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ORIGINAL INVESTIGATION

Acute effects of nocturnal doses of MDMA on measures of impulsivity and psychomotor performance throughout the night

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Abstract
Introduction Previous studies on the acute effects of MDMA on psychomotor performance and impulsivity showed that MDMA acts as a stimulant. These studies assessed performance during daytime, whereas in real life, dance-attendees leaving a party use the drug during the night.
Objectives The present study aimed to assess the effects of nocturnal doses of MDMA on psychomotor performance and impulsivity during the night and after a night of sleep deprivation.
Materials and methods Fourteen healthy subjects participated in a double-blind, placebo-controlled, two-way within-subject study. The treatment was MDMA (75 and 50 mg) divided over the evening or double placebo. Psychomotor and impulsivity tasks were conducted four times throughout the evening and night. A vigilance test was conducted once, at 5 A.M., and a sleepiness scale was presented to the subjects ten times throughout the evening and night.
Results MDMA impaired tracking performance in a simple tracking task. Divided attention task performance was also impaired as indicated by a decrease in secondary task performance under the influence of MDMA compared with placebo. MDMA did not affect impulsivity measures. Vigilance performance decreased as a function of time on task, but this decrement was less during MDMA treatment compared to placebo. After the administration of MDMA, the sleepiness scale scores were lower during the night when compared with placebo. This difference between MDMA and placebo disappeared in the morning.
Conclusion It is concluded that nocturnal doses of MDMA may produce impairments of tracking performance and divided attention throughout the night that are additive to performance impairment produced by sleep loss.

Keywords MDMA · Sleep deprivation · Psychomotor · Impulsivity · Repeated dose

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Introduction

Several acute studies have shown that MDMA acts as a psychomotor stimulant (Kuypers et al. 2006; Lamers et al. 2003; Ramaekers and Kuypers 2006; Ramaekers et al. 2006; see also review by Dumont and Verkes 2006). Lamers et al. (2003) demonstrated that a single dose of MDMA improved simple reaction time and tracking performance under single and dual-task conditions. Ramaekers and Kuypers (2006) demonstrated that MDMA caused increased impulse control in a stop-signal task as shown by a decrease in stop reaction time. In addition, two actual driving studies showed improvement on automated driving skills after a single dose of MDMA, as indicated by a reduction in weaving index (Kuypers et al. 2006; Ramaekers et al. 2006). When combined with alcohol, however, MDMA's stimulant effects were not strong

enough to overcome the alcohol-induced impairment on psychomotor function and impulse control (Hernandez-Lopez et al. 2002; Ramaekers and Kuypers 2006).

Studies showing the stimulant effects of MDMA usually employed daytime dosing to subjects who had a normal night of sleep (Kuypers et al. 2006; Lamers et al. 2003; Ramaekers and Kuypers 2006; Ramaekers et al. 2006). Ecstasy users, however, usually take the drug in single or repeated doses during the evening or night before going to a party or while partying (Farre et al. 2004; Hammersley et al. 1999; ter Bogt and Engels 2005; Winstock et al. 2001). They subsequently stay awake the whole night while partying and dancing for hours on end (Parrott 2001).

The aim of the present study was to assess the acute effects of MDMA on psychomotor performance and impulsivity (behavioural inhibition and cognitive impulsivity) after repeated dosing during a night of sleep deprivation. The study was conducted according to a double-blind, placebo-controlled, within-subject design. Subjects received two doses of MDMA, separated by an interval of 4 h, and were tested four times throughout the evening and night, i.e., at 6:30 P.M., 9:30 P.M., 1:30 A.M., and 7 A.M. The vigilance task was conducted only once at 5 A.M..

The data presented in this paper were part of a larger study on the acute effects of MDMA on memory after repeated dosing during a night of sleep deprivation. These results showed, on the one hand, impairment of verbal and spatial memory after the administration of MDMA, independent of the level of sleep loss. On the other hand, it was shown that the response time improved after the administration of MDMA, but this stimulating effect disappeared in the morning when levels of sleep loss were maximal. This pattern was also found in the subjective ratings of mood. These results have been submitted for publication elsewhere.

