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Dissociable effects of a single dose of ecstasy (MDMA) on psychomotor skills and attentional performance

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Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) is a psychoactive recreational drug widely used by young people visiting dance parties, and has been associated with poor cognitive function. The current study assessed the influence of a single dose of MDMA 75 mg and alcohol 0.5 g/kg on cognition, psychomotor performance and driving-related task performance. Twelve healthy recreational ecstasy users participated in an experimental study conducted according to a double-blind, double-dummy, placebo-controlled three-way cross-over design. MDMA improved psychomotor performance, such as movement speed and tracking performance in a single task, as well as in a divided attention task. MDMA impaired the ability to predict object movement under divided attention. However, the inability to accurately predict object movement after MDMA may indicate impairment of particular performance skills relevant to driving. There was no effect of MDMA on visual search, planning or retrieval from semantic memory.

Key words: alcohol, cognition, ecstasy, MDMA, psychomotor performance, traffic safety

Introduction

The party drug ecstasy (3,4-methylenedioxymethamphetamine, MDMA) is structurally related to mescaline and stimulant drugs such as amphetamines (de Man, 1994; Morgan, 2000). The widespread use of MDMA by young people causes concern, especially due to its associated risk of traffic accidents (Henry *et al*., 1992). Epidemiological research and case studies have shown that impaired judgement and higher risk taking are the most likely contributors to methamphetamine-related traffic accidents (Schifano, 1995; Logan and Couper, 2001). However, no experimental studies addressing the relation between MDMA and driving performance have been reported to date. Previous psychopharmacological studies have largely focused on the chronic effects of MDMA on the brain and behaviour (Krystal *et al*., 1992; McCann *et al*., 1999; Morgan, 1999; Gouzoulis Mayfrank *et al*., 2000; Verkes *et al*., 2001), while publications about its acute effects have largely focused on its acute medical adverse effects and associated emergency medical affairs (Henry, 1992; de Man, 1994; Vollenweider Scherpenhuyzen and Vollenweider, 1998). Previous studies conducted under controlled conditions showed that single doses of MDMA (range 0.9–1.9 mg/kg) did not affect performance on tasks of immediate recall, digit repetition and selective attention (Downing, 1986; Vollenweider *et al*., 1998). Cami *et al*. (2000) observed slight impairment of performance on the digit-symbol substitution test and esophoria (squinting) in subjects after MDMA 125 mg, but not after 75 mg MDMA compared to placebo. They did not observe a significant effect of a single dose of MDMA (75 or 125 mg) on simple reaction time compared to placebo (Cami *et al*., 2000).

The present study was designed to further investigate the acute effects of a normal single recreational dose of MDMA (75 mg) on psychomotor and cognitive performance in recreational ecstasy users under experimentally controlled conditions. Placebo treatment was used as a passive control. Performance effects were assessed in tests previously shown to be sensitive to a variety of psychoactive drugs covering a wide range of cognitive and psychomotor constructs. In addition, well validated tasks were added to specifically measure the effects of MDMA and alcohol on skills related to driving (Riedel *et al*., 1995; Ramaekers *et al*., 1998; Vermeeren and O'Hanlon, 1998). Alcohol was chosen as a reference because of its ability to impair driving related skills, even at low doses.

Materials and methods

Subjects

Fourteen Dutch recreational users of MDMA were recruited by an advertisement posted in the University of Maastricht and in bars and discotheques in the Maastricht region. Inclusion criteria were experience with ecstasy (> 4 times/year) and alcohol consumption (> 3 units/week) and good physical and psychological health. Volunteers were excluded if they had a history of medical or

psychiatric illness, alcohol or drug addiction, hypertension and history of severe adverse side-effects of MDMA. Subjects underwent a standard medical screening and a shortened version of the Structured Clinical Interview for DSM-IV (Ventura *et al*., 1998) to confirm absence of any physical illness or Axis I and II diagnoses. Subjects were screened for previous convictions for drug possession or drug trafficking by the public prosecutor. Female volunteers were screened for pregnancy before entering the study and at the beginning of test days. Written informed consent was obtained from all subjects, who were paid for their participation.

The study was conducted according to the declaration of Helsinki (1969) and its subsequent amendments and approval was obtained from the Medical Ethics Committee of the University Hospital of Maastricht.

