mean (±SD) age of the group was 27.3±6.7 years (range 18–40 years), and their mean pre-morbid verbal IQ as measured by the National Adult Reading Test (NART; Nelson 1982) was 100.3±6.3 (range 90–115). A detailed drug history was taken prior to testing. The mean number of ecstasy tablets consumed was 172.0±227.36 (range 10–1000) and the mean duration of usage was 51.9±25.9 months (range 3–122 months). Although ecstasy was the preferred drug of use for the participants, all 20 were also polydrug users. All 20 ecstasy users had also reported cannabis use, 18 had used amphetamine, 17 had used cocaine, 15 had used lysergic acid (LSD) and 10 had used psilocybin mushrooms. The use of benzodiazepines, opiates, solvents and anabolic steroids were limited (5, 4, 5 and 1, respectively). Of the 20 ecstasy users, 16 were smokers and 14 consumed alcohol on at least a weekly basis. All subjects indicated that they had been free of psychoactive drugs for at least 2 weeks prior to testing.

Controls

Twenty participants were recruited (12 females, 8 males) either via the snowball technique or from advertisements placed on web sites. Mean age of the group was 27.5±7.6 years (range 19–48 years) and their mean pre-morbid verbal IQ was 103.0±3.6 (range 98–110). A detailed drug history was taken prior to testing. None of the control group had ever consumed ecstasy. However, they were all polydrug users. All 20 of the control group had consumed cannabis, 11 had reported amphetamine use and 11 cocaine use, 5 had used LSD and 6 had used psilocybin mushrooms. The use of opiates and solvents was again limited (3 and 1 users, respectively) and none of the control group had used either benzodiazepines or anabolic steroids. Of the 20 polydrug users, 12 were smokers and 18 consumed alcohol on at least a weekly basis. All subjects indicated that they had been free of psychoactive drugs for at least 2 weeks prior to testing.

Exclusion criteria for both groups were a history of psychiatric or neurological illness, and alcohol dependence. All participants gave written informed consent, and the University of East London Ethics Committee approved the study.

Procedure

Verbal fluency

Participants completed both the letter and semantic categories of the Verbal Fluency Task (Benton 1968). In the letter category, participants were asked to produce as many words as possible beginning with a specified letter in 1 min. The three letters chosen were F, A and S. In the semantic category, participants were asked to produce as many different members of a particular semantic category as possible in 1 min. The category “animals” was chosen for the semantic condition. Mean word generation was calculated for both “letter” and “semantic” conditions. In the letter conditions, participants were also scored for semantic and phonemic strategy use. For the “semantic score”, participants were given two points for two consecutively semantically linked words, three points for three semantically linked words, and so on. For the “phonemic” score, an identical scoring method was employed for consecutive words that used the same sounds, such as “flash, flake, flat” or “square, share”.

Computerised tasks

The majority of tasks were administered from CANTAB (Cambridge Cognition, CeNeS Ltd. Cambridge UK) using a portable microcomputer with a Datalux touch-sensitive screen. Participants were seated approximately 0.5 m from the screen and given a motor screening task in order to familiarise themselves with the equipment. Following completion, the remaining tasks were administered in the following order. All tasks were counterbalanced.

Spatial working memory

This task was described in detail by Owen et al. (1992) and required participants to search through a display of boxes in order to find a certain number of "hidden" blue tokens. Only one token was hidden at any one time, and once a token had been found in a particular box, that box would not be used again in order to conceal another counter. As a result, each participant was scored for two types of search error: returning to a box in which they had previously found a blue token ("between search error") and returning to a box (in the same search sequence) that had previously been shown to be empty ("within search error"). Each participant was required to attempt four 3-box trials, four 4-box trials, four 6-box trials and four 8-box trials. The 3-box trials were used for practice purposes only and not included in the subsequent analysis. Participants also received a "search strategy" score reflecting their ability to employ an optimal repetitive searching strategy, in order to successfully minimise "between" and "within" search errors.

3-D IDED attentional shift

This task is based on a version taken from the CANTAB battery (Downes et al. 1989); however, the version employed in the current study also incorporated an additional dimension, making a total of three (shape, colour and number). The task assessed ability to form, maintain and shift attentional set and comprised eight stages that have been described in detail elsewhere (Elliott et al. 1995; Rogers et al. 1999). In all conditions, participants were requested to learn a series of two alternative forced choice discriminations and their reversals. The stimuli used varied along three possible dimensions (one, relevant and two, irrelevant). In the simple visual discrimination stage, the two stimuli differed along only one of the possible three dimensions and, in the following reversal stage, the previously incorrect stimulus became the correct stimulus. In the compound visual stage the contingencies from the previous stage remained the same (i.e. colour); however, the stimuli differed along all three possible dimensions. In the "intradimensional shift" stage, the relevant dimension (i.e. colour) still remained unchanged despite the introduction of two completely novel stimuli. In the final "extra-dimensional shift" stage, participants were required to "shift" response set to a previously irrelevant dimension (i.e. shape). Each of the four stages also preceded a "reversal" stage where the previously non-reinforced stimulus became the reinforced target. In order to proceed along each stage, participants were expected to achieve six correct successive discriminations in a row. If these discriminations were not achieved following 50 attempts, the task was terminated. Errors and response latencies were recorded for each of the eight stages.