Materials and methods

Design and treatments

The study was conducted according to a double-blind, placebo-controlled, two-way within-subject design. The treatments consisted of two subsequent doses of MDMA (75 and 50 mg) and double placebo. According to the annual report of the 'Drugs Information and Monitoring System' (DIMS 2005) of the Netherlands, the average recreational doses of MDMA may vary between 0 and 200 mg, taken as one or two pills per evening. Doses up to 150 mg have previously been studied in acute studies. It was shown that side effects were limited with doses up to 125 mg but appeared to be more frequent with 150-mg doses (Cami et al. 2000; de la Torre et al. 2000). Dose administration was separated in time by 4 h at respectively 8 P.M. and 12 P.M. A 4-h interval was chosen because subjects tend to take an additional dose when the subjective effects have worn off, and that is approximately after 4 h (Cami et al. 2000; Hammersley et al. 1999). Placebo and MDMA were administered orally in identically appearing formulations. MDMA was administered as a 25-ml solution in bitter orange peel syrup and placebo was given as 25-ml bitter orange peel syrup, both were mixed with 200-ml orange or apple juice.

Participants

Twenty volunteers underwent medical examination. Two volunteers were excluded from participation, as they did not meet the inclusion or exclusion criteria. The remaining subjects passed the medical screening and entered the training. Four subjects dropped-out prematurely either because of private matters (3×) or because of not feeling well on the first test day after placebo treatment (1×).

In total, 14 subjects (7 males, 7 females), aged 19–33 years (mean, 22.93; SD, 3.75), completed all study treatments. They all had used MDMA before the onset of the study. The lifetime use of MDMA varied from light (<25 times) in nine subjects to moderate (between 30–35 times) in five subjects.

The subjects were recruited by means of advertisements in the local newspapers and by the snowball technique. Potential candidates were questioned about their drug use and medical condition and were given information about the study. Thereupon, they were sent a detailed brochure with information about the study procedure and two questionnaires for medical history and detailed history of drug use. The inclusion criteria were experience with MDMA use, free from psychotropic medication, good physical health, absence of major medical endocrine and neurological conditions, and normal weight (body mass index, 18–28 kg/m^2). The exclusion criteria were history of drug abuse (other than MDMA) or addiction, pregnancy or lactation, cardiovascular abnormalities [assessed by a standard 12-lead electrocardiogram (ECG)], excessive drinking (>20 alcoholic consumptions), hypertension (diastolic, >100; systolic, >170), and history of psychiatric or neurological disorders. A medical doctor checked the completed medical questionnaire, and upon approval, the subjects were invited for a medical examination. Blood and urine samples were taken for examination and they underwent an ECG measurement. When medically fit, they were contacted and sent a brochure with information about the study and a number of rules they had to obey during the period of the study. The subjects signed an informed consent. They were paid for participating upon completion of the study.

The study was performed in accordance with the 1975 Declaration of Helsinki, adjusted in Edinburgh (2000), and was approved by the Medical Ethics Committee of the Academic Hospital of Maastricht and the University of Maastricht. A permit for obtaining, storing, and administering MDMA was obtained from the Dutch drug enforcement administration.

Study procedure

Before study onset, the participants were familiarized with the tests on a training day. The participants were requested to abstain from any drug use 1 week before the medical examination until 14 days after the last test day. They were asked not to use any caffeinated or alcoholic beverages 24 h before testing and to get a normal night's sleep. Participants were screened for alcohol use in breath and for recent drug use in urine (THC/opiates/cocaine/amphetamines/methamphetamines) upon arrival at the laboratory test facilities at 6 P.M. Women were given a pregnancy test. When positive, subjects were sent home. Subjects received a light meal and were given a sleep questionnaire. Cognitive tests were assessed four times during the evening and night, i.e., at 6:30 P.M. (baseline measure), 9:30 P.M., 1:30 A.M., and 7 A.M.; 1.5-h pre-dosing and 1.5-h, 5.5-h, and 11-h post-dosing (first dose), respectively (Fig. 1). A sleepiness scale was presented to the subjects ten times throughout the evening and night to assess their current level of sleepiness. The Mackworth clock task was conducted once, at 5 P.M. A test day ended at 8:15 A.M. A blood sample was collected before each test session, except at baseline, to determine the MDMA and 3,4-methylenedioxyamphetamine (MDA) concentrations in the blood serum. The participants were kept awake the whole night (for example, they played party games, watched TV, and/or listened to music). The testing days were minimally separated by 7 days.