Experimental design and treatment

The study was conducted according to a double-blind, double-dummy, placebo-controlled, three-way cross-over design. MDMA, alcohol and placebo were administered on separate occasions spaced at least 2 weeks apart. On all test days, subjects received a solution of 25 ml of bitter orange syrup in a small cup with or without MDMA 75 mg in a powder form, which had to be consumed at once. They also received a beverage of 500 ml of orange juice with or without alcohol, to be consumed within 15 min. In the alcohol condition, the beverage consisted of 0.5 g/kg pure ethanol adjusted to 500 ml with orange juice. That dose was chosen to achieve an estimated blood alcohol concentration (BAC) of approximately 0.4–0.5 mg/ml (Lamers and Ramaekers, 2001). This BAC level was previously shown to produce significant performance impairment in tests identical to those in the present studies (Ramaekers *et al*., 1996). The alcohol-placebo condition was administered as 500 ml of orange juice with a few drops of ethanol on top.

The double-dummy procedure was employed to ensure that subjects were unaware of whether an active drug was delivered via syrup or orange juice.

Performance assessments

The battery consisted of tests measuring psychomotor skills (Critical Tracking Test, Motor Choice Reaction Time), attentional functions (Divided Attention Task, Object Movement Estimation Under Divided Attention, visual search) and executive functions (Word Fluency, Tower of London). Apart from the Word Fluency test, all test administration was computerized and presented on a 17-inch monitor with subjects sitting approximately 50 cm from the monitor. To minimize learning effects, subjects conducted a practice session of each test several days before entering the experiment.

The Critical Tracking Test (CTT) measures the ability to control an inherently unstable error signal in a first-order compensatory tracking task (Jex *et al*., 1966). Subjects attempt to keep a cursor centred in a target area in the middle of a display using a joystick. The cursor appears at the centre of the screen and tends to move away from the centre. The operator's input introduces error, which is magnified by the system, making it increasingly necessary to respond to the velocity of the cursor as well as its position. Compensatory movements increase in frequency until these lag the cursor's last movement by 180°, whereupon control is lost. The point where this occurs is defined as the 'critical frequency' or λ_c expressed in radians per second (rad/s). A single test involves five repetitions of this task, each lasting approximately 45 s. The median value of these trials is taken as the test score. Theoretically, λ_c is the reciprocal of the operating delay lag in human closed-loop control.

The Divided Attention Task (DAT) assesses the subjects' ability to divide attention between tracking and monitoring tasks performed simultaneously (Moskowitz, 1973). The tracking subtask is similar to the CTT described above, except that the error signal velocity is fixed at a constant level (i.e. 50% of individual's optimal performance during the training sessions) ($\lambda_c/2$). Tracking error is measured as the average absolute distance (mm) between the cursor's position and display centre over the entire 12-min tests. The other subtask is of a more cognitive nature and consists of monitoring 24 peripheral LED displays fixed to the four corner sides of the main display. These displays each present numerals, 0–9, which change asynchronously every 5 s. The subject removes his or her foot from a pedal-switch as quickly as possible after detecting the target numeral, '2'. Median correct reaction time (ms) to targets is the second response measure.

The Motor Choice Reaction Time (MCRT) is a test in which reaction time (RT) is studied as a function of task complexity (Houx and Jolles, 1993). The subject is presented with a computerized panel with one central red and five white buttons. The subject is asked to hold down the central red button until one of the white buttons lights up. The response set consisted of pressing the only one button lit up (simple RT), pressing one of three buttons which lit up (choice RT), or pressing the button located to the right of the lit button (incompatible RT). Reaction time was dissected into an initiation phase (i.e. time from stimulus onset until release of the red button), and a movement phase (i.e. time between release of the red button and pressing the response button). Initiation time represents the time needed for perception, decision and motor planning whereas movement time represents the time needed for actual movement execution. Dependent measures are median initiation time for simple, choice and incompatible RT and median movement time for the three RT tasks together.

The Object Movement Estimation under Divided Attention (OMEDA) consists of a task to estimate time to contact (TTC) of a moving object to a fixed point (Read *et al*., 2000). The subject is seated in front of a computer screen in which the corners are covered by green triangles and a yellow circle occludes the centre of the screen. The occlusion circle varies in size per trial (2, 100 or 200 pixels). From one of the corners, a red dot (target) travels towards the centre of the screen. Once it encounters the edge of the occlusion circle, it travels underneath and is no longer visible. For the primary task, the subjects have to indicate at what point in time the target reaches the centre of the computer screen, by pressing a foot pedal. During movement of the target, five geometrical shapes appear; one on top of the occlusion circle and one on top of each of the triangles in the corners. For the secondary task, the subject is required to press a button in case the geometric shape at the occlusion circle matches one of the others. Absolute TTC error (defined as the absolute mean difference between estimated and actual TTC) and the number of correct responses to the geometric targets (divided attention) are the primary and secondary measures. The test was designed to assess effects of diseases and drugs on higher level cognitive functions, including working memory, time-

to-contact estimates, collision judgement and divided attention in particular in traffic situations (i.e. intersection approach). Preliminary findings showed a clear detrimental effect of age on OMEDA performance, especially the estimation of time-to-contact (Read *et al*., 2000). Similar impairments were found when comparing a group of cannabis users with age-matched normal controls (Ward *et al*., 2000). The Duration of the test is approximately 20–25 min.

