Psychopharmacology (2004) 175:331–341
DOI 10.1007/s00213-004-1832-8

ORIGINAL INVESTIGATION

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Impaired executive function in male MDMA ("ecstasy") users

Received: 30 September 2003 / Accepted: 2 February 2004 / Published online: 18 March 2004

Abstract *Rationale:* Long-term users of ecstasy have shown impaired performance on a multitude of cognitive abilities (most notably memory, attention, executive function). Research into the pattern of MDMA effects on executive functions remains fragmented, however. *Objectives:* To determine more systematically what aspects of executive function are affected by a history of MDMA use, by using a model that divides executive functions into cognitive flexibility, information updating and monitoring, and inhibition of pre-potent responses. *Methods:* MDMA users and controls who abstained from ecstasy and other substances for at least 2 weeks were tested with a computerized cognitive test battery to assess their abilities on tasks that measure the three submodalities of executive function, and their combined contribution on two more complex executive tasks. Because of sex-differential effects of MDMA reported in the literature, data from males and females were analyzed separately. *Results:* Male MDMA users performed significantly worse on the tasks that tap on cognitive flexibility and on the combined executive function tasks; no differences were found on the other cognitive tasks. Female users showed no impairments on any of the tasks. *Conclusions:* The present data suggest that a history of MDMA use selectively impairs executive function. In male users, cognitive flexibility was impaired and increased perseverative behavior was observed. The inability to adjust behavior rapidly and flexibly may have repercussions for daily life activities.

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Keywords Ecstasy · MDMA · Executive function · Working memory · Flexibility · Inhibition · Serotonin · Dopamine · Neurotoxity

Introduction

Neurocognitive effects of MDMA

3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") appears to be a potent neurotoxin in rats (Mokler et al. 1987), dogs (Frith et al. 1987), and non-human primates (Ricaurte and McCann 1992). MDMA is toxic to the serotonin (5-HT) system (Battaglia et al. 1988; Pan and Wang 1990), and, to a lesser extent, to the dopamine (DA) system (O'Shea et al. 2001). This neurotoxic effect presumably also occurs in humans (McCann et al. 1998). Long-term use of MDMA reduces 5-HT metabolites such as 5-HIAA (McCann et al. 1994), neuroendocrine functioning (Gerra et al. 2000), and the number of serotonin re-uptake transporters (McCann et al. 1998). Moreover, histological evidence shows that in MDMA-treated animals, 5-HT axon terminals are damaged and degenerated (Commins et al. 1986).

In animals, MDMA reduces 5-HT in the medial prefrontal cortex (Pan and Wang 1990), confirming the 5-HT depleting properties of MDMA (Schmidt et al. 1986; Gibb et al. 1987; Mokler et al. 1987). In human volunteers, a history of heavy MDMA use reduced 5-HT transporter binding in the frontal cortex, striatal regions, and hypothalamus (McCann et al. 1998). Studies in cognitive neuroscience indicate that the frontal serotonergic system is crucial in controlling learning and memory processes (e.g. Hunter 1989; Epstein et al. 2002) and in behavior involving high cognitive demands (Buhot 1997). Not surprisingly, long-term MDMA use impairs performance in several cognitive domains such as complex attention (McCann et al. 1999; Gouzoulis-Mayfrank et al. 2000), verbal memory (Morgan 1999; Fox et al. 2001a), visual memory (Bolla et al. 1998), and retrospective (but not prospective) memory (Zakzanis and Young 2001a).

Effects of MDMA on executive functions

Executive functions can be described as general-purpose control mechanisms that modulate the operation of various cognitive subprocesses and thereby regulate the dynamics of human cognition (Miyake et al. 2000). In comparison with the extensive study of neurotoxic effects on serotonergic neurocognitive function, the effects on DA-mediated executive functions (EF) of the human frontal lobes have been explored less systematically. However, reports have begun to highlight toxic effects of MDMA on the DA system (O'Shea et al. 2001) and on executive function in human MDMA users. For instance, MDMA users scored lower on the Behavioral Assessment of Dysexecutive Syndrome, a test designed to measure mental organization, planning strategies, thinking ahead, mental rule forming, and the estimation of temporal activities (Zakzanis and Young 2001b). MDMA users show increased impulsivity (Morgan 1998), working memory (WM) impairments (e.g. Bolla et al. 1998; Wareing et al. 2000; Verkes et al. 2001), and impaired performance on cognitive flexibility tasks (Fox et al. 2001b, 2002) and planning tasks (Fox et al. 2001b).

Thus far, however, the pattern of MDMA effects on EF remains fragmented. Miyake et al. (2000) introduced a differentiated theoretical framework for the systematic study of EF. From their reading of the EF literature Miyake and colleagues derived three core functions: shifting between tasks and mental sets, updating and monitoring of WM representations, and inhibition of dominant or pre-potent responses. They assembled a battery of tasks that included relatively simple tasks (considered to differentially tap each of the core functions) as well as a set of frequently used complex EF tasks such as the Wisconsin Card Sorting Task and the Tower of Hanoi. The results of this study indicated that, although the core functions are moderately correlated with one another, they are clearly separable. Moreover, structural equations modeling suggested that the three functions contribute differentially to the performance on the complex EF tasks.