Pattern and spatial recognition

Both pattern and spatial recognition (Sahakian et al. 1988; Owen et al. 1995) were presented to each participant in two phases; a "presentation phase" followed by a "recognition phase". In the initial "presentation" stage of the pattern recognition task, participants were shown 12 coloured abstract patterns, one at a time, for 3 s. In the following "recognition" phase, the 12 "target" patterns were shown in reverse order and paired with a novel pattern. Participants were instructed to touch the pattern they recognised from the "presentation" phase. This procedure was then repeated with 12 novel patterns.

In the "presentation" phase of the spatial recognition task, five white boxes were shown (one at a time for 3 s) in different locations on the screen. In the following "recognition" phase, the five "target" boxes were shown again in reverse order and paired with a second box, located in a novel location. Participants had to touch the box that was in the same location as the one shown in the "presentation" condition. The task was repeated with three further sets of boxes. In both tasks, all error measures were expressed as a percentage. Response latency was also measured.

Paired associates learning

The PAL task (Sahakian et al. 1988; Owen et al. 1995) comprised both a paired associates memory component and a conditional learning component. Participants were presented with a set of six white boxes positioned in a circle around the screen. Each of the boxes opened up in a random sequence revealing an abstract pattern "inside". The patterns were then displayed individually in the centre of the screen and participants were requested to touch the box in which they had seen each of the patterns. All participants performed two trials of "one pattern-location association", two trials of "two pattern-locations", and two trials of three. In the subsequent trial, participants were expected to remember six pattern locations and eight in the final trial. If an error was made, a "reminder" phase was shown. Each participant was allowed nine "reminder" phases for each trial, making a total of ten attempts prior to the task being terminated. There were three performance measures all analysed across the eight trials. These comprised the number of presentations required on each trial, a memory score reflecting the total number of patterns successfully located on initial presentation (26 being the maximum score) and the total number of errors made on each trial.

Go/no go

This represents a task of response set and shifting of response set. The task consisted of ten separate blocks, each of which involved 18 symbols appearing rapidly on the centre of the screen. Half of the symbols were "targets" and half were "non-targets" and comprised either letters (A–G) or numbers (2–9). Participants were told to tap the space bar as quickly as possible only when they saw the target for that block. The target was switched from letters to numbers (or vice versa) following every two blocks. The initial two blocks were practice blocks where the target was counterbalanced across participants. All participants were scored for mean number of errors made across trials (i.e. failure to tap the space bar), mean number of "distractors" (i.e. the number of times they had responded to a non-target) and mean reaction time.

One-touch TOL

In order to familiarise participants with this task, the 1- to 4-move trials taken from the modified version of the TOL planning task were used for training (Owen et al. 1995). All rules governing the movement of the balls remained the same as for the original TOL task (Shallice 1982).

In the one-touch TOL task, participants were shown two arrangements of balls hanging in stockings, one at the top of the screen and one at the bottom of the screen. They were requested to determine the minimum number of moves it would take in order to match the bottom arrangement to the top arrangement without actually moving the balls. Instead, participants were presented with a panel of six boxes labelled "1" to "6" at the bottom of the screen, and were requested to touch the number that corresponded to the minimum number of moves required in order to complete the task. Each participant was given 24 trials randomly, comprising

four 1-move trials, four 2-move trials, four 3-move trials, four 4-move trials, four 5-move trials and four 6-move trials. Trials were then collapsed into two categories: "easy" (trials 1, 2 and 3) and "difficult" (trials 4, 5 and 6). Three performance measures were calculated for each of the two difficulty levels: the percentage correct, mean number of attempts taken for each participant to complete each trial and mean latency prior to the first response.

Decision-making task

This task was intended to assess decision-making behaviour and is explained in detail in Rogers et al. (1999). An array of ten red and blue boxes were displayed at the top of the screen. Participants were informed that the computer had hidden a yellow counter at random "inside" one of the boxes, and that it was their task to decide whether the counter was more likely to be found inside a blue or red box. The ratio of the blue and red boxes was changed in a pseudo-random fashion from trial to trial. Participants had to "stake or place a bet" on the chances of their choice being correct. If their choices were correct, the "stake" was added to a starting score of 100 points, and subtracted if incorrect.

Participants indicated whether they thought the counter to be "inside" a blue or red box by pressing a panel in the centre of the screen. The available bets then appeared in a box at the right hand side of the screen, one at a time. Participants were able to select any one of these bets by touching the box as the appropriate bet was shown. Immediately following bet selection, the box containing the yellow counter "opened up" and either the phrase "you win" or "you lose" was displayed. Each participant performed the task under two separate "counterbalanced" conditions; one in which the bets were displayed from 5% finishing with 95% ("ascending" condition) and the other in which the bets began with 95% and finished with 5% ("descending" condition). Under both conditions, all participants performed four blocks comprising nine trials each, with a final score being given at the end of each block of nine trials. The trial was terminated if participants' scores dropped to one point.