The original version of the Tower of London (TOL) consists of three coloured balls, which must be arranged on three sticks to match the target configuration on a picture while only one ball can be moved at a time (Shallice, 1982). The present version consists of computer-generated images of begin- and end-arrangements of the balls. Every time a ball is moved counts as one step. The subject decides as quickly as possible, whether the end-arrangement can be accomplished in 2, 3, 4 or 5 steps from the begin arrangement by pushing the corresponding number coded button (Owen *et al*., 1995). Six different versions of this test were assessed balanced over test days and time of assessment per six subjects. Reaction times and errors are the main performance measures. A new analytical procedure was applied to reduce the set of RT data across levels of difficulty. Transformation and regression functions of RT on the number of steps have been determined to obtain slope and intercept coefficients, based on previous data obtained in groups of 20 young- and 20 elderly volunteers (Riedel, 2000). Briefly, each RT value is transformed according to the equation: $y = \sqrt{[10 \log(x)]}$, so that transformed RTs are a linear function of the number of steps. Regression analyses are then carried out on transformed RTs to yield individual slopes and intercepts of the RT on steps function. Slope is considered the primary outcome variable measuring problem solving ability. Intercept is a variable measuring response speed unrelated to problem solving ability. Because no consistent association has been established between the number of errors and the number of steps, the total number of errors is the other outcome variable.

In the Word Fluency Task, subjects are asked to name as many four-letter words as possible beginning with a particular letter (B, H, R, L, P or M) within 1 min. The fluency test measures strategy-driven retrieval of information from semantic memory (Luteijn and van der Ploeg, 1983). Order of the six versions over test days and time of assessments were balanced per six subjects. The dependent variable is the number of correctly produced words.

The Signal Detection Task (SDT) is a visual search task. Small white squares (3 × 3 mm) are presented in a pseudo-random fashion on a computer screen. Twenty squares are randomly assigned to a 10 × 6 grid, all squares being 2.5 cm apart. Targets are defined as a set of four stimuli forming a square of 2.5 × 2.5 cm. Every 3 s, three squares move to a different location within the matrix. Subjects are required to respond to the target stimuli with their dominant hand by pressing a button as fast as possible. Total number of squares presented is 400, and the total number of target stimuli is 56, yielding a signal probability of 0.14. The task lasts 6.40 min. Sensitivity (A′) defined as the non-parametric proportion of correctly identified targets corrected for false positives is the dependent measure according to the signal detection theory (Pollack and Norman, 1964).

Repetitions of the psychomotor and cognitive tests were scheduled at 1 and 3 h post drug with the exception of the CTT and the OMEDA. The former test, which is easy to administer and only takes a few minutes to complete, was conducted before, and at 1, 2, 3 and 5 h post drug. The OMEDA was conducted 4–5 h after drug intake.

Toxicological assessments

Blood samples were taken every 60 min starting just before, and up to 5 h after drug intake using glass venotubes with sodium fluoride and potassium oxalate as anticoagulant. MDMA concentrations were determined in the corresponding plasma samples using solid-phase extraction and gas chromatography with mass spectrometric detection with a limit of quantification of 10 ng/ml.

Blood alcohol levels were estimated every 30 min, starting just before and up to 5.5 h after drug intake using Lion SD-400 Breath Alcohol Analyser® (Lion Laboratories, Barry, Vale of Glamorgan, UK).

Study procedures

On test days subjects arrived at the research facility between 11.45 h and 12.00 h. The use of drugs other than the study drugs was prohibited throughout the study. Subjects were prohibited from consuming alcohol for 24 h and caffeine for 16 h before treatments. Smoking was not allowed during experimental sessions. Upon arrival, subjects were questioned about possible use of alcohol, drugs or medication in preceding weeks. The presence of alcohol was explored using a Lion SD-4 Breath Alcohol Analyser®. Urine, collected upon arrival, was tested for recent use of THC, amphetamine, methamphetamine, cocaine and opiates by means of the qualitative Syva Rapid Test® (Dade Behring, Liederbach, Germany). Female subjects were also tested for pregnancy with a QuickVue® One-step HcG Urine Pregnancy Test (Quickdel, San Diego, USA). When inclusion or exclusion criteria were violated, the test day was postponed.

At 12.30 h subjects consumed a light lunch consisting of two slices of bread and unlimited fruit juice or mineral water. At 13.15 h, MDMA, alcohol or placebo was administered. During the day, subjects had free access to mineral and tap water, fruit juice, an isotonic drink and sugar-free chewing gum.

