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Psychological and Cardiovascular Effects and Short-Term Sequelae of MDMA ("Ecstasy") in MDMA-Naïve Healthy Volunteers

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3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") is a recreational drug reported to produce a different psychological profile than that of classic hallucinogens and stimulants. It has, therefore, been tentatively classified into a novel pharmacological class termed entactogens. This double-blind placebo-controlled study examined the effects of a typical recreational dose of MDMA (1.7 mg/kg) in 13 MDMA-naïve healthy volunteers. MDMA produced an affective state of enhanced mood, well-being, and increased emotional sensitiveness, little anxiety, but no hallucinations or panic reactions. Mild depersonalization and derealization phenomena occurred together with moderate thought disorder, first signs of loss of body control, and alterations in the meaning of percepts. Subjects also displayed changes in the sense of space and time, heightened sensory awareness, and increased psychomotor drive. MDMA did not impair selective attention as measured by the Stroop test. MDMA increased blood pressure moderately, with the exception of one subject who showed a transient hypertensive reaction. This severe increase in blood pressure indicates that the hypertensive effects of MDMA, even at recreational doses, should not be underestimated, particularly in subjects with latent cardiovascular problems. Most frequent acute somatic complaints during the MDMA challenge were jaw clenching, lack of appetite, impaired gait, and restless legs. Adverse sequelae during the following 24 hours included lack of energy and appetite, feelings of restlessness, insomnia, jaw clenching, occasional difficulty concentrating, and brooding. The present findings are consistent with the hypothesis that MDMA produces a different psychological profile than classic hallucinogens or psychostimulants. ***[Neuropsychopharmacology 19:241–251, 1998]*** *© 1998 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

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3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") is a phenylethylamine with structural similarities to both amphetamine and mescaline. In the mid-1970s, Shulgin and Nichols reported that MDMA produces an "easily controlled altered state of consciousness with emotional and sensual overtones" and suggested that MDMA might be useful as an adjunct in insight-oriented psychotherapy (Greer 1985; Downing 1986; Greer and Tolbert 1986; Nichols 1986; Shulgin 1986). Around that time, MDMA also acquired popularity as a recreational psychoactive substance. Concern over its increasing abuse and its possible neurotoxicity in humans led to the assignment of MDMA as a Schedule I agent by the U.S. Drug Enforcement Agency in 1985 (Ricaurte et al. 1985; Peroutka et al. 1988). Since then, there have been ongoing controversies regarding whether

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MDMA is medically useful as an adjunct in psychotherapy (Grob et al. 1990; Grob et al. 1992; Liester et al. 1992; Strassman 1995) and whether the neurotoxic findings seen after high or repeated doses of MDMA in experimental animals are relevant for humans (Schmidt 1987; Battaglia et al. 1988; Ricaurte et al. 1988; Steele et al. 1994; Granquist 1995).

MDMA is a potent indirect monoaminergic agonist producing both carrier-mediated release and reuptake inhibition of serotonin (5-HT) and to a lesser extent of dopamine (DA) (Johnson et al. 1986; Schmidt 1987; Rupp et al. 1994). In experimental animals, a subchronic regimen of MDMA (usually 5–20 mg/kg given twice daily for 4 days) has been found to lead to serotonin depletion and long-term axon terminal damage (Ricaurte et al. 1988; Insel et al. 1989). In nonhuman primates, 2.5 mg/kg of MDMA given PO once every 2 weeks for a total of eight doses over 4 months did not produce any neurotoxic response in 5-HT and 5-HIAA assays of eight brain regions (Ricaurte G., cited in Granquist 1995). In addition, MDMA at doses of 2.5 mg/kg IM given twice daily for 4 consecutive days (cumulative dose = 20 mg/kg IM) decreased 5-HT and 5-HIAA levels, but did not reduce the number of 5-HT uptake sites, indicating that the structural integrity of 5-HT nerve terminals was preserved (Insel et al. 1989). These results strongly suggest that a single recreational dose of MDMA (1.5–2.0 mg/kg) is unlikely to produce long-term serotonergic deficits in humans. However, it can be expected that multiple or regular use of MDMA in humans may lead to long-term serotonergic damage similar to that seen in animal studies.

During the past few years, recreational use of MDMA by young people has increased markedly in western Europe and the United States, most often taken at dance clubs and "raves." In Switzerland, a recent survey provided evidence that 3.5% of 15- to 34-year-olds had taken at least one recreational dose of MDMA (SFA/ISPA 1996; Giroud et al. 1997). In England, two recent reports indicate that 4.5 to 6 % of 14- and 15-year-olds had taken MDMA (Saunders 1995). The increasing use of MDMA raises questions about psychological and physical effects and complications of acute and chronic MDMA use. However, systematic data on the phenomenology of the MDMA-induced state, including behavioral and psychological sequelae are limited. To our knowledge, only three prospective studies have explored the acute psychological and physical effects of a single recreational dose of MDMA. In a study by Downing (1986), 21 MDMA users were asked to report on their subjective emotional experiences after a single dose of MDMA (0.8–1.9 mg/kg). Cardiovascular, biochemical, and neurological effects of MDMA were also evaluated in some of the subjects. In the second study, Greer and Tolbert (1986) summarized the psychological and possible beneficial effects of MDMA (75–150 mg) in psychiatric patients who received the drug as a psychotherapeutic adjunct. Both studies indicate that MDMA produces a peaceful emotional experience with enhanced insight, feelings of increased closeness to others, euphoria, heightened sensory awareness, and symptoms of sympathetic arousal (e.g., tachycardia, tremor etc.). Downing (1986) also reported that the acute effects of MDMA could be prolonged by taking an additional dose of the drug, but that increasing doses were associated with autonomic hyperarousal, restlessness, and anxiety. More recently, Grob et al. (1996) reported that a single dose of MDMA (0.25–1.0 mg/kg) was experienced without physical discomfort in six subjects with prior experience with MDMA, and that MDMA, at doses of 0.75 mg/kg, stimulated both ACTH and prolactin. As noted by Downing, it is unclear to what extent such studies in users are biased by previous experience; reduction of anxiety because of the absence of first-time discomfort might play an important role inasmuch as only subjects with previously positive experiences would be likely to volunteer.