Based on Miyake et al.'s (2000) model, here we use a broad range of EF tasks to clarify the possible influences of MDMA on the executive processes. The first category of EF is cognitive flexibility. Chronic amphetamine users perform worse on extra-dimensional shift tasks (Ornstein et al. 2000). Research in MDMA (a ring-substituted amphetamine) users induced fewer errors on a similar task (Fox et al. 2002). The second category of EF is working memory updating and maintenance. Impairments of WM have been found in MDMA users (Bolla et al. 1998; Wareing et al. 2000; Verkes et al. 2001). The third category of EF is response inhibition. Increased impulsivity has been indicated in MDMA users (Morgan 1998). However, on a go/no-go inhibition task, MDMA users performed equally well as controls (Fox et al. 2002). Tests assessing each of the three components of EF were administered, together with more complex EF tasks to explore situations that place higher cognitive demands on multiple types of EF simultaneously. Previous research has shown MDMA users to make more perseverative errors on more complex EF task such as the Wisconsin Card Sorting Test (WCST) and to use increased planning times on the Tower of London (TOL) (Fox et al. 2001b).

Several psychiatric and/or psychobiological problems are associated with MDMA usage. These include sleep disorders, depressed mood, persistent high anxiety, and impulsiveness and hostility (Morgan 2000). In previous research, MDMA users scored higher on several dimensions of the Symptom Check List 90 (SCL-90): paranoid ideation, psychoticism, summarization, obsessionality, anxiety, hostility, phobic anxiety, altered appetite, restless sleep, and greater impulsiveness (Parrot et al. 2000). Dughiero et al. (2001) also reported higher scores by MDMA users on several scales of the SCL-90: obsession-compulsion, phobic anxiety, psychoticism, and sleep disturbances. In order to obtain a clear perspective of the effects of MDMA on psychological distress, we therefore administered the SCL-90 clinical symptom self-rating scale.

We also distinguished between male and female MDMA users because of the different findings for the two sexes. McCann et al. (1994) reported increased reductions in the 5-HT metabolite 5-HIAA in female users. Liechti et al. (2001) found a stronger subjective response in female users compared to male users. Reneman et al. (2001) reported a stronger dose-dependent reduction in 5-HT binding ratios in female than in male MDMA users. Finally, Verheyden et al. (2002) reported higher depression scores in females several days following weekend use of MDMA. In this study, both men and women reported increased self-rated aggression.

The present study contributes to the literature a more detailed and systematic analysis of the effects of MDMA on EF. The selected cognitive test battery was designed to tap into each of the three lower-order categories separately and their combined contribution to performance on more demanding cognitive tasks. This approach enables us to study more systematically the neurotoxic effects of MDMA on cognitive flexibility, working memory updating and maintenance, and response inhibition, in simple and complex cognitive tasks.

Materials and methods

Participants

Fifty-nine participants (29 males, 30 females) were recruited, of whom 26 were MDMA users and 33 were not. Participants were first-year psychology students who received study credits for participation. All were between 18 and 26 years of age, otherwise healthy, and without psychiatric history according to self-report. In order to participate in the MDMA group, a total minimum consumption of ten ecstasy tablets was required with at least one occasion in the most recent year. Because all participants were university students, comparable intelligence levels were assumed. Participants agreed to abstain from use of all psychoactive drugs for at least 2 weeks before the study. Compliance with this instruction was stimulated by the announcement that saliva samples would be

taken. At the beginning of the testing session, all participants were interviewed on drug use within the last 2 weeks, pregnancy, and medical or psychiatric illness. Written informed consent was obtained from all participants, and the nature and possible consequences of the study were explained to them. Experimental procedures were conducted in compliance with relevant laws and institutional guidelines, and were approved by the local departmental ethical committee.

Cognitive performance

The tasks used in this experiment were from a task battery developed by Huizinga and van der Molen (unpublished data). They adopted the approach described in the study reported by Miyake et al. (2000), and examined developmental patterns in the following executive functions: (1) updating and monitoring of WM representations, (2) shifting between tasks and mental sets, and (3) inhibition of dominant or pre-potent responses. The tasks have been validated and found reliable in the literature (as indicated below) or were developed by adopting appropriate analogues of existing paradigms (Huizinga and van der Molen, unpublished data).

In the present study, the battery consisted of eight tasks: two task switching paradigms (Dots-Triangles and Local-Global), two WM tasks [Tic Tac Toe (visual information) and Mental Counters (numerical information)], two response inhibition tasks (Eriksen Flankers and Stop Signal) and two complex EF tasks (WCST and TOL).

Flexibility

Dots-Triangles

The Dots-Triangles test (derived from Miyake et al. 2000) involves the maintenance and switching of response set. In a 4×4 grid on the screen, varying numbers of either dots or triangles appear. With dots, participants have to decide whether there are more dots in the left or in the right part of the screen (block 1; 30 practice trials, 50 experimental trials). With triangles, participants have to decide whether there are more triangles in the top or in the bottom part of the screen (block 2; 30 practice trials, 50 experimental trials). Blocks 1 and 2 were administered in randomized order. In a third block (90 practice trials, 150 experimental trials), participants alternated between series of four "dots" trials and series of four "triangles" trials. A stimulus remained on the screen until a response was made; the maximum RT was 3500 ms, the interval between the response and a new stimulus was 1000 ms.

Local-Global

The Local-Global test (derived from Miyake et al. 2000) requires participants to respond to randomly presented rectangles or squares by pressing a left or right response button, respectively. Larger (global) rectangles/squares consist of smaller (local) rectangles or squares. Participants respond only to the local figure, or only to the global figure (blocks 1 and 2, in randomized order; 30 practice trial and 50 experimental trials per block), in the third block, they had to alternate between series of four "local" trials and series of four "global" trials (block 3; 90 practice trials, 150 experimental trials). A cue instructed participants as to which aspect (global or local) should be responsed to; the stimulus remained on the screen until a response was made, the maximum RT was 3500 ms, the interval between the presentation of the cue and the presentation of the stimulus was 500 ms, the interval between the response and the presentation of the new cue was fixed at 1000 ms.