A physician was on call during all experimental sessions, which took place at the Maastricht University Hospital. Additional clinical blood chemistry, with particular reference to liver and renal functions was conducted 7 and 11 days after each treatment. Subjects were asked to contact the medical supervisor or one of the researchers when experiencing any sign of nausea, vomiting, intolerance of fatty food, yellowish colour of skin, or tiredness during the 2 weeks after test days.

Statistical analyses

All variables were tested in repeated-measures multivariate analysis of variance (MANOVA) for the main effects of Treatment (three levels) and Treatment by Time (two or five levels). In case of the TOL, MCRT and OMEDA, the factorial models were expanded with one additional factor (i.e. Task complexity or Occlusion diameter). Following a significant overall effect of Treatment or its interaction with Time, Task complexity or Occlusion diameter, univariate *F*-tests for establishing differences between drugs and placebo were conducted. All univariate *F*-tests were conducted across all times of testing.

A special proceeding was followed in case of the OMEDA. The alcohol treatment was dropped from the analysis because, at the time of testing, blood alcohol concentrations had dropped to

Table 1 Overview of the subjects' characteristics and their alcohol and recreational drug use, where Total use = lifetime use (number of occasions)

Variable	*n*	Mean	SD	Min	Max
Age (years)	12	23.5	3	21	30
Weight (kg)	12	65.9	4.0	60.0	73.0
Years of education	12	16	2.5	13	22
Ecstasy use per year (times)	12	9	6	5	25
Total ecstasy use (times)	12	39	34	5	125
Marijuana use per year (times)	12	91	114	0.5	318
Total marijuana use (times)	12	760	1076	3	3500
Alcohol per week (units)	12	17	17	4	50
Total amphetamine use (times)	8	7	10	1	30
Total cocaine use (times)	7	13	17	2	50
Total psilocybine use (times)	3	14	11	3	25
Total LSD use (times)	3	1	0	1	1

0.0 mg/ml and was no longer active. A univariate *F*-test was conducted to assess performance differences between placebo and MDMA. The α-probability criterion for determining the significance of mean differences was set at $p = 0.05$.

Results

Twelve subjects (eight male and four female) completed the study. Their demographic characteristics are summarized in Table 1. Data of the MCRT of one subject are missing due to computer failure. An overview of all statistical comparisons of main effects of Treatment and interactions including Treatment of the subjects' performance tests is given in Table 2. No serious adverse events were observed and none of the subjects needed special care during or after the experimental sessions.

Performance assessments

Critical tracking did not differ between treatments at baseline [$F(2,10) = 0.339$, p = not sifnificant] (Fig. 1). MANOVA

Table 2 Overview of effects of the statistical comparisons of the subjects' cognitive and psychomotor performance

Test	Construct	Factor	d.f.	Overall effect		Placebo–alcohol		Placebo–MDMA	
				F	*P*	*F*	*p*	*F*	*P*
CTT	λ_C	Treatment	2.10	4.52	0.04	0.01	NS	5.92	0.03↑
		Treatment × Time	6.6	2.01	NS				
DAT	Tracking error	Treatment	2.10	6.19	0.02	2.53	NS	6.83	0.02↑
		Treatment × Time	2.10	1.62	NS				
DAT	Reaction time	Treatment	2.10	0.13	NS				
		Treatment × Time	2.10	0.17	NS				
MCRT	Initiation time	Treatment	2.9	0.08	NS				
		Treatment × Time	2.9	0.74	NS				
		Treatment × Complexity	4.7	1.16	NS				
		Treatment × Time × Complexity	4.7	0.91	NS				
MCRT	Movement time	Treatment	2.9	5.26	0.03	0.25	NS	9.63	0.01↑
		Treatment × Time	2.9	0.74	NS				
Omeda	TTC error	Treatment						4.59	0.06↓
		Treatment × Occlusion						4.18	0.07↓
Omeda	Divided attention error	Treatment						0.44	NS
		Treatment × Occlusion						0.00	NS
TOL	Slope/intercept	Treatment	4.7	0.76	NS				
		Treatment × Time	4.7	1.09	NS				
TOL	Number of errors	Treatment	2.9	7.39	0.01	10.50	0.01↑	0.52	NS
		Treatment × Time	2.9	0.03	NS				
Word fluency	Number of words	Treatment	2.10	0.59	NS				
		Treatment × Time	2.10	1.75	NS				
SDT	Sensitivity (A′)	Treatment	2.10	1.09	NS				
		Treatment × Time	2.10	0.16	NS				

All *p*-values exceeding 0.10 are shown as NS (not significant). The arrows indicate improvement (↑) and impairment (↓) relative to placebo.