Assessments

Cognitive assessments

Critical tracking task The critical tracking task (Jex et al. 1966) measures the subject's ability to control a displayed error signal in a first-order compensatory tracking task. The error appeared as a horizontal deviation of a cursor from midpoint on a horizontal, linear scale. Subjects had to null the error by returning the cursor to the midpoint by means of compensatory joystick movements. The frequency of cursor deviations and, therefore, its velocity increased as a stochastic, linear function of time. The subject was required to make compensatory movements with a progressively higher frequency. Eventually his/her response frequency lagged the error signal by 180°, and control was lost. The frequency at which control loss occurs is commonly called the critical frequency or lambda-c (λ_c). The test was repeated five times and the median lambda-c over the five trials was used as the dependent variable.

Divided attention task The divided attention task (Moskowitz 1973) assesses the ability to divide attention between two tasks performed simultaneously. The primary task is the same as the critical tracking task described above with the exception that the velocity of the error signal was kept constant at 50% of the subject's optimal performance on the training session ($\lambda_c/2$). The tracking error was measured by the absolute distance (mm) between the cursor's position and the center. The secondary task involved monitoring 24 single-digit numbers (0–9) that were displayed in the four corners of the screen. The numbers changed asynchronously every 5 s. The requirement was to react as rapidly as possible by lifting their foot from a pedal any time a target, the numeral "2", appeared. The test duration was 12 min, and the dependent variables were the tracking error for the primary task and the reaction time of correct detections for the secondary task.

Stop-signal task The stop-signal task requires subjects to make quick key responses to visually presented go signals and to inhibit any response when a visual stop signal is presented (Fillmore et al. 2002; Ramaekers and Kuypers 2006). The go signals were four 1.5-cm letters (A, B, C, D) presented one at a time in the center of a computer screen. The subjects were required to respond to each letter as quickly as possible by pressing on one of two response buttons. One button was pressed to indicate that "A" or "C" appeared and the other to indicate that "B" or "D" appeared. Letters were displayed for maximally 500 ms, and the computer screen was blank for 1.5 s before the next letter was displayed. This provided a period of maximally 2 s in which the subject could respond to the displayed letter.

A single test consisted of 176 trials in which each of the four-letter stimuli were often presented equally. A stop signal occurred in 48 trials during a test. The stop signal

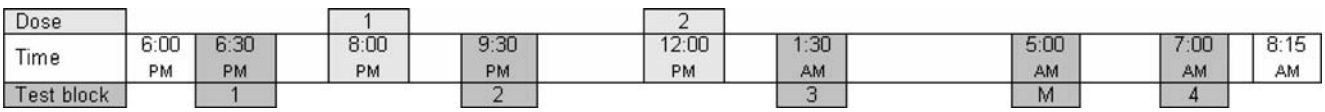

Fig. 1 Schematic representation of a test day. *Test block* contains all the cognitive tasks described in the methods section except the Mackworth clock task (*M*)

consisted of a visual cue, i.e., "*", that appeared in one of the four corners of the screen. The subjects were required to withhold any response in case a stop signal was presented. Stop signals were presented 12 times at each of the four delays, i.e., 50, 150, 250, and 350 ms after the onset of a letter, 27% of the trials in total.

The dependent variables were the percentage of correct responses on go trials and the proportion of inhibitions on stop trials and their respective reaction times, i.e., GoRT and stopRT. The stop reaction time to stop-signal trials represented the estimated mean time required to inhibit a response.

Discounting task The current discounting task was an adjusted version of Mitchell and colleagues' (1999) task. It consisted of two subtasks, a delay and a probability task. For each of the two tasks, the subjects were presented 137 questions. For each question, the subjects had to indicate which of two hypothetical rewards they preferred, the 'standard' or the 'alternative' item. In the delay task, the standard item 10 was available after one of five delays (0, 7, 30, 180, or 365 days). In the probability task, the standard item 10 was available with one of five probabilities (1.00, 0.75, 0.50, 0.25, or 0.10). The alternative item was an amount of money (0.01, 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.50, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 7.50, 8.00, 8.50, 8.50, 9.00, 9.50, 10.00, or 10.50) available after 0 days (delay task) or with a probability of 1.00 (probability task). During both subtasks, a standard and an alternative item were selected at random without replacement to form the question. That is, the alternative items were not presented in either a descending or ascending order for any standard item, and the standard items were not presented in a systematic order. Subjects expressed their preference for an item by pressing one of two buttons. Response choices were recorded and used afterwards to calculate the switch points at which the subject prefers the alternative item to the standard item. The task duration was 10 min.