Working memory

The essence of this function lies in the requirement to monitor and code incoming information for relevance and replace information held in WM that is no longer relevant by new, relevant information. Two tasks are chosen that are assumed to tap this updating function, differing in the information that needs to be updated as well as in the goals of the tasks.

Tic Tac Toe

In the Tic Tac Toe test (modified from Milner 1971), participants are required to keep visual information active in WM about the orientation of a pattern of figures. In a 3×3 grid on the screen, Xs and Os are presented briefly during a memorizing phase. In the recognition phase, Xs and Os are presented one after another in the grid. The task is to press a button as soon as the combination of presented Xs and Os matches the pre-specified pattern. Memory load is varied using patterns consisting of three or four stimuli. The number of trials per block was 15, and the series length of the stimulus presentation until the pre-specified pattern was reached varied from four to nine presentations. The maximum RT was 3500 ms, the interval between the presentation of stimuli was between 900 and 1100 ms (randomly drawn from a uniform distribution).

Mental Counters

The Mental Counters test (adapted from Larson et al. 1998) requires participants to keep numerical information active in WM. Participants must keep track of the values of two or three (blocked) independent "counters" which change rapidly and in random order. The counters consist of a horizontal line, above or below which squares appear.

Participants were to add 1 to the value of the counter when a square appeared above the line, and to subtract 1 when it appeared below the line. When any counter reaches a given criterion value, participants have to press a button. The length of the series of stimuli presented was five or seven (randomly but equiprobably); the maximum RT was 3500 ms, the interval between consecutive presentations of squares was between 1000 and 1300 ms (randomly drawn from a uniform distribution).

Response inhibition

Eriksen Flankers

In the arrow version of the Eriksen Flankers test (Ridderinkhof and van der Molen 1995), the participant's task is to respond to a left versus right pointing arrow in the center of the screen by pressing a left or right response button. The central arrow is flanked by four arrows pointing in the same direction (congruent condition). Occasionally and unpredictably, the flankers will point in the opposite direction (incongruent condition), thereby activating the competing response. The stimulus was presented in a rectangle, and this rectangle served as the warning stimulus, that is, after an interval of 500 ms the target stimulus appeared in the rectangle. The stimulus remained on the screen until a response was made; the maximum RT was 3500 ms, the interval between the response and the presentation of the warning stimulus was fixed at 1000 ms. There were 50 practice trials, and 100 experimental trials.

Stop Signal Task

In this version of the Stop Signal task (Van Boxtel et al. 2001), participants have to respond as fast as possible to a left versus right pointing arrow by issuing a left versus right button press. Occasionally and unpredictably (on 25% of all trials), the color

of the arrow changes from green to red indicating that the response should be inhibited. The time interval between arrow presentation and arrow color change ranges from 200 to 1250 ms: the longer it takes the arrow to change color, the more difficult it is to stop the pre-potent response. The length of this interval is controlled by a tracking algorithm through which stop accuracy approximates 50%. There were 50 practice trials, and two blocks of 100 experimental trials. The stimulus remained on the screen until a response was made; the maximum RT was set at 1250 ms, the interval between the response and the new stimulus varied between 1650 and 2150 ms (drawn randomly from a uniform distribution).

Complex executive functions

Tower of London (TOL)

The TOL (Shallice 1982; Schnirman et al. 1998) requires the movement of three different-colored balls across three different-sized pegs in order to duplicate the goal configuration. The smallest peg can hold one ball, the middle-sized two, and the largest can hold three balls. Only the highest ball on a peg can be moved and only one ball can be moved at the same time. Several trial types have to be completed: 4-move trials, 5-move trials, and 6-move trials. Trials are scored for planning time and solution time. Participants' performance is also scored for percentage of excess moves, and total number of moves needed to complete the configuration.

Wisconsin Card Sorting Task (WCST)

The WCST (Grant and Berg 1948; Heaton et al. 1993) requires the deduction of correct sorting rules and the flexible execution of these rules. This task engages WM operations as well as switch capacities and inhibitory control. Four stimulus cards with figures appear on the screen. These figures vary along three dimensions: number (1–4), color (red, green, yellow, blue), and form (triangles, stars, crosses, circles). A response card, which matches the stimulus cards on one or two dimensions, is presented on the bottom of the screen. Participants have to respond with a button press (keys 1, 2, 3, or 4) to select the stimulus card that matches the response card best according to one of the three sorting dimensions. The sorting dimension is changed after ten correct responses, and participants have to figure out the new sorting dimension in order to respond successfully. Participants' performance was scored for the number of conceptual level responses (series of three or more consecutive correct responses), the total number of correct responses, the number of correct responses on ambiguous trials, the number of errors on ambiguous trials, and, most importantly, the number of perseverative errors (trials following a switch of sorting dimension, on which participants persist in sorting according to the preceding sorting dimension that is now incorrect).

Symptom Checklist-90 (SCL-90)

A Dutch computerized version of the SCL-90 self-rating scale (Derogatis 1994) was administered at the end of the testing session. The test consists of 90 symptoms, which are divided into several psychiatric and psychobiological dimensions: depression, anxiety, agoraphobia, insufficiency of thought and behavior, sensitivity, somatization, hostility, and sleeping problems. The SCL-90 was used because all nine dimensions are strongly associated with 5-HT regulation. Example questions are: "feelings of worthlessness" (depression subscale) and "feeling easily annoyed and irritated" (hostility subscale). Each question has five possible responses, ranging from not at all (1) to extremely (5). The response is to be based on the last 4 weeks. Dependent measures are the sum scores on each dimension and the total SCL-90 score (i.e. the sum of all nine subscale sum scores; minimum score=50, maximum score=450).