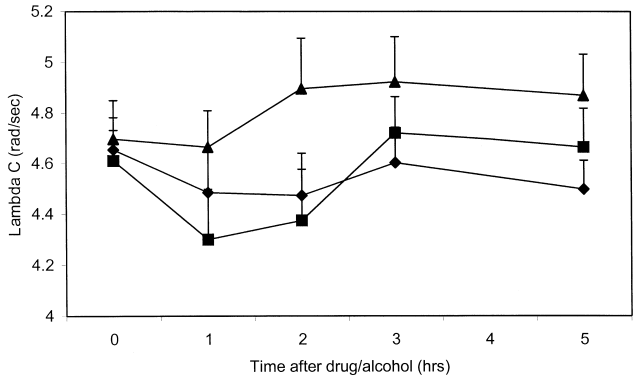

Figure 1 Mean (± SE) critical tracking error (rad/s) in the Critical Tracking Test at baseline and 1, 2, 3, 4 and 5 h after placebo (◆), alcohol (■) and MDMA (▲) administration

showed a main effect of Treatment on tracking performance. There was no interaction with Time. Separate drug–placebo comparisons revealed a significant effect of MDMA indicating improved tracking performance relative to placebo.

MANOVA revealed an overall effect of Treatment on sub-critical tracking performance in the Divided Attention Task (Fig. 2). There was no overall interaction between Treatment and Time. Separate drug-placebo comparison showed that MDMA significantly improved tracking performance by lowering tracking error as compared to placebo. Alcohol had no effect on tracking error.

MANOVA showed a significant overall effect of Treatment on movement time in the MCRT. There was no overall interaction between Treatment and Time. Separate comparison between MDMA and placebo indicated that movement time significantly improved after MDMA administration (100 and 108 ms, respectively), while alcohol did not affect movement time (110 ms).

The results of the primary and secondary task of the OMEDA are presented in Table 2 and Fig. 3. Univariate *F*-comparison strongly suggested that MDMA elevated TTC error and that this effect increased as a function of occlusion. Increments in estimated absolute TTC resulted from increments in overestimation, as well as increments in underestimation of the actual TTC. Performance

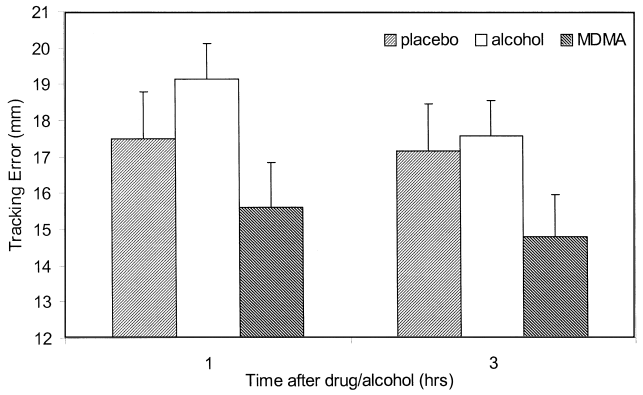

Figure 2 Mean (± SE) Tracking Error in the Divided Attention Task 1 and 3 h after placebo, alcohol and MDMA

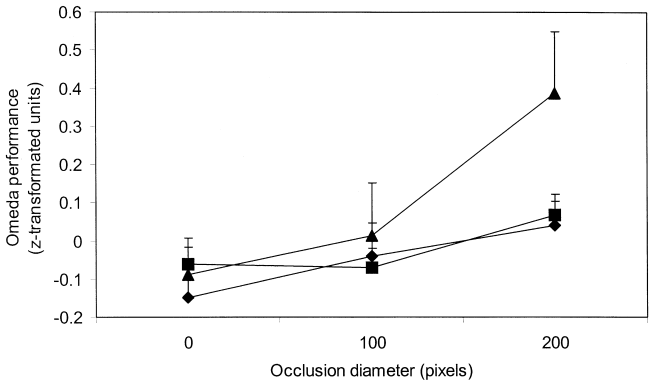

Figure 3 Mean (± SE) Z-scores of Time to Contact Error and Divided Attention Error in the OMEDA task as a function of occlusion diameter 4–5 h after placebo (◆), alcohol (■) and MDMA (▲) administration. Both TTC error and divided attention error scores in all conditions were first separately subjected to *Z*-transformation and subsequently averaged to obtain compound scores, reflecting 'whole-task' performance

on the secondary task of the OMEDA (DA) was not affected by Treatment or the interaction between Treatment and Occlusion.

MANOVA analysis of slope and intercept of TOL-RT as a function of steps showed no overall effects of Treatment. The intercept of the transformed RT, √[10 log(RT)], was 1.89 at 3 h after MDMA and 1.91 in all other conditions. Overall mean slope was 0.04, and MANOVA revealed no overall effect of Treatment or interaction between Treatment and Time. MANOVA showed that there was an overall effect of Treatment on number of errors. Drug–placebo comparison between alcohol and placebo showed that fewer errors were made after alcohol relative to placebo (6.8% versus 11.4% errors, respectively). Comparison between MDMA and placebo showed no effect of MDMA on number of errors (mean 12.7%) in the TOL.