Mackworth clock task The Mackworth clock task is a vigilance task that assesses sustained attention (Mackworth 1950; Ramaekers et al. 1995). The subjects were seated in front of a computer screen displaying a circular arrangement of 60 gray dots simulating the second mark on a clock. The dots were briefly illuminated in clockwise rotation at a rate of 0.5 s. Occasionally, the rotation proceeded with a 'double jump' by skipping one of the dots in the normal sequence. A total of 30 signals were presented during the whole task so that the target probability (0.56%) was very low. The subjects had to detect the occurrence of these skips and respond to this by pressing a button. Within each period of 15 min (=one block), ten signals were given. The test consisted of three blocks, and the test duration was 45 min. The dependent variable was the proportion of correct detections.

Sleep assessments

Stanford sleepiness scale The Stanford sleepiness scale (Hoddes et al. 1973) consists of seven statements describing stages of sleepiness ranging form feeling active and wide awake (1) to losing the struggle to remain awake and being nearly asleep (7). The subjects were asked every hour to choose the statement describing their current level of sleepiness.

Pharmacokinetic assessments

Blood samples were taken at 1.5, 5.5, and 11 h post dosing (1st dose), centrifuged immediately at 4,000×*g* for 10 min, and the corresponding serum samples were subsequently frozen at −20°C until the analysis for pharmacokinetic assessment. MDMA and MDA concentrations were determined using an integrated on-line solid-phase extraction combined with liquid chromatography mass spectrometry (SPE–LC–MS system; Symbiosis Pharma, Spark Holland) with tandem mass spectrometric detection (Quattro Premier, Water Corporation) using deuterated analogues for internal standardization. The quantification limits were 5.0 ng/ml for MDMA and 2.5 ng/ml for MDA.

Statistical analyses

All statistical analyses were conducted by means of the Statistical Package for the Social Sciences (SPSS version 11.5 for Windows). Paired *t* tests were used to check for differences between baseline measures in the placebo test session and the MDMA test session. Difference scores (score minus baseline) were calculated for performance measures. These difference scores entered the general linear model univariate repeated measures procedures with MDMA (two levels) and Time (three or ten levels) as main within-subject factors. In the discounting task, an extra factor Delay (five levels) for the delay discounting task or Probability (five levels) for the probability-discounting task was included. The Mackworth clock task was only conducted once so that the factor Time was omitted in this study from the analysis, and the factor Time on task (three levels) was introduced. When there was no sphericity, *F* tests were corrected by means of the greenhouse–Geisser epsilon correction. The alpha criterion level of significance was set at $p=0.05$. In case of significant main effects of MDMA or time, post-hoc analyses were conducted, and alpha was then corrected for multiple comparisons.

Results

There were no statistically significant differences between the baseline scores of the cognitive tasks or the sleep assessment. Nevertheless, it was also clear that some baseline differences existed that just failed to reach significance. To correct for this potential confounder, it was decided to calculate difference scores from the baseline for each performance measure.

Cognitive assessments

Critical tracking task

The analysis revealed significant main effects of MDMA ($F_{1,13}$=6.432; p=0.025) and Time ($F_{2,26}$=3.471; p=0.046) on critical tracking (Fig. 2). Further analysis of the MDMA effect showed that lambda scores were lower under the influence of MDMA compared with placebo. Contrast analysis (polynomial) of the time effect revealed a quadratic relation between sessions ($F_{1,13}$=6.369; p=0.025). There was no significant MDMA by the time interaction effect critical tracking.

Divided attention task

Primary task measures The ANOVA revealed significant effects of Time ($F_{2,26}$=15.737; p<0.001) and MDMA by Time ($F_{2,26}$=5.403; p=0.011) on tracking error (Fig. 3). During placebo treatment, the tracking error increased almost linearly during the night. During MDMA treatment, the tracking decreased during the night but returned to baseline levels early in the morning.

The analysis revealed a significant effect of MDMA on the number of control losses ($F_{1,13}$=11.60; p=0.005). Under the influence of MDMA, the number of control losses was larger compared with placebo. There was no significant effect of Time or MDMA by Time on the number of control losses.