Statistical analyses

Homogeneity differences between the four groups were investigated by χ^2 analysis. Independent samples *t*-tests were performed for analysis of age differences between MDMA users and controls, and between sexes. Sex differences in MDMA use were analyzed by one-way analysis of variance (ANOVA). Differences between groups in cognitive task measures were analyzed using ANOVA with MDMA usage and sex as between-subjects independent variables. Within the MDMA group, a median split was performed to discriminate between high and low use of other drugs, and to control for the variance in XTC-related performance impairments accounted for by the concomitant use of these other drugs (using ANOVA). Independent samples *t*-tests were performed on the SCL-90 scores of MDMA users and controls. An alpha level of 0.05 was used for all analyses.

Results

Demographics and drug-usage data

Demographics of the participants are provided in Table 1. The χ^2 analysis indicated a non-homogeneous composition of the groups [$\chi^2(59)=4.901$, $P=0.03$]. There were no

Table 1 Demographics, SCL-90 scores, and use of other recreational drugs

	Men controls (*n*=12)	Men MDMA (*n*=17)	*p*	Women controls (*n*=21)	Women MDMA (*n*=9)	*P*-value
Demographics						
Age (years)	22.0 (2.0)	21.4 (1.3)		21.4 (2.2)	21.7 (1.3)	
SCL-90	104.33 (7.25)	121.82 (24.64)	b	117.33 (21.32)	120 (12.52)	
Other recreational drug use[a]						
Cannabis	0.54 (1.42)	10.59 (12.07)	b	0.07 (0.18)	3.89 (8.08)	b
Amphetamine	0	4.35 (8.75)		0	2.78 (5.26)	b
LSD	0	0.88 (1.73)		0	0.22 (0.44)	b
Psilocybin	0.08 (0.29)	2.82 (2.65)	b	0	3.00 (2.96)	c
Cocaine	0	6.88 (7.28)	b	0	3.33 (4.03)	c
GHB	0	0.35 (1.22)		0	4.11 (6.94)	c
Sedatives	0.17 (0.56)	2.35 (6.64)		0.29 (1.1)	0	
Herbal	0	11.35 (18.26)	a	0	9.13 (10.68)	c

[a] Total number of occasions that the drug was used, with the exception of cannabis: the number of cannabis joints per month
[b] Significant difference at $\alpha=0.05$
[c] Significant difference at $\alpha=0.01$

Table 2 Characteristics of ecstasy use

MDMA (n=26)	Men (n=17)	Women (n=9)
Total cumulative number of ecstasy tablets	53.82 (35.56), range: 10–120	38.78 (14.95), range: 14–60
Frequency of ecstasy use[a]	1.96 (2.44), range: 0.25–10	1.44 (1.20), range: 0.25–4
Duration of use in years	2.28	2.24

[a] Number of ecstasy tablets per month.

age differences between the control and MDMA groups [$t(57)=0.23$, $P=0.82$], either for men [$t(27)=0.929$ $P=0.36$], or for women [$t(28)=-0.378$, $P=0.71$]. Male MDMA users consumed significantly more cannabis, cocaine, psilocybin mushrooms, and herbal ecstasy than the male controls. Female MDMA users consumed significantly more of all other (non-MDMA) drugs than the female controls, except for sedatives.

The average number of ecstasy tablets used by the MDMA group was 46.30, SD 30.56 (Table 2). The average frequency of ecstasy use was 1.70 tablets per month, SD 2.08. The tendency that on average males used higher quantities of MDMA than females was not statistically reliable [$F(1,24)=1.452$, $P=0.24$].

Task data

The results per cognitive task are summarized below, and can be seen in Table 3. Due to technical failure, for a few participants' data from some of the tasks were incomplete, hence sample sizes are indicated per task. Participants were excluded from the analyses if their accuracy was below 55% on relevant conditions. Results are described for males and females separately.

Flexibility

Switch costs are defined as the decrease in response speed or accuracy in task-alternations compared to task-repetition trials within mixed-task blocks. Mixing costs are defined as the decrease in response speed or accuracy in task-repetition trials in mixed-task blocks compared to task-repetition trials within single-task (non-switch) blocks. Mean reaction times (RTs) and accuracy (i.e. the percentage correct) were submitted to a separate repeated measures ANOVA with Switch trial type (repetition versus switch) or Mixing trial type (repetitions in single-task blocks versus repetitions in mixed blocks) as within-subjects factor, and group (MDMA users versus controls).

Dots-Triangles (n=57)

Switch costs; RT. Results showed that male MDMA users responded more slowly [$F(1,26)=9.634$, $P=0.01$] than controls, and in this group responses to switch trials were significantly slower than to repetition trials [$F(1,26)=40.134$, $P<0.01$]. Moreover, male MDMA users had higher switch costs [$F(1,26)=4.913$, $P=0.04$] than controls. In the female group, there was no main effect for Group, but the main effect for Switch trial type was significant [$F(1,27)=42.632$, $P<0.01$]. The Group×Switch trial type interaction failed to reach significance.