In the Word Fluency Test, an average of 12 words were retrieved within 1 min across treatments and time of assessments with the exception of an average of 11 words 1 h after MDMA intake. MANOVA showed no effect of Treatment or interaction of Treatment with Time.

In the SDT, subjects detected 87.4% of the signals after placebo, 84.9% after alcohol and 84.7% after MDMA administration. MANOVA showed no effect of Treatment or interaction with Time.

Toxicological assessments

Figure 4 shows mean (± SE) MDMA blood plasma concentration and BAC as a function of time after consuming MDMA 75 mg or drinking ethanol 0.5 g/kg. Mean C_{max} of MDMA was 178 ng/ml (range 85–295 ng/ml) at 3 h after drug intake. Mean BAC peak concentration (0.3 mg/ml) was reached 60 min after alcohol intake. During the second repetition of the test battery BAC dropped to 0.1 mg/ml and BACs had dropped to 0.0 mg/ml during last assessments in all subjects.

Effect of treatment order

The order of treatment was not completely balanced as a result of the exclusion of subjects after violation of excluding criteria. Four

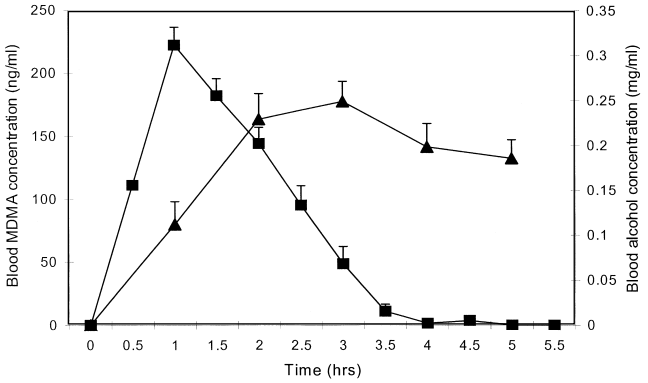

Figure 4 Mean (± SE) blood plasma concentrations of MDMA (▲) and mean (± SE) blood alcohol concentration (■) as a function of time after drug/alcohol intake

subjects received MDMA on their first, three on their second and five on their third test day. Alcohol was administered to three subjects on their first, five on their second and four on their third test day. To control for Treatment order effect, performance as a function of order of MDMA was analysed by means of ANOVA for the dependent variables affected by MDMA [e.g. λ_C (CTT)], Tracking error (DAT), movement time (MCRT) and TTC error (OMEDA). None of the dependent variables analysed differed as a function of MDMA order except DAT tracking error in the placebo condition ($F = 807$, $p = 0.022$) indicating that subjects receiving MDMA on their first test day performed better when they received placebo on one of their next test days compared to subjects after placebo who received MDMA on their second or third test day. It could be suggested that MDMA improved the learning process of this test but, because none of the other dependent variables showed an effect of MDMA treatment order, this conclusion is unlikely.

Discussion

Briefly summarized, the results showed that a single recreational dose of MDMA improved tracking performance either under single task conditions as well as under divided attention or double task conditions. Movement time in the choice reaction time paradigm improved after MDMA, whereas object movement estimation under divided attention was impaired after MDMA. Number of errors in the TOL test was slightly reduced after alcohol administration. Before any conclusions can be made, several limitations of the study need to be addressed.

Duration of effects

MDMA improved tracking performance by 5.6% to 13.7% and movement time decreased by an average of 7.6% relative to placebo. MDMA blood plasma concentrations peaked approximately 2 h post administration and remained virtually unchanged until the last measurement at 5 h post administration. MDMA induced changes in performance also remained constant during the assessment period. It is likely these performance effects lasted during the rest of the day given that MDMA has an elimination half-life of approximately 8 h (Mas *et al*., 1999). Future studies need to assess performance effects for a longer time period to establish the exact duration of MDMA effects.

Magnitude of effects

In the current study, a single dose of MDMA did not affect visual search and executive functions, including divided attention while performing a tracking task, planning or retrieval from semantic memory. These findings appear in line with those of previous studies. Vollenweider *et al*. (1998) reported no effect of a single dose of MDMA on Stroop performance while Downing (1986) reported difficulties with multiplication and decision making after MDMA administration in only a minority of the subjects. These findings appear to indicate that a single dose of MDMA may cause relatively minor disturbances of cognitive performance, although these can be considered typical for acute effects of psychostimulants. An alternative explanation for the observed minor cognitive impairment could be that the sample size in this study was relatively small. However, even though only 12 subjects completed the study, the number of subjects provided sufficient statistical power to detect changes in many tests (e.g. CTT, DAT, MCRT OMEDA). However, it cannot be excluded that other tests were not sensitive enough to detect MDMA effects.