Secondary task measures There was a significant MDMA effect ($F_{1,13}$=9.969; p=0.008) on reaction time (Fig. 4). After the administration of MDMA, the subjects were slower in detecting targets compared to placebo. The analysis also revealed significant effects of MDMA ($F_{1,13}$= 4.79; p=0.047) and Time ($F_{2,26}$=4.66; p=0.019) on the number of correct detections. Under the influence of MDMA, the number of correct detections was lower compared to placebo.

Stop signal task

Response inhibition measures There was no significant effect of MDMA, Time, or MDMA by Time on stopRT or proportion of correct inhibitions.

Response execution measures The analysis revealed a significant effect of Time ($F_{2,26}$=4.65; p=0.019) on the proportion of correct responses on the go trials. There was no significant effect of MDMA, Time, or MDMA by Time on go RT.

Discounting task

Two subjects displayed a random answer pattern on the discounting task, and therefore, their scores were omitted from the analysis. In both the subtasks, the switch point curves displayed a normal hyperbola-like pattern. The factor Delay or Probability (five levels) was significant ($F_{4,44}$=5.154, p=0.002; $F_{4,44}$=5.024, p=0.002, respectively) for the delay and probability task. There were no significant effects of MDMA, Time, or MDMA by Time on switch points in the delay or probability task.

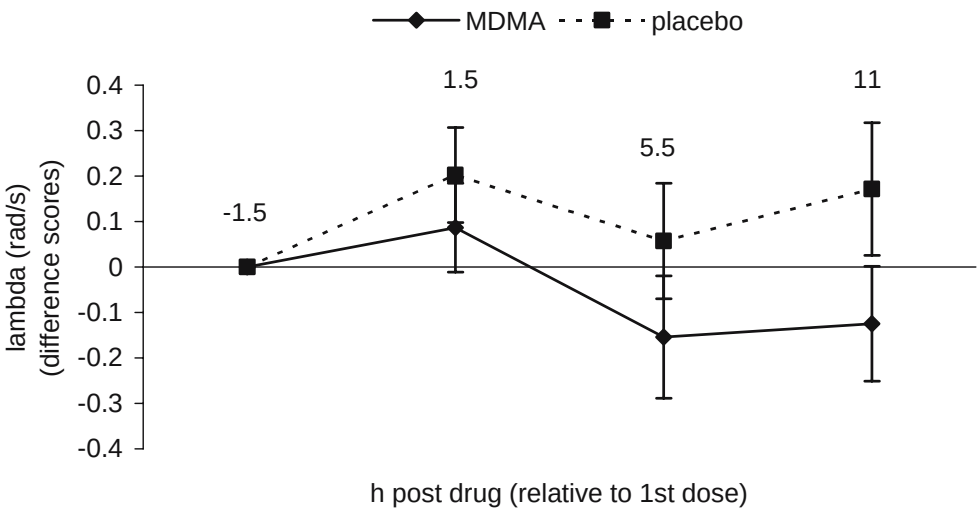

Fig. 2 In this graph, critical tracking frequency in the critical tracking task for both treatment conditions are shown as difference scores (relative changes to baseline)