Switch costs; accuracy. Male MDMA users were more accurate than controls [$F(1,26)=5.049$, $P=0.03$], and in this group the Switch trial type effect was significant [$F(1,26)=16.579$, $P<0.01$]. Male MDMA users, however, did not differ in switch costs [$F(1,26)=0.07$, $P=0.79$] from controls. In female users, there was no main effect for Group, but the Switch trial type effect was significant [$F(1,27)=64.216$, $P<0.01$]. Moreover, in this group switch costs for MDMA users were larger compared to controls [$F(1,27)=5.360$, $P=0.03$].

Mixing costs; RT and accuracy. In the male group, there were only main effects of Group on RT and accuracy [$F(1,26)=6.094$, $P=0.02$; and $F(1,26)=6.064$, $P=0.04$, respectively]. Furthermore, the main effect of Mixing trial type on accuracy was significant [$F(1,26)=83.243$, $P<0.01$]. In the female group, no main effects were found for Group, and the main effect for Mixing trial type was significant only on RT [$F(1,27)=70.437$, $P<0.01$]. Mixing costs on RT and accuracy did not differ between MDMA users and controls.

Local-Global (n=57)

Switch costs; RT. Compared to controls, male MDMA users were slower than controls [$F(1,27)=5.178$, $P=0.03$], and a main effect of Switch trial type was found [$F(1,27)=37.023$, $P<0.01$]. Moreover, male MDMA users showed higher switch costs [$F(1,27)=8.705$, $P=0.01$]. Within the female group there were no significant MDMA differences for RT latency, although the main effect of Switch trial type was significant [$F(1,26)=18.924$, $P<0.01$]. Moreover, the Group×Switch trial type interaction failed to reach significance.

Switch costs; accuracy. In both the male and female groups, the main effects and the interaction between the factors failed to reach significance.

Mixing costs; RT and accuracy. In the male group, there was only a main effect of group [$F(1,27)=5.071$, $P=0.03$] on accuracy. In the female group, there was only a main effect for Mixing trial type [$F(1,26)=11.912$, $P<0.01$].

Table 3 Means and standard deviations of all relevant measures on all tasks and SCL-90 scores for men and women

	Costs and effects	Men		*p*	Women		*p*
		Controls	MDMA		Controls	MDMA	
Flexibility							
Dots-Triangles	RT (ms)	697.8 (62.2)	910.38 (50.1)	b	826.69 (46.2)	938.64 (68.9)	
	% Correct	89.2 (2.5)	94.9 (2.0)	a	86.0 (1.8)	92.3 (2.7)	
	Switch Cost (ms)	134.7	279.6	a	200.7	274.80	
	Switch Cost (%)	3.8	4.3		4.8	8.7	a
	Mixing Cost (ms)	169.4	243.7		195.4	226.4	
	Mixing Cost (%)	4.1	1.5		6.0	−1.3	
Local-Global	RT (ms)	412.1 (17.9)	459.2 (15.0)	a	457.2 (13.9)	440.3 (21.9)	
	% Correct	95.3 (0.7)	97.0 (0.6)		96.2 (0.6)	97.1 (0.9)	
	Switch Cost (ms)	17.6	50.7	b	59.8	36.8	
	Switch Cost (%)	0.2	0.7		0.1	−0.1	
	Mixing Cost (ms)	21.7	0.6		22.0	24.2	
	Mixing Cost (%)	0.7	0.5		0.6	0.0	
WM							
Tic Tac Toe	RT (ms)	376.6 (17.4)	385.6 (16.1)		379.1 (13.1)	376.8 (20.0)	
	Load effect	−23.9	19.2	a	25.5	16.1	
	% Correct	94.9 (2.4)	91.1 (2.2)		93.0 (1.8)	93.0 (2.7)	
	Load effect	1.4	5.6		3.0	1.9	
Mental Counters	RT (ms)	413.6 (44.1)	586.2 (34.2)	a	540.3 (33.1)	544.7 (50.0)	
	% Correct	92.9 (1.6)	89.6 (1.2)		89.7 (1.2)	89.7 (1.8)	
Inhibition							
Eriksen Flankers	RT (ms)	414.6 (15.4)	445.6 (12.4)		437.6 (9.3)	417.8 (14.0)	
	Interf. Cost (ms)	53.5	50.1		44.9	51.7	
	% Correct	96.7 (1.5)	96.6 (1.2)		96.7 (0.6)	99.3 (0.9)	a
	Interf. Cost (%)	6.2	5.9		5.8	0.8	a
Stop signal	SSRT (ms)	204.9 (62.6)	195.2 (39.0)		202.8 (68.4)	236.8 (91.9)	
Complex EF							
TOL	% Excess moves	31.7 (4.4)	54.1 (3.7)	b	55.2 (3.3)	55.6 (5.1)	
	Total moves	27.3 (1.5)	31.9 (1.3)	b	33.1 (1.2)	34.7 (1.8)	
	Planning time (s)	14.5 (2.0)	7.7 (1.7)	b	10.1 (1.5)	8.8 (2.3)	
	Total time (s)	30.7 (2.5)	26.5 (2.1)		33.4 (1.9)	33.5 (2.8)	
WCST	Total no. correct	77.1 (3.1)	70.8 (2.6)		69.2 (2.3)	75.7 (3.6)	
	No.correct ambig.	1.5 (0.6)	3.2 (0.5)		2.0 (0.5)	1.6 (0.7)	
	No. persever. error	11.3 (2.6)	18.8 (2.2)	a	14.4 (2.0)	14.4 (3.0)	
	No. ambig. error	10.2 (2.0)	15.8 (1.6)	a	12.2 (1.5)	12.8 (2.2)	
	Conceptual level	70.8 (3.7)	59.5 (3.1)	a	62.2 (2.8)	67.0 (4.3)	
SCL-90							
	Anxiety	10.6 (0.9)	13.2 (3.2)	b	13.8 (3.2)	13.7 (1.6)	
	Agoraphobia	7.2 (0.4)	8.1 (2.6)		7.9 (1.7)	7.6 (1.0)	
	Depression	18.8 (2.3)	21.1 (5.5)		21.9 (5.4)	21.9 (3.1)	
	Somatization	15.2 (2.0)	16.2 (3.9)		15.9 (3.8)	16.4 (3.0)	
	Insufficiency	11.7 (1.2)	15.9 (4.5)	a	13.3 (3.7)	15.3 (4.5)	
	Sensitivity	20.8 (2.2)	25.2 (6.1)	a	22.4 (4.5)	23.1 (2.8)	
	Hostility	7.0 (1.3)	7.6 (2.1)		6.8 (1.1)	7.0 (1.0)	
	Sleeping problem	3.5 (0.7)	4.3 (1.9)		4.9 (2.9)	4.1 (1.0)	
	Total SCL-90	104.3 (7.3)	121.8 (24.6)	a	117.3 (21.3)	120 (12.5)	