In contrast to our data, Parrott and Lasky (1998) found an impairing effect of MDMA on visual scanning in an uncontrolled study. In the present study, MDMA was administered under controlled circumstances in otherwise drug free subjects. However, the subjects in Parrott and Laskys' study were tested at a party under less than perfect circumstances while taking different amounts of MDMA. Furthermore, polydrug use was reported among the subjects while tested at the party (alcohol, cannabis, cocaine and amphetamine). Therefore, factors other than acute MDMA use may have contributed to the effects found by Parrott and Lasky (1998). Alternatively, the number of subjects in our study might have been too low to detect effects on these cognitive functions.

Different effects in different divided attention tasks

Two divided attention tasks were conducted in this experiment, the DAT and the OMEDA task. The influence of MDMA on these two divided attention tasks in this study was opposing. MDMA improved performance of the primary task in the DAT (continuous tracking), while MDMA impaired performance in the primary OMEDA task (object movement estimation) compared to placebo in both tasks. The nature of both tasks differs considerably. Whereas the former test depends more on psychomotor capacity, the latter is more of a cognitive nature (i.e. time estimation). The motor components of both primary tasks also differ; in the DAT, motor execution is central, whereas in the OMEDA task, inhibition and delay of the response are more important. Although the improved performance on the DAT likely reflects improved psychomotor performance, impairment of TTC error in the OMEDA most likely results from impaired time estimation, whereas impaired working memory may also play a role.

Implications for MDMA effects on driving safety

Tracking performance and object movement under divided attention were assessed in this experiment to study the influence of psychoactive substances on task performance, related to driving. The tests used in the current study all have a strong validity with respect to traffic safety. The results show a clear dissociation of effects on different aspects of performance. Whilst MDMA enhanced speed of manual movement and capacity to steer or track

fast moving objects, it impaired the ability to perceive and predict motion. The prediction of Time to Contact in actual traffic would mean the ability to judge whether another car will collide with one's own car. This ability depends on adequate perception of actual motion and the capacity to predict if, when and where a collision will occur. Estimating other vehicles' speeds is required of any traffic participant for safe manoeuvring in traffic, such as crossing an intersection. Any drug-induced impairment of these abilities is unacceptable due to its compromising effect on traffic safety and may lead to increased risk taking. Although increments in TTC include both overestimation and underestimation of the actual TTC, it can be inferred that this observation may be in line with an independent other observation that the use of MDMA will lead to shorter gap acceptance in car-following behaviour. This realistic driving-simulator study showed that MDMA users indeed accepted shorter gaps, especially when MDMA was combined with other drugs (Waard *et al*., 2000). Furthermore, the observed MDMA blood levels in this experiment (85–295 ng/ml), were within the range of methamphetamine concentrations reported after toxicological analyses of methamphetamine-related traffic deaths, which ranged from 50 to 2600 ng/ml (median 350 ng/ml) (Logan, 1996). Therefore, it is likely that the observed impairment of movement estimation reflects an impairment due to actual MDMA intoxication rather than to impairments associated with the so-called 'crash phase', which refers to a period during and shortly after elimination of the substance in which feelings of depression may emerge. Dangerous driving and accidents after MDMA use have already been reported in the past (Henry *et al*., 1992; Schifano, 1995; Logan and Couper, 2001). Impairment in coordination, difficulty concentrating and hallucinations have all been observed in people while under the influence of MDMA (Downing, 1986; Schifano, 1995; Vollenweider *et al*., 1998). These factors, possibly combined with exhaustion after a night of dancing, have already led to involvement in sometimes fatal car accidents of MDMA users in the past (Henry *et al*., 1992; Moeller and Hartung, 1997; Morland, 2000). Furthermore, in real life, MDMA dosages taken may be higher than in the present study and may be taken in combination with sedative psychoactive substances such as marijuana and alcohol.

Effects of alcohol

Alcohol was used as a comparator drug to compare the effects of MDMA with the effects of alcohol at BACs close to the legally permitted BAC for participating in traffic in most European countries (0.5 mg/ml). The alcohol dose used in the current study has been shown to produce BACs ranging from 0.6 mg/ml when given alone (Ramaekers *et al*., 1996) to 0.4 mg/ml when combined with a small lunch (Lamers and Ramaekers, 2001).