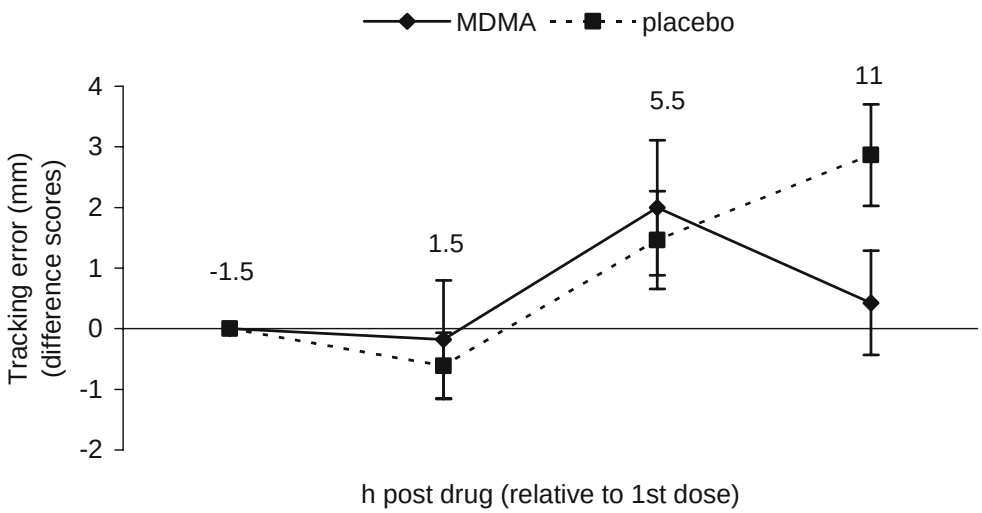

Fig. 3 In this graph, mean tracking error (mm; +SE) in the primary task of the divided attention task for both treatment are shown as difference scores (relative changes to baseline)

Mackworth clock task

The analysis revealed the effects of Time on task (block; $F_{2,26}$=13.42, p<0.001) and Time on task by MDMA ($F_{2,26}$= 5.19; p=0.013) on the proportion of correct detections. Vigilance performance decreased as a function of time on task, but this decrement was less during MDMA treatment as compared to placebo (Table 1).

Sleep assessments

The analysis revealed significant effects of MDMA ($F_{1,13}$= 5.892, p=0.030), Time ($F_{3.5;45.6}$=47.33, p<0.001), and MDMA by Time ($F_{9,117}$=2.629, p=0.008) on sleepiness (Fig. 5). The subjects progressively felt more fatigued. After the administration of MDMA, the subjects scored lower on the sleepiness scale compared with placebo. This difference between MDMA and placebo disappeared in the morning when scores were equally high for both conditions.

Pharmacokinetic assessments

The mean (SD) blood serum concentrations of MDMA (ng/ml) were 171.79 (54.63), 298.25 (65.38), and 199.27 (51.90), respectively 1.5, 5.5, and 11 h post dosing (first dose). The higher concentrations in the second and third measurement are in agreement with the expected levels after the administration of a second dose 4 h after the first dose. The mean (SD) concentrations of MDA were 6.35 (3.04), 17.84 (7.48), and 21.94 (9.17), respectively 1.5 h, 5.5, and 11 h post dosing (first dose).

Discussion

The results showed that MDMA impaired performance in the critical tracking task. MDMA also negatively affected divided attention task performance as indicated by the impairment of the secondary task performance. Under the

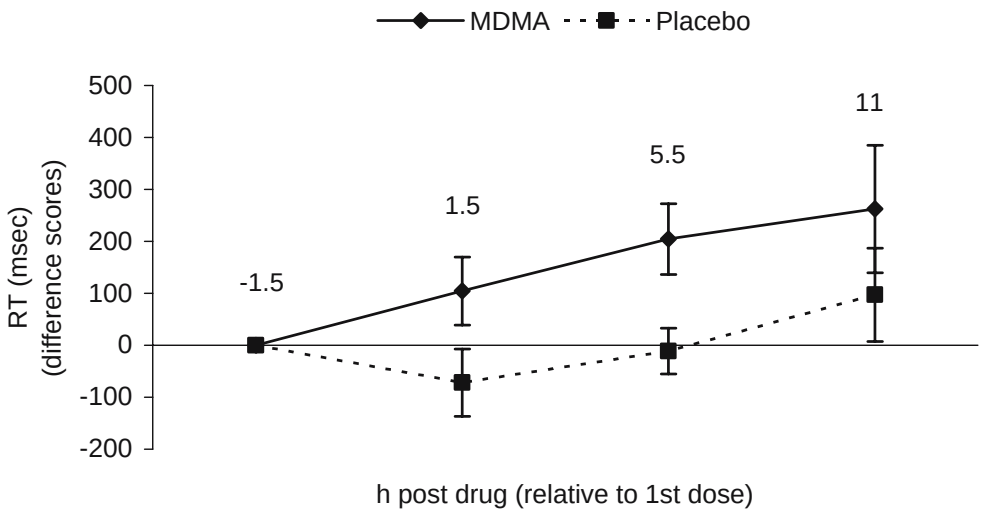

Fig. 4 In this graph, mean reaction time (msec; +SE) of the correct detections in the secondary task of the divided attention task for both treatment conditions are shown as difference scores (relative changes to baseline)

Table 1 Mean scores and SD's of dependent variables of the psychomotor and impulsivity tests, and p values of main and interaction effects on those variables