The mean percentage of total points bet, mean deliberation time (i.e. time taken to make a choice between blue or red) and the mean probability of choosing the most likely outcome were recorded for each of the four ratios (i.e. 9:1, 8:2, 7:3 and 6:4). The means for all three of these measures were averaged across each of the four blocks. Two lots of scores were provided; one for the "ascending" condition and one for the "descending" condition.

Data analysis

All data were processed using the Statistical Package for the Social Sciences (SPSS) version 8 in Windows '98. Independent samples *t*-tests were performed for analysis of motor screening, pattern/spatial recognition and the search strategy component of the spatial working memory task. Repeated-measures analyses of variance (ANOVAs) were used for all other tasks, with the experimental groups as the between-subjects factors and difficulty level as the within-subjects factors. Significant interactions were investigated using simple main-effects analysis. Where either probability or percentage scores were used, the data was arcsine transformed in order to prevent skewness (Howell 1997). Any latency data that was skewed was log10 transformed. Where sphericity was not assumed, Greenhouse-Geisser degrees of freedom were used. A standard multiple regression analysis was conducted for verbal fluency scores using NART, age, use of phonemic strategy and use of semantic strategy as independent variables.

As drug use data were unable to satisfy parametric requirements, a series of Mann Whitney U analyses were conducted. Participant characteristics were analysed using independent samples *t*-tests. Analysis of covariance (ANCOVA) was performed in order to control for the consumption of those drugs that varied significantly between the ecstasy polydrug group and controls.

Results

Participant data

No significant group differences were shown for age, t=–0.09, P=0.93 or pre-morbid intelligence, as measured by the NART, t=1.58, P=0.12. Table 1 shows a summary of drug use for the two groups. The ecstasy group had consumed significantly higher quantities of amphetamine, cocaine and LSD.

Task data

Verbal fluency

Ecstasy users generated significantly fewer words than the polydrug control in the "letter" condition, t=2.26, P=0.03 but not the "semantic" fluency condition t=–0.54, P=0.59 (Table 2). Standard multi regression analysis of "letter" fluency data indicated that effective use of phonemic strategy accounted for the majority of the variance (P=0.03) and the use of semantic strategy approached significance (P=0.1). Both NART and age produced non-significant beta weightings. The regression analysis accounted for 40% of the total variance, and ANOVA indicated that the result of the regression model was highly significant (P=0.007).

Spatial working memory

"Between" search errors increased significantly as "trial size" or difficulty increased ($F_{2,76}$=39.59, P<0.001). There was also a highly significant group effect ($F_{1,38}$=6.85, P=0.01) with the ecstasy participants demonstrating a higher number of "between search" errors than controls. The "group by trial size" interaction was also significant ($F_{2,76}$=5.06, P<0.02) and simple effects analysis indicated that the ecstasy users performed significantly more errors at the most difficult 8-box level only ($F_{1,38}$=6.76, P=0.01; Fig. 1).

The number of "within search" errors also increased significantly as a function of task difficulty ($F_{2,76}$=10.63,

Table 1 Drug consumption (means and standard deviations)

Drug	Control	Ecstasy	*P* value
Ecstasy	0	172.0 (227.4)	
Cannabis	275.8 (317.9)	450.0 (360.6)	0.24
Amphetamine	13.5 (21.1)	101.4 (231.5)	0.01
Cocaine	2.0 (4.4)	30.5 (38.8)	<0.001
Lysergic acid	0.5 (1.0)	26.1 (68.6)	0.001
Barbiturates	0	2.6 (7.0)	0.18
Opiates	0.74 (0.7)	5.4 (22.3)	0.65
Psilocybin mushrooms	0.4 (0.7)	4.0 (6.7)	0.10
Steroids	0	0.5 (2.2)	0.80
Solvents	0.8 (3.4)	7.0 (22.3)	0.30
Nicotine (no. of cigarettes smoked per day)	7.0 (8.5)	8.4 (5.7)	0.22
Alcohol (units per week)	10.7 (15.0)	8.7 (9.5)	0.62

Table 2 Task data (means and standard deviations)