[a] Significant difference at α=0.05
[b] Significant difference at α=0.01

Working memory

Tic Tac Toe (n=56)

Mean RTs and accuracy (i.e. the percentage correct) were submitted to a separate repeated measures ANOVA with WM load (low versus high) as within-subjects factor, and Group (MDMA users versus controls) as between-subjects factor. The only significant finding for RT was a cross-over interaction between WM-load and MDMA use in males [$F(1,24)=5.115$, $P=0.03$]. This interaction reflects the pattern that male MDMA users responded more slowly in when WM load increased, whereas controls were in fact faster under the higher WM load. In the female group, all effects failed to reach significance. There were no significant effects on accuracy in either the male or the female group.

Mental Counters

Due to data storage failure, only 47 participants successfully completed this task. Mean RTs and accuracy were submitted to separate repeated measures ANOVA with WM load (low versus high) and series length (short versus long) as within-subjects factors, and Group (MDMA users

versus controls) as between-subjects factor. Male MDMA users were slower than controls [$F(1,22)=7.141$, $P=0.01$], and there was a main effect for series length on RT [$F(1,22)=7.601$, $P=0.01$]. The interactions failed to reach significance. Within the female group, no significant effects on RT were found. The only significant effect on accuracy was for WM load [$F(1,20)=6.365$, $P=0.02$] in the female group.

Inhibition

Eriksen Flankers (n=54)

Mean RTs and accuracy were submitted to a separate repeated measures ANOVA with interference (congruent versus incongruent) as a within-subjects factor and Group (MDMA users versus controls) as a between-subjects factor. An interference effect on RT was observed for males [$F(1,26)=139.168$, $P<0.01$] and females [$F(1,24)=228.794$, $P<0.01$], indicating that responses to incongruent stimuli were slower than to congruent stimuli. This effect did not differ between MDMA groups. For accuracy, an interference effect was also observed for males [$F(1,26)=9.935$, $P<0.01$] as well as females [$F(1,24)=9.167$, $P=0.01$]. In the female group, there was also a significant effect of Group [$F(1,24)=5.773$, $P=0.02$] and a Group×Interference interaction effect [$F(1,24)=5.362$, $P=0.02$]. This indicates that accuracy in females with a history of MDMA use was impaired in incongruent (compared to congruent) conditions more than in their controls.

Stop Signal (n=57)

The dependent variable in the Stop Signal task was the stop-signal RT (SS-RT) an index of the efficiency of response inhibition. The data of five MDMA users (two females) and of nine controls (six females) were excluded because they failed to inhibit on more than 85% of the trials. Male and female MDMA users did not differ significantly on SS-RTs. An additional analysis was conducted to establish whether the speed of stopping was distinct from go-RT. Analysis of covariance (ANCOVA) on simple SS-RT, entering go-RT as a covariate, yielded a no significant main effect of SS-RT.

Complex tasks

Tower of London (n=59)

Four dependent variables (i.e. the number of extra moves, the number of total moves, planning time, and total time) were submitted to univariate ANOVAs. Significant differences between the male MDMA users and controls were found on most dependent measures. Male users needed more extra moves [$F(1,27)=13.806$, $P<0.001$], and hence had more total moves [$F(1,27)=8.101$, $P=0.01$]. Compared to controls, male users needed less planning time to make the initial response [$F(1,27)=7.164$, $P=0.01$], and completed the configuration in less total time, although the latter difference was not significant. There were no significant differences between the female users and their controls.

Wisconsin Card Sorting Task (n=59)

Six dependent variables (i.e. the number of correct responses, the number of correct responses on ambiguous trials, the number of perseverative errors, and conceptual level responses) were submitted to univariate ANOVAs. There were no significant group differences in the number of correct responses on ambiguous trials or in the total number of correct responses. Compared to controls, male MDMA users made more perseverative errors [$F(1,27)=6.32$, $P=0.02$], more errors on ambiguous trials [$F(1,27)=6.81$, $P=0.02$], and had an impaired conceptual level response [$F(1,27)=6.41$, $P=0.02$]. Within the female group, there were no significant differences between the users and controls.

Symptom Checklist-90 (SCL-90)

Male users scored higher on the overall SCL-90 score [$F(1,27)=16.21$, $P=0.03$], on the subscales sensitivity [$F(1,27)=12.36$, $P=0.02$], anxiety [$F(1,27)=9.95$, $P=0.01$] and insufficiency of thought and behavior [$F(1,27)=12.40$, $P=0.02$]. The amount of MDMA used correlated significantly with the scores on the subscales insufficiency of thought and behavior ($r=0.308$, $P=0.018$) and sensitivity ($r=0.293$, $P=0.024$). Within the female participant group, no significant differences were observed.