	Treatment			ANOVA (difference scores)		
	Session	MDMA	Placebo	MDMA	Time	MDMA × Time
Critical tracking task						
Λ_c	1	4.46 (0.15)	4.56 (0.18)	0.025	0.046	–
	2	4.54 (0.18)	4.76 (0.21)			
	3	4.30 (0.19)	4.61 (0.18)			
	4	4.33 (0.17)	4.73 (0.19)			
Divided attention task						
Primary task						
Tracking error	1	14.37 (1.38)	11.86 (0.83)	–	0.000	0.011
	2	14.20 (1.26)	11.25 (0.81)			
	3	16.37 (1.28)	13.32 (1.15)			
	4	14.80 (1.20)	14.72 (1.25)			
Control losses (number)	1	0.50 (0.37)	0.36 (0.25)	0.005	–	–
	2	2.14 (0.69)	0.29 (0.22)			
	3	5.14 (1.63)	1.29 (0.67)			
	4	15.57 (6.84)	6.93 (4.12)			
Secondary task						
RT (correct detections)	1	1916.86 (113.27)	1947.07 (87.15)	0.008	–	–
	2	2021.14 (110.23)	1875.29 (98.12)			
	3	2121.14 (101.85)	1936.07 (104.79)			
	4	2179.29 (157.25)	2044.21 (138.06)			
Correct detections (number)	1	44.57 (1.34)	44.93 (.82)	0.047	0.019	–
	2	44.07 (1.34)	46.14 (.80)			
	3	40.21 (2.22)	43.57 (1.73)			
	4	39.86 (2.66)	42.57 (2.82)			
Stop signal task						
Response inhibition measures						
StopRT	1	287.37 (13.80)	281.12 (13.41)	–	–	–
	2	304.12 (23.59)	259.61 (14.66)			
	3	297.46 (17.17)	292.14 (15.41)			
	4	292.43 (19.15)	304.77 (22.77)			
Proportion of correct inhibitions	1	69.43 (6.02)	71.29 (6.34)	–	–	–
	2	66.86 (5.96)	73.50 (6.52)			
	3	64.30 (5.89)	65.86 (5.18)			
	4	61.41 (6.93)	59.72 (6.13)			
Response execution measures						
GoRT	1	572.61 (35.49)	584.75 (39.47)	–	–	–
	2	569.73 (35.11)	572.93 (36.17)			
	3	586.02 (41.69)	567.38 (33.48)			
	4	588.80 (30.25)	566.64 (33.04)			
Proportion of correct go-responses	1	0.963 (0.008)	0.967 (0.006)	–	0.019	–
	2	0.969 (0.007)	0.972 (0.007)			
	3	0.960 (0.012)	0.959 (0.012)			
	4	0.890 (0.035)	0.922 (0.024)			
Discounting task						
Delay task						
Switch point	1	6.55 (0.673)	6.37 (0.577)	–	–	–
	2	6.63 (0.705)	6.81 (0.652)			
	3	6.50 (0.753)	6.93 (0.673)			
	4	6.55 (0.664)	6.85 (0.729)			
Probability task						
Switch point	1	5.72 (0.285)	5.53 (0.246)	–	–	–
	2	5.63 (0.414)	5.97 (0.266)			
	3	5.55 (0.385)	6.05 (0.298)			
	4	5.67 (0.336)	5.98 (0.326)			

Table 1 (continued)

	Treatment			ANOVA (difference scores)		
	Session	MDMA	Placebo	MDMA	Time	MDMA × Time
Mackworth clock task						
Proportion correct detections				MDMA	Block	MDMA × block
	Block 1	0.664 (0.089)	0.671 (0.056)	–	<0.001	0.013
	Block 2	0.486 (0.080)	0.479 (0.070)			
	Block 3	0.536 (0.094)	0.336 (0.037)			

influence of MDMA, subjects detected fewer targets, and the corresponding reaction times were slower compared with placebo. This decrement in secondary task performance occurred in parallel with an MDMA-induced improvement of primary task performance. Primary task performance (i.e., tracking) sharply decreased during the night during both treatments. However, after MDMA, primary task performance also returned to baseline level in the morning. Measures of impulsivity, i.e., the stop-signal task and the discounting task, were not affected by MDMA. The presence of impairment in the critical tracking task and the divided attention task, as well as the absence of any MDMA effect on impulsivity tasks, are in sharp contrast with previous studies that have demonstrated improvement of tracking performance and motor impulse control after a single, daytime dose of MDMA (Lamers et al. 2003; Ramaekers and Kuypers 2006). The main differences between these studies and the present study design are the time of testing and time of drug administration. Previous studies have administered MDMA doses during the day and conducted performance testing during daytime. The present study employed nocturnal doses and assessed the effects of MDMA during the night and early in the morning after a night of sleep deprivation.