	Control	Ecstasy	*P* value	Simple effects analysis
Verbal fluency				
Letter category	30.95	26.95	0.03	
Semantic category	15.6 (3.0)	15.1 (3.4)	0.59	
Pattern recognition				
% Correct	95.2 (4.5)	87.5 (8.9)	<0.001	
Latency (s)	2.09 (0.45)	2.05 (0.47)	0.77	
Spatial recognition				
% Correct	84.0 (8.2)	85.8 (6.5)	0.68	
Latency (s)	2.29 (0.51)	2.40 (0.77)	0.59	
Paired associates learning				
No. of presentations				
6-box trial	1.8 (1.0)	1.7 (0.8)	0.63	
8-box trial	2.9 (1.1)	3.8 (2.5)		
Memory score				
6-box trial	4.5 (1.8)	4.7 (1.5)	0.57	
8-box trial	5.0 (1.6)	4.6 (2.2)		
No. of errors made				
6-box trial	2.2 (2.9)	1.7 (2.1)	0.07(Int)	0.57
8-box trial	4.7 (2.9)	7.7 (7.0)		0.07
Spatial working memory task				
Between errors				
4-box	0.1 (0.3)	0.6 (2.1)	0.02(Int)	0.30
6-box	3.8 (4.8)	5.8 (4.7)		0.21
8-box	8.3 (5.8)	17.1 (14.2)		0.01
Within errors				
4-box	0.1 (0.2)	0.1 (0.2)	0.02(Int)	1.0
6-box	0.7 (1.6)	0.9 (1.6)		0.69
8-box	0.7 (1.1)	2.9 (3.3)		>0.01
Search strategy score	32.0 (4.1)	32.7 (5.3)	0.64	
IDED errors				
Simple dimensional	0.2 (0.5)	0.7 (1.1)	0.26	
Compound dimensional	1.4 (1.7)	2.2 (3.7)		
Intra-dimensional	0.9 (0.9)	1.2 (1.0)		
Extra-dimensional	3.9 (3.2)	4.5 (5.4)		
Simple dimensional (reversal)	1.5 (1.2)	2.5 (3.3)	0.07(Int)	0.21
Compound dimensional (reversal)	1.3 (0.5)	1.9 (1.7)		0.15
Intra-dimensional (reversal)	1.1 (0.3)	1.4 (0.9)		0.20
Extra-dimensional (reversal)	2.2 (2.6)	1.3 (0.5)		0.14
IDED latency (s)				
Simple dimensional	2.56 (1.30)	3.91 (2.27)	0.17	
Compound dimensional	3.17 (3.59)	3.42 (3.01)		
Intra-dimensional	2.15 (0.90)	2.60 (0.93)		
Extra-dimensional	2.18 (0.62)	2.30 (1.07)		
Simple dimensional (reversal)	2.03 (0.73)	3.02 (1.97)	0.04	
Compound dimensional (reversal)	1.85 (0.52)	2.37 (0.91)		
Intra-dimensional (reversal)	1.57 (0.49)	1.92 (0.77)		
Extra-dimensional (reversal)	1.83 (0.58)	1.84 (0.61)		

P=0.001). A significant group effect ($F_{1,38}$=6.10, P=0.02) revealed that the ecstasy participants made a significantly greater number of "within" search errors than controls. Simple main-effects analysis again indicated that a significant "group by trial size" interaction ($F_{2,76}$=5.01, P=0.02) was due to group performance differences at the most difficult 8-box level ($F_{1,26}$=4.50, P=0.04). No significant group differences were established with regard to "search strategy" (t=0.47, P=0.64; Fig. 2).

Attentional set-shifting task

Ninety percent of both experimental groups successfully completed all stages of the task. As a result, no statisti-

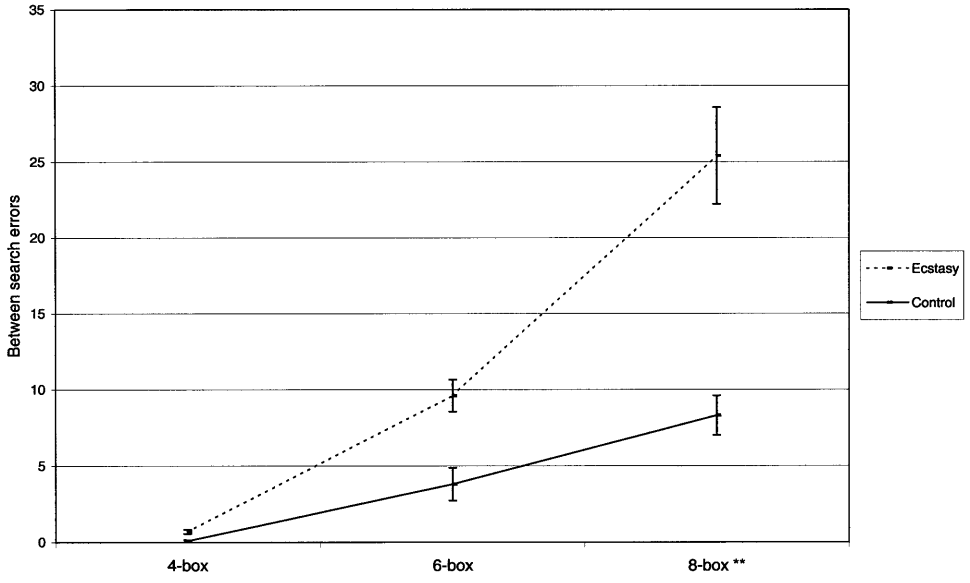

Fig. 1 Group differences in mean number of "between-search" errors made for 4-, 6- and 8-box trials on the spatial working memory task. *Bars* indicate standard error. ***P*=0.01