Post hoc analyses

To investigate the influence of polydrug use on our findings, those analyses that were reported above to yield significant effects of MDMA use were followed up by additional analyses to examine whether task performance *within* the MDMA user groups varied as a function of the quantities of recreational consumption of other drugs. These follow-up analyses featured an additional between-subjects factor: high-cannabis versus low-cannabis use, high-cocaine versus low-cocaine use, high-psilocybin versus low-psilocybin mushroom use, or high-herbal versus low-herbal ecstasy use (in separate ANOVAs). High-use versus low-use on each of these drugs was determined using a median split within the male and female MDMA groups separately. None of these additional factors modulated the main or interaction effects reported above, either in males or in females, except in one isolated instance. Among male MDMA users, who showed RT higher switch costs than controls in the Local-Global task, these switch costs were greater in magnitude

for high compared to low users of herbal ecstasy [$F(1,15)=5.13$, $P=0.039$]. Possibly, the power of these analyses was limited due to small sample size. As an additional approach therefore, correlation coefficients were calculated between total MDMA use and the total amount of other drugs that were used within the MDMA group. All correlation coefficients were low and non-significant. Thus, both analytical approaches converged on the conclusion that within the MDMA group the use of other drugs had no measurable impact on the cognitive scores, with the possible exception of a modulatory effect of herbal ecstasy on cognitive flexibility.

Discussion

Thus far, the literature on neurocognitive effects of MDMA consumption has emphasized 5-HT mediated effects on memory. Reports of effects on (presumably DA-mediated) executive functions also begin to emerge but the patterns are still fragmentary. The framework of Miyake et al. (2000) was used here for a more systematic study of ecstasy effects on EFs, using an experimental test battery designed to examine the EF categories of cognitive flexibility, working memory updating, and inhibition of pre-potent responses.

Consistent with previous findings, we observed selective cognitive impairments in recreational ecstasy users (e.g. Bolla et al. 1998; Fox et al. 2001a). Considerable impairments were observed in male users compared to non-users on response speed and switch costs in set shifting tasks, and on performance in the more complex executive function tasks, as well as on the SCL-90 self-rating scale. Thus, having a history of MDMA consumption selectively impaired performance on complex EF tasks and on one of its subcategories, set shifting, while leaving the subcategories of working memory updating and response inhibition relatively preserved. In female participants, virtually no significant differences were found between users and non-users.

Speeded performance in the task-switch paradigm was affected by MDMA in the male user group. On both the Dots-Triangles task and (to a lesser extent) the Local-Global task, switch costs were higher in the user group, indicating that mental set-switching abilities were impaired. Previously, Fox et al. (2002) reported only minor effects of MDMA on attention switching, but considerable shortcomings in verbal memory. These authors assumed that the detrimental effects of MDMA on EFs are noticeable only after prolonged use, while verbal WM abilities are affected already after shorter periods of MDMA consumption. The present study, however, revealed negative effects of MDMA on cognitive flexibility using an apparently more sensitive measure, namely switch costs in task switching.

In the present study, the effects of MDMA use on WM tasks remained small and were much less pronounced compared with the results of some other studies (e.g. Wareing et al. 2000; Fox et al. 2001a, 2002; Verkes et al. 2001). The only effect in the present study was a cross-over interaction between WM-load and MDMA use on RT in the Tic Tac Toe task, with male users suffering from higher WM loads while controls showed the opposite pattern. One possible explanation for the discrepancy between our findings and the more clear-cut findings on WM tasks found elsewhere could relate to the nature of the WM tasks used. While most previous studies used verbal WM tasks, the WM demands in the present study were more visual and numerical in nature. Verbal WM capacities may be more sensitive to the effects of MDMA, although visual WM impairments have also been reported (Bolla et al. 1998). Another factor that may play a role in the current lack of deterioration concerns the precise WM operations engaged in the tasks: the present tasks capitalized on information *updating* in WM, involving primarily the central executive, whereas in previous studies more emphasis may have been put on the efficiency of *storage* and *retrieval* of relevant information in WM stores. Possibly, memory-storage functions are more susceptible to MDMA-induced decline than memory updating functions.

Performance on inhibition tasks was hardly affected by MDMA use in the present research. The Stop Signal task and the Eriksen Flankers task both draw on the capability to suppress responses that are inappropriately activated (Ridderinkhof et al. 1999). In terms of both SS-RT and flanker interference effects on RT, MDMA users and non-users performed equally well. The only MDMA effect on inhibition was observed in the Eriksen Flankers task, where female MDMA users showed a stronger effect of incongruence on accuracy than controls. Overall, these findings are consistent with reports showing no differences between MDMA users and controls in performance on a *go/no-go* task (Fox et al. 2002). Since all these paradigms appear to be highly sensitive to individual differences in the efficiency of response inhibition, the conclusion seems warranted that inhibitory capacities (presumably mediated by lateral prefrontal cortex) are largely preserved in recreational ecstasy users.