In the present study, consumption of a standard lunch may also explain why mean BAC did not rise above 0.3 mg/ml. Performance changes were also rather minimal. Alcohol reduced the number of errors in the TOL. Alcohol is known to impair task performance (Franks *et al*., 1976; Heishman, 1997) and because stimulating effects of alcohol on cognitive functioning are not supported by other studies, this may present a spurious finding. Critical tracking performance declined 1 and 2 h after drinking. However, the latter effect did not reach statistically significance, possibly as a result of the limited study sample.

MDMA blood plasma levels

Blood plasma concentrations of MDMA were as expected. Our subjects received MDMA 75 mg (1.03–1.25 mg/kg). Maximal blood concentrations of MDMA were slightly higher than those found in previous studies using the same dosage: 170 ng/ml versus 131 ng/ml (Mas *et al*., 1999) and 126 ng/ml (de la Torre *et al*., 1999). The t_{max} for the current study differed somewhat from previous studies. Although Mas (1999) and de la Torre (1999) found a t_{max} of approximately 2 h, mean highest concentrations in the present study were measured at 3 h post MDMA.

Awareness of drug treatment

Previous knowledge about treatment effects, obtained through informed consent and prior experience of subjects, as well as conscious and unconscious drug discrimination during the experiment, can contribute or counteract to the observed effects of that treatment. To prevent this from happening, active control conditions are often used in experimental drug studies. We chose an active control, alcohol, on the basis of its recognized impairing effects on psychomotor and driving performance. From the point of view of preventing drug discrimination of MDMA and placebo, it would have been more logical to choose amphetamine as an active control condition. However, the effects of amphetamine on psychomotor and driving performance are hypothesized to be similar to MDMA but, more importantly, just as unprecedented in controlled experimental studies. The question arises as to whether subjects could have manipulated their performance once they were aware of the drug they had received. It is unlikely that subjects could have manipulated their results. It could be argued that, by performing badly under placebo, subjects could have manipulated results in a way to indicate that MDMA improved performance. The CTT showed MDMA-induced improvement and was assessed before and after drug treatment. If subjects performed worse after placebo on purpose, their performance would have been low compared to findings in other studies using the CTT. However, subjects' placebo performance on this test is comparable to findings of other studies after placebo (Ramaekers *et al*., 1992, 1996; Vermeeren and O'Hanlon, 1998). This finding not only indicates that it is unlikely that the MDMA-induced effects observed in this study are a result of awareness of the kind of drug subjects received, but also that the lack of alcohol-induced impairment is not a result of bad performance after placebo, and instead is a result of the low alcohol concentration.

Implications of possible neural damage due to previous drug use or tolerance in terms of laboratory cognitive performance

It is possible that performance of subjects during placebo treatment was impaired relative to non-drug users. Impaired cognitive performance has been reported in previous studies in abstinent (poly drug) MDMA users and is often regarded as a result of serotonergic neurotoxicity (Parrott *et al*., 1998; McCann *et al*., 1999; Gouzoulis Mayfrank *et al*., 2000; Verkes *et al*., 2001). As described earlier, performance after placebo on at least some of the tests was not affected in MDMA users compared to non-drug users. However, if subjects in the current study were cognitively impaired, the impairment might have been counteracted somewhat by the acute effects of increased cellular serotonin and dopamine levels after MDMA. Tolerance might also have influenced the

results observed in this study; it cannot be excluded that tolerance to the drug might have diminished MDMA-induced effects relative to the effect that the drug might have on naive MDMA users. The sample of the current study is too small to analyse a possible influence of tolerance to MDMA by relating subjects' prior exposure to ecstasy with performance changes after MDMA.

Implications for predicting real life effects

Performance effects after MDMA administration observed in the present study may not always be present at the same level in the real life setting at dance parties. In the latter situation, other factors have to be taken into consideration to predict the effect of MDMA on cognitive and psychomotor performance. Dehydration, exhaustion, lack of sleep and hyperthermia are only some of those factors that may affect performance. They may produce detrimental effects in performance that were not observed in the present study. Furthermore, it is known that MDMA users at times take higher doses than the one used in our study. Often, MDMA users take a second, or third dose when they feel the effect of the first dose is subsiding or they combine MDMA with other drugs. The subjects in our study all stated that they were poly drug users. In a recreational setting, 10 subjects in this study often combined MDMA with other psychoactive substances such as marijuana, alcohol or amphetamine. A higher, or multiple dose of MDMA, or combined use of MDMA with other drugs, may be associated with more adverse events.

In conclusion, the primary findings of our study constitute dissociative effects of a single acute dose of MDMA (75 mg) on psychomotor and perceptual performance under divided attention. MDMA impaired object movement estimation under divided attention, which can lead to increased risk taking and impaired traffic safety. MDMA improved psychomotor performance, such as compensatory tracking and manual movement speed. Visual search, planning or retrieval from semantic memory were not affected by MDMA. The dissociative effects of MDMA on different divided attention tasks need further investigation.

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