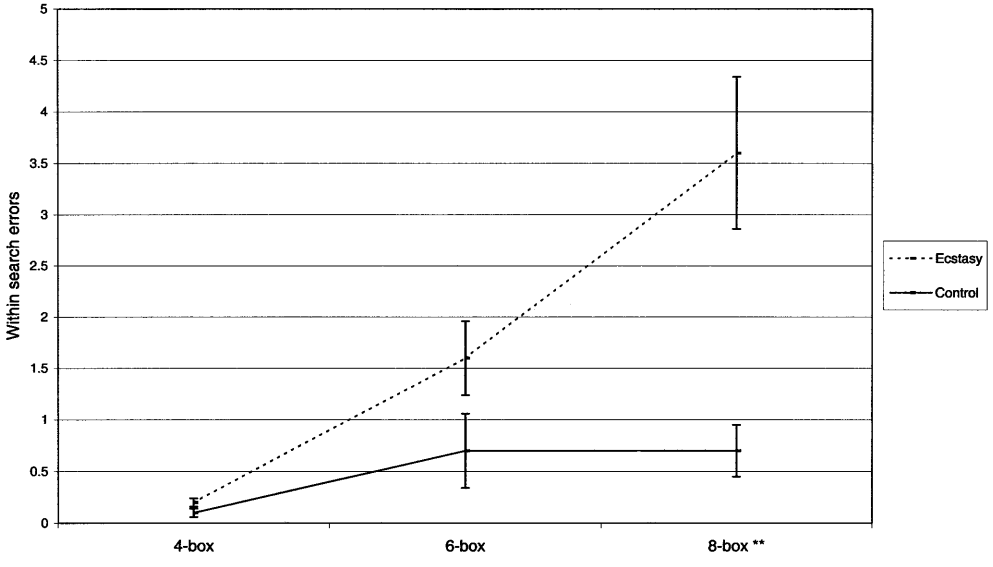

Fig. 2 Group differences in mean number of "within-search" errors made for 4-, 6- and 8-box trials on the spatial working memory task. *Bars* indicate standard error. ***P*>0.01

cal analysis was conducted on this gross performance index. Non-reversal trials: no significant group effect for errors was established at any of the difficulty levels ($F_{1,34}$=1.32, P=0.26). A highly significant within-group effect indicated a significant increase in errors as the trials became more difficult ($F_{3,102}$=13.73, P<0.001), and no significant interaction indicated this to be the case across both groups ($F_{3,102}$=0.06, P=0.93). In relation to latency, no significant group main effect was established at any level ($F_{1,34}$=1.2, P=0.17). A highly significant within-group effect indicated a significant increase in latency as trials became more difficult ($F_{3,102}$=6.36, P=0.001), and no significant interaction indicated this to be the case across both groups ($F_{3,102}$=1.81, P=0.15). For reversal trials, in relation to errors, the group × difficulty interaction approached statistical significance ($F_{3,102}$=2.57, P<0.07), showing that ecstasy users made a greater number of errors on the simple and compound reversal trials, but slightly fewer errors on the extra-dimensional reversal than controls. A significant between-group effect for latency also indicated that ecstasy users performed more slowly than controls ($F_{1,34}$=4.52, P=0.04) at all levels (interaction, $F_{3,102}$=2.00, P=0.12).

Pattern and spatial recognition

The ecstasy group made a significantly greater number of errors than the controls on pattern recognition (t=–3.46, P=<0.001). No group effect was established for errors on spatial recognition (t=0.42, P=0.68). No significant differences were found for either task with regard to response latencies (Fig. 3).

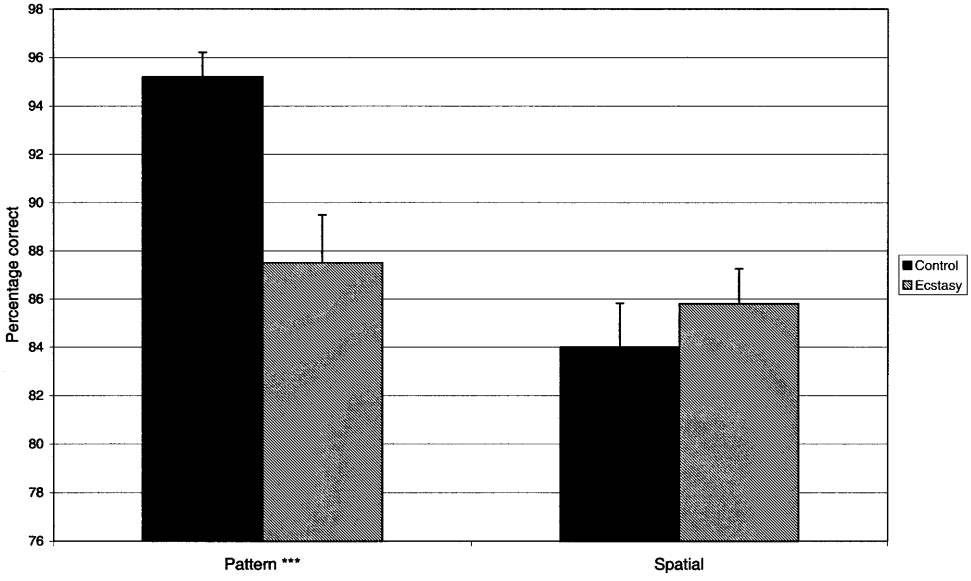

Fig. 3 Mean percentage correct scores for the pattern and spatial recognition tasks. *Bars* indicate standard error. ***$P<0.001$

Paired associates learning

No significant "between-group" differences were shown for the number of presentations required ($F_{1,38}=0.24$, $P=0.63$), memory score ($F_{1,38}=0.34$, $P=0.57$) or number of errors ($F_{1,38}=1.87$, $P=0.18$). On all three performance measures, a highly significant "within-group" effect ($P<0.001$) reflected the increase in task difficulty. In relation to the number of errors made on each trial, the "group × trial" interaction approached significance ($F_{7,266}=2.61$, $P=0.07$). Post-hoc analysis indicated that the ecstasy group made a greater number of errors on the 8-box trial than the controls.