Significant differences between male MDMA users and controls were found on the complex EF tasks. In the WCST, users performed worse on virtually all the dependent measures. This finding is consistent with those reported by Fox et al. (2001b), who also observed more errors of perservation in MDMA users. Thus, the recreational consumption of ecstasy results in deficiencies in the adaptive ability to adjust behavior in response to changing environmental demands. Fox et al. (2001b) also observed group differences on TOL performance. In their study, MDMA users needed longer planning times in the TOL, whereas in our research, shorter planning times were found. This difference may be explained by higher impulsivity in MDMA users in the present sample, as also reported in previous research (Morgan 1998). Because of their impulsivity, MDMA users may commence the TOL sooner, and spend less time on planning the steps to be taken. As a result, planning times are shorter, but the number of excess moves is higher.

The MDMA-induced rises in perseverative behavior on the WCST and in switch costs in task switching are both linked to adaptive control. In studies of cognitive development and aging, age-related increases in perseverative behavior in experimental analogues of the WCST were found to be generated primarily by deficiencies in the ability to shift set (Ridderinkhof et al. 2002b; Crone et al. 2004). Similar to individual differences brought about by age, those brought about by MDMA usage may also be closely related to task switching abilities. Both perseverative behavior and switch costs emanate from failure to shift set or to adjust a cognitive strategy in order to successfully complete a new task. These adaptive control failures are consistent with the results of studies on differences between MDMA users and controls in their performance on a multitude of executive tasks (Milani and Schifano 2000; Wareing et al. 2000; Fox et al. 2001b). The considerable effects of MDMA on cognitive flexibility (in switch tasks and the WCST) in the absence of effects on WM updating and response inhibition warrants the inference that sustained MDMA consumption incurs a selective impairment on one category of EF (as defined in the model Miyake et al. 2000), namely cognitive flexibility.

It should be noted that all participants in the MDMA group were recreational users with a mean consumption of 1.7 XTC tablets per month. This form of drug use can be described as moderate, with the users living generally healthy, having a regular daily routine, and not suffering from obvious adverse effects, either mentally or physically. The exposure to MDMA is at the lower end of the range reported elsewhere in the literature (Bolla et al. 1998; Fox et al. 2001a). The present finding of mild cognitive impairment in moderate users may implicate more profound effects for users who consume MDMA more frequently or have a more prolonged history of drug use. Furthermore, clear disparities were observed between males and females in the effects of MDMA on task performance. Our choice to analyze the sexes separately was motivated by several findings (e.g. McCann et al. 1994; Liechti et al. 2001; Reneman et al. 2001; Verheyden et al. 2002) in which long-term effects of MDMA were more pronounced in females than in males. This difference is typically explained by the lower average body weight in females, which makes them potentially more susceptible to the neurotoxic effects of MDMA. In our research, however, differences in task performance were found almost exclusively in the male user group. It should be noted that the male users had a history of higher MDMA consumption than females, measured as the cumulative number of ecstasy tablets: on average 53.82 versus 38.78 tablets, respectively. Although this difference failed to obtain statistical significance, due presumably to substantial within-group variability in MDMA consumption, it may well have played a role in producing the present sex differences.

A considerable number of our MDMA users were polydrug users. These polydrug users had a history of consumption of cannabis and cocaine in substantial amounts, and of several other (non-MDMA) drugs in more moderate quantities. Since cannabis and cocaine have been reported to impair various aspects of cognitive function (e.g. Schwartz et al. 1989; Mittenberg and Motta 1993; Rosselli and Ardila 1996), the effects of MDMA in our sample could potentially be explained (or at least aggravated) by this polydrug use. Nevertheless, correlations between total MDMA use and use of other drugs were low and not significant. Furthermore, within the MDMA group, median split analyses indicated no interactions of the degree of other drug use with the effects of MDMA, except for a modulatory effect of the concomitant use of herbal ecstasy on RT switch costs in males. Thus, with the exception of an isolated effect of herbal ecstasy, within the MDMA group the use of other drugs had no measurable impact, although it should be noted that the power of these additional analyses was limited by the small sample sizes.

It should be noted further that the present sample consisted of first-year psychology students, which may constrain external validity. Because of the relatively young age of the participants and their presumed above average level of intelligence, it is not clear how our results generalize to the population at large. Previous research has indicated that individuals with lower intellectual abilities show greater decrements in cognitive performance (Bolla et al. 1998). These authors posit that individuals with higher intellect have a higher threshold for developing cognitive problems after possible brain injury. Following this line of reasoning, long-term effects of MDMA use within the general population might result in even more profound cognitive impairments than within the present sample.

In conclusion, male recreational ecstasy users were found to be impaired in the adaptive control capacities involved in task switching and the WCST. They experienced greater switch costs and increased perseverative behavior compared to controls, which may well have repercussions for daily life activities such as dealing with traffic situations. Other executive functions, in particular WM updating and response inhibition, were much less subject to performance decrements. These new findings were afforded by the use of a theoretical framework proposed by Miyake et al. (2000) to systematically study the efficiency of EFs. Adaptive control pertains not only to those executive processes involved in adjusting behavior rapidly and flexibly in response to changes in environmental demands, but also to those in performance monitoring to signal the need to instigate such changes. An important aspect of performance monitoring is the ability to monitor on-going processing in the neurocognitive system for signs of conflict or erroneous outcome. Psychophysiological and neuroimaging studies conclude that the anterior cingulate cortex is the central component of the neural circuit for action monitoring. This dopaminergic control system is involved in detecting the activation of erroneous or conflicting responses (for reviews, see Botvinick et al. 2001; Holroyd and Coles 2002). Alcohol consumption has been found to impair this

adaptive control function (Ridderinkhof et al. 2002a). Considering the reported effects of MDMA consumption on the DA system (O'Shea et al. 2001) and its effects on adaptive control observed in the present study, future research should aim also at addressing the effects of MDMA on action monitoring.

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