Collectively, these data, seem to suggest that single doses of MDMA produce stimulant effects on psychomotor performance during the daytime but induce psychomotor impairment when taken in the evening or during the night. The mechanisms behind this differential effect of MDMA on performance are presently unknown but may be related to fluctuations in circadian rhythm and sleep loss during the night. Previous work has indicated that serotonin is important in the regulation of the circadian clock, which is located in the suprachiasmatic nuclei of the hypothalamus. Animal studies have shown that repeated exposure to MDMA can attenuate phase shifting in the body's circadian clock (Balogh et al. 2004; Colbron et al. 2002; Dafters and Biello 2003). It has been suggested that circadian rhythm disorders underlie the changes in sleep patterns, mood, and mental performance that have often been reported in abstinent MDMA users (Colbron et al. 2002). In any case, performance impairment produced by MDMA was additive to the effect of sleep loss that caused a performance decrement throughout the night. After placebo treatment, performance in the critical tracking task and the divided attention task progressively decreased during the night due to sleepiness and sleep loss. MDMA did not counteract the effect of sleep loss but rather added more impairment. Additive impairment appeared to be constant during critical tracking task performance and secondary task performance in the divided attention test. It first appeared in the evening shortly after the first dose of MDMA and remained stable until early in the morning, as evinced by the absence of an MDMA by time after drug interaction.

Besides signs of impairment, there was also a clear indication of performance improvement during MDMA intoxication. The performance on the Mackworth clock task, a measure of sustained attention, deteriorated as a function of time on task. This was evident from a progressive decrease in the proportion of correct detections that was observed during

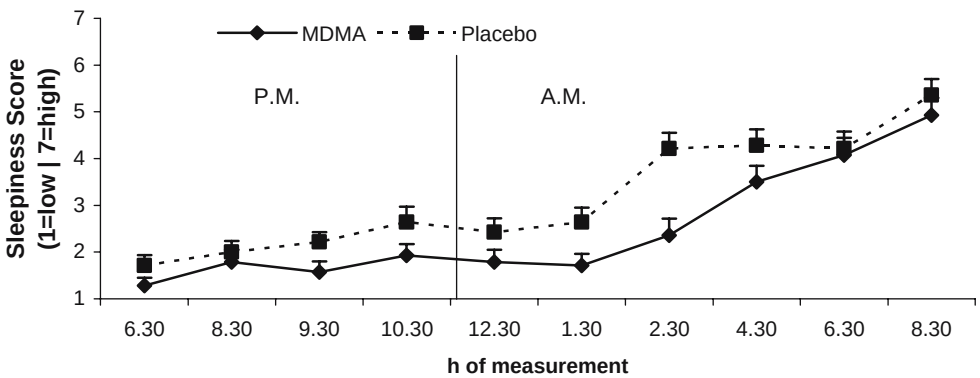

Fig. 5 Mean scores (+SE) on the Stanford sleepiness scale as the function of the hour of measurement

this 45-min task. This is basically a replication of the classical vigilance decrement that has repeatedly been shown under non-drug conditions in the same paradigm (Mackworth 1950; Teichner 1974). When under the influence of MDMA, the subjects' performance deteriorated after the first 15 min, but stayed relatively stable over the last 30 min of the task. This was not due to an increase in overall response rate, as there was no significant effect on the proportion of false alarms. It seems that MDMA mitigated the usual vigilance decrement that can be interpreted as stimulant activity. A similar impression emerged from subjective sleep recordings. These showed that subjects felt less sleepy during MDMA intoxication as compared to placebo. Many stimulant drugs have been shown to improve sustained attention during the day or during sleep loss (Bonnet et al. 2005; Koelega 1993), and the present vigilance data corroborate these findings.

It is concluded that nocturnal doses of MDMA may produce impairments of tracking performance and divided attention throughout the night that are additive to performance impairment produced by sleep loss.

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