Go/no go

For distractor errors, both groups made significantly more errors under the "switch" conditions than the "non-switch" conditions ($F_{1,38}=8.58$, $P=0.006$). However, no between-group differences were shown ($F_{1,38}=0.57$, $P=0.45$). For latency, no between-group differences were shown relative to reaction times ($F_{1,38}=0.17$, $P=0.45$) and no differences were shown between "switch" and "non-switch" trials ($F_{1,38}=0.15$, $P=0.68$), in either group (interaction, $F_{1,38}=0.50$, $P=0.49$). No statistical analysis was conducted for the number of "omission errors" made, as both groups scored predominantly "zero".

One-touch TOL

No significant group differences were indicated for either the percentage correct ($F_{1,38}=0.43$, $P=0.52$) mean number of attempts required in order to complete each set of moves ($F_{1,38}=2.25$, $P=0.14$) or the mean latency taken to make an initial response ($F_{1,38}=0.30$, $P=0.59$). In each case a highly significant within-groups effect was demonstrated, representing the increase in task difficulty from the "easy" to "difficult" trials. No significant interactions were found.

Decision making

For "percentage of total points bet", a highly significant "within-group" effect was shown ($F_{3,210}=201.0$, $P<0.001$) due to the fact that both groups gambled a lower amount of their points under "higher risk" conditions. However, there were no significant between-group differences and no significant "group × ratio" interactions. Both groups bet a significantly higher number of points under the descending condition ($F_{1,70}=2.9$, $P<0.001$). However, again, there was no significant "condition × ratio interaction" ($F_{3,210}=0.38$, $P=0.67$). No significant group differences were established either with regard to "probability of choosing the most likely outcome" or "deliberation time".

ANCOVA

Significant group differences for pattern recognition, "between errors" and "within errors" on the spatial working memory task remained significant after amphetamine, cocaine and LSD had been used as covariates.

Discussion

Ecstasy users displayed cognitive deficits in tasks that were predominantly sensitive to temporal lobe dysfunction, with relative sparing on measures of executive functioning. The ecstasy group made significantly more errors on the visual recognition task for patterns, but not for spatial location. Ecstasy users also made a greater

number of errors on the most challenging "8-box" trial of the spatial working memory task. This disproportionate increase in errors was not, however, related to the inefficient use of search strategy. In relation to learning, ecstasy users revealed a trend for making a higher number of errors on the most difficult 8-box trial of PAL. They also performed significantly slower on all trials of the 3D-IDED and showed a trend towards reduced learning when acquiring a reversal shift rule.

A deficit for serially presented complex visual designs is generally consistent with studies that have found users to be impaired on immediate recall of complex visual arrangements (Gouzoulis-Mayfrank et al. 2000) as well as delayed visual recall of tasks such as the Rey-Osterrieth Complex Figure task (Bolla et al. 1998). It also expands on some of the psychophysiological findings in drug-free ecstasy users. Dafters et al. (1999) demonstrated that ecstasy use was negatively associated with coherence in brain areas thought to overlie the main visual association pathways.

The PAL task analyses visual and spatial recognition processes within an associative learning paradigm. As such, any problems associated with visual recognition may account for the higher trend in the number of errors shown on the more difficult 8-box trial. Although initial memory scores were similar to controls, the number of subsequent presentations required to learn the appropriate visuo-spatial associations approached statistical significance compared with polydrug controls. As such, findings may provide tentative support for Rodgers (2000) who found ecstasy/cannabis users to be impaired on a task of visual paired associates compared with both a cannabis and non-user control.

The 3D-IDED task also represents a task of learning with a prominent visual component. Furthermore, ecstasy users responded significantly more slowly across all trials. In relation to the number of errors made, ecstasy users performed a greater number of errors on the initial simple reversal trials but performed better than control levels in the extra-dimensional reversal trials. However, this interaction only approached statistical significance and the subsequent simple effects analysis showed no significant group differences. Ecstasy users were also able to complete successful intra- and extra-dimensional shifts.

The results of these visual learning paradigms support data from studies that have administered verbal learning tasks such as the Rey Auditory Verbal Learning Task (RAVLT) to drug-free ecstasy polydrug users (Gouzoulis-Mayfrank et al. 2000; Fox et al. 2001c). In all cases ecstasy users either required a greater number of trial presentations or made an increased number of initial errors in order to effectively acquire the information. Data from both the current study and prior research would therefore suggest that some of the processes necessary to learn information are still intact and that any reductions in the learning curve are more likely to highlight difficulties relating to the storage and/or retrieval of information, rather than capacity per se.

This deficit profile shown by the ecstasy group is similar to those seen in patients with more posterior cortical damage. Previous studies have shown double dissociations on the pattern and spatial recognition tasks in both frontal and temporal excision patients (Owen et al. 1995, 1996). Whilst frontal patients have been found to be impaired on spatial but not pattern recognition task, this has been reversed in both temporal lobe (TL) and amygdalo-hippocampectomy (AH) groups. Similarly, the increase in errors demonstrated by the ecstasy group on the most difficult trial only of the spatial working memory task is also comparable to those seen in TL and AH patients (Owen et al. 1995, 1996). Moreover, successful strategy implementation on this task may again indicate that processes underlying visuo-spatial decrement are not necessarily executive in nature. Furthermore, deficits in short-term memory seem to be the most consistent and robust sequelae of drug abuse (Sahakian 2001).

The similar pattern of performance deficits between the ecstasy users and temporal excision patients may not be unexpected in view of both comparative and human data. The pattern recognition task employed in CANTAB is analogous to those previously used to define the neural substrates of visual memory in non-human primates (Gaffan 1974; Mishkin 1982). Visual recognition memory was disrupted in monkeys by lesion damage to the inferotemporal cortex, hippocampus and amygdala as well as sub-cortical structures including the mediodorsal nucleus of the thalamus (Mishkin and Manning 1978; Squire and Zolamorgan 1991). This is consistent with regions found to be sensitive to the neurodegenerative effects of ecstasy in rats. De Souza et al. (1990) reported substantial reductions in paroxetine-labelled uptake sites within thalamic nuclei and regions of the hippocampus 2 weeks following a 4-day regime of 20 mg/kg ecstasy twice daily. In humans, a recent pathology study also indicated that striatal levels of 5-HT and its metabolite (5-HIAA) were depleted by as much as 50–80% in the brain of a chronic human ecstasy user (Kish et al. 2000).

The possibility of executive problems in the ecstasy group cannot, however, be entirely discounted due to performance on the verbal fluency task, as well as a trend towards conditional and reversal learning difficulties. In relation to verbal fluency, ecstasy users generated significantly fewer words than the control participants, possibly due to the fact that they applied less effective semantic and phonemic generation strategies. This was further reinforced by the fact that the ecstasy group was able to perform normally when the need for strategy use was reduced by the enforcement of a determined category in the "semantic fluency" condition. Deficits in strategy use are certainly consistent with previous data (Milani and Schifano 2000; Wareing et al. 2000; Fox et al. 2001b). However, in this study at least, it would appear that certain other executive processes may be spared in ecstasy users who have consumed approximately 170 tablets over 4 years.

The ecstasy group showed no impairment on certain tests sensitive to prefrontal functioning. These extended

to the new TOL planning task as well as extra-dimensional shifting. In relation to impulsivity and inhibitory mechanisms, no impairment was seen on the go/no go task, and there was no simultaneous indication of sub-optimal betting strategies or increase in actual betting time on the decision-making task.

As a serotonergic depletor, these results may seem somewhat paradoxical in recreational ecstasy users. However, the current data does show some conformity with previous studies. Although increased impulsivity has been associated with depletions in 5-HT functioning (Evenden 1999), behavioural impulsivity (Morgan 1998) and self-reported impulsivity (Parrott et al. 2000; Fox et al. 2001a) in ecstasy users has not always been replicated (McCann et al. 1994; Gouzoulis-Mayfrank et al. 2000). Similarly, planning deficits on tasks sensitive to prefrontal functioning have been found to be both impaired (Milani and Schifano 2000; Fox et al. 2001b) and unimpaired (Morgan 1999). In relation to attentional shifting, recreational users have tended to perform at control levels on tasks analogous with the 3D-IDED, such as the computerised version of the Wisconsin Card Sorting Task (Turner et al. 1999; Fox et al. 2001b) and a classification task (Verkes et al. 2001). A lack of perseveration in these studies and a failure to demonstrate problems with extra-dimensional shifting in the present study may indicate that processes underlying concept formation and set-shifting are not implicated in the earlier stages of ecstasy pathology.

From a neuropsychological perspective, whilst a disruption of temporal mesial structures would be consistent with the neuropathology of ecstasy abuse (Sharkey et al. 1991), a predominant lack of impairment on many of these executive paradigms would seem rather unusual for several reasons. Primarily, the frontal cortex is extensively innervated with 5-HT neuronal projections (Brodkin et al. 1993; Rogers and Robbins 2001), the integrity of which is paramount to the development and maintenance of learning and mnemonic processes (Hunter 1988). Secondly, there exists a vast interaction between prefrontal and sub-cortical temporal structures by way of ascending monoaminergic systems and output from the striatum (Robbins 1998) making a combination of both frontal and temporal deficits highly likely.

It may be the case then that some of these executive processes are still essentially sub-clinical with respect to the recreational ecstasy users in the present study. As mentioned in previous literature, working memory deficits have generally been reported in heavy ecstasy users (Morgan 2000; Wareing et al. 2000). Participants in the current study had taken an average of approximately 170 tablets over a 4-year period. In relation to planning tasks, studies showing normal latency times employed participants who had consumed approximately 35 tablets over 2 years (Morgan 1999). Conversely, in studies where increased latencies have been demonstrated, ecstasy users have consumed much heavier dosages, i.e. at least 500 tablets over 5 years (Fox et al. 2001b) and 300 tablets over 1.5 years (Milani and Schifano 2000).

Sub-clinical factors may also account for the fact that ecstasy users in the current study revealed a less typically "frontal" profile than those shown by other methamphetamine derivatives. Chronic amphetamine users showed impairment on tasks not only known to be sensitive to ecstasy users in the present study but other measures of fronto-striatal function as well, including extra-dimensional shift (Ornstein et al. 2000) and sub-optimal betting decisions (Rogers et al. 1999). Importantly, the mean duration of amphetamine consumption in these two studies was approximately 13 years, which is considerably higher than the 4-year ecstasy use in the current sample. In line with this, computational theories have also claimed that the disruption of inhibitory mechanisms may occur at a later stage in the neurodegenerative process, compared with mnemonic functioning (Cohen et al. 1998). This may explain why ecstasy users in the present study began to show signs of difficulties in relation to acquiring a reversal rule, but demonstrated no problems relative to any other form of inhibitory measure (including go/no go).

Conversely, other explanations for a predominantly temporal profile may reflect a specific mnemonic role for the 5-HT system compared with dopaminergic drugs. Data from the current study are similar to findings shown by Park et al. (1994), where healthy volunteers were given a low-dose tryptophan drink in order to induce a global sedation of the 5-HT system. Participants made an increased number of errors and required more trials to learn all of the visuo-spatial associations on PAL. These learning deficits were also demonstrated in the absence of impaired "first trial" memory score. Participants also demonstrated reduced reversal learning of visual discrimination predominantly in the "compound reversal" stage of the 2-D IDED task, but had no problems in performing and extra-dimensional shift. Although lengthened planning times were shown on the New Tower task, this was only demonstrated on the second trial of a within cross-over designed study, and therefore interpreted as reflecting deficits of learning rather than planning. A more recent study by Rubinsztein et al. (2001) also found that "low-dose tryptophan" participants were impaired on the same delayed recognition task sensitive to moderate ecstasy users in the current study.

Park and colleagues suggested that the inconsistency of their findings with frontal lobe dysfunction might serve to highlight a specific learning and mnemonic role for the serotonergic system more directly associated with parahippocampal functioning (Grasby et al. 1993). This is also endorsed by animal research that has associated temporal lesions with many of the cognitive deficits induced by low-dose tryptophan drinks (Nomura et al. 1992; Kesner et al. 2001). As such, findings in the current research may provide some support for the serotonergic model of ecstasy neurotoxicity.

In consideration of these results, it is important to highlight some of the methodological cautions relating to the present study with regard to the monitoring and pro-

filing of participant drug use. First, although participants were expected to have abstained from ecstasy use for 2 weeks prior to testing, no biological assays of ecstasy consumption were taken. Furthermore, all drug use data was reliant on self-reported estimates of consumption. Second, although significant findings remained significant after treating amphetamine, cocaine and LSD consumption as covariates, the ecstasy polydrug users were still heavier drug consumers in general than controls. As such, the profile of deficits shown in the present study may also implicate the involvement of other monoaminergic systems due to higher consumption pattern of drugs such as amphetamine and cocaine. Results from the present study should therefore be interpreted as reflecting the cognitive profiles of ecstasy polydrug users who consume ecstasy as a drug of preference. It is also important to mention that the number of participants tested in the current study is relatively small and, although not unrepresentative of studies in the literature, data must be interpreted with caution.

It must also be noted that certain deficits in ecstasy polydrug users may be underestimated in the present study due to the fact that a drug-naive control group was not included. Drug-naive individuals were not used as they would not act as the best controls for the population under study, that of ecstasy polydrug users. Future studies may utilise multiple control groups.

The present study has compared polydrug ecstasy users with a group of polydrug controls on a battery of tasks validated within neuropsychiatric populations. The tasks selected were chosen for their sensitivity to frontal, temporal and fronto-striatal functioning in patients with low serotonergic disorders. Ecstasy users demonstrated performance deficits on short-term memory tasks, sensitive to the involvement of temporal sub-clinical structures (pattern recognition) or in a manner that was similar to "temporal" patients (spatial working memory). They also demonstrated that they were beginning to have difficulties acquiring visual material particularly in associative learning paradigms. The possibility of dysfunction of limbic areas may also predispose ecstasy polydrug users to problems, not only related to memory, but also emotion, visceral responses to such emotions, motivation, mood, eating and sexual disorders (Turner et al. 1998; Parrott et al. 2000; Parrott 2001). Although ecstasy users remained unimpaired on most measures of prefrontal functioning, it is suggested that certain executive processes are possibly still sub-clinical in the earlier stages of ecstasy polydrug use. As such, future research may benefit from comparing the cognitive profiles of users such as these with individuals who have been taking the drug for at least 10 years. It is also important to note that these initial cognitive impairments were demonstrated on a task battery originally developed for use in neurosurgical and neuropsychiatric populations. This may raise concern regarding the heavy long-term use of the drug, as deficits in short-term memory are already apparent even in these non-dependent drug users.

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