Furthermore, because MDMA was reported to increase sensory awareness and the level of arousal, and because overarousal worsens cognitive performance, it is conceivable that MDMA may impair cognitive functioning (Corcoran 1965). Attentional deficits especially are thought to be a consequence of badly controlled arousal and inadequate inhibitory "gating" processes at the level of sensory input (McGhie and Chapman 1961). The Stroop color-naming test is a paradigm designed to assess central inhibitory processes in human cognition (Stroop 1935; MacLeod 1991). In this task, a fast overlearned process of reading (semantic information) interferes with a slow intentional process of color naming (contextual information).

To date, the subjective effects of MDMA in MDMA-naive healthy volunteers have not been explored. The present study attempted to determine the acute psychological and physical effects, as well as short-term sequelae of a typical recreational dose of MDMA in MDMA-naive normals in a clinical setting. A trial-by-trial version of the Stroop color-naming test was administered to investigate whether MDMA subjects demonstrate selective attention deficits.

MATERIALS AND METHOD

The study was approved by the Ethics Committee of the Psychiatric University Hospital, Zürich, and the use of 3,4-methylenedioxymethamphetamine (MDMA) by the Swiss Federal Health Office, Department of Pharmacology and Narcotics, Bern. All subjects were examined at the Research Department of the Psychiatric University Hospital, Zürich (PUK).

SUBSTANCE

Racemic MDMA (3,4-methylenedioxymethamphetamine) was obtained through the Swiss Federal Health Office (BAG), Department of Pharmacology and Narcotics, Bern, from EPROVA AG, Schaffhausen, and prepared as capsules (10 and 50 mg) at the Pharmacy of the Kantonal Hospital of Lucerne, Switzerland.

SUBJECTS

Thirteen healthy volunteers (male = 10, female = 3) aged between 23 and 47 years (mean ± SD = 29 ± 7) were recruited from university and hospital staff. All subjects were fully informed of previous toxicology study results at time of their participation and gave written informed consent. The subjects were screened by psychiatric interview to ensure that they had neither personal nor family histories of major psychiatric disorders in first-degree relatives. Subjects with a history of illicit drug abuse were excluded from the study. Because subjects with very low "openness" and very high "neuroticism" scores of the Freiburg Personality Inventory (FPI) (Fahrenberg et al. 1984) have been shown to be particularly liable to prolonged and severe responses to stimulant and hallucinogenic drugs (Dittrich 1994), we used scores exceeding two standard deviations of the mean values of normative data as additional exclusion criterion. However, in the present study, none of the applicants had to be excluded based on this criterion. Subjects were healthy according to physical examination, electrocardiogram, and blood and urine analyses.

STUDY DESIGN

A randomized double-blind placebo-controlled design was used. Subjects were tested at monthly intervals with either placebo or MDMA. Subjects received MDMA at a dose of 1.7 mg/kg, a typical dose taken for recreational use (Greer and Tolbert 1986). Upon arriving at the PUK Research Department (12 A.M.), fasting subjects were examined using the Adjective Mood Rating Scale (EWL) (Janke and Debus 1978) and the Altered State of Consciousness (APZ-OAV) rating scale (Dittrich 1996). Following these baseline measures, placebo or MDMA was given orally in capsules (13.30 A.M.). The EWL and APZ-OAV ratings were performed again 75 minutes after placebo or MDMA intake to coincide with the peak effects of MDMA (Helmlin et al. 1996). Blood pressure, pulse, and body temperature were obtained at 0, 75, 150, and 300 minutes after MDMA ingestion. The Vegetative lability scale (BL) (von Zerssen 1976) was used to assess acute adverse effects for the whole duration of the MDMA session (between 0 and 360 minutes post drug ingestion) and for the following day. After the effects of MDMA had subsided completely, subjects remained in the hospital for another 2 to 3 hours and were monitored clinically and cardiovascularly. In addition to the described psychological and physical measurements, sensorimotor gating and putative attentional deficits were also assessed in all of the subjects 75 minutes after drug ingestion using the prepulse inhibition of acoustic startle technique (PPI) (Geyer et al. 1990) and the Stroop test (Carter et al. 1996). Analysis of the startle response findings are in progress and will be reported separately (Vollenweider et al. 1997a, in preparation).

PSYCHOMETRIC SCALES

The EWL (Janke and Debus 1978) and the APZ-OAV rating scale, a visual-analog scale and slightly modified version of the original APZ rating scale (66 instead of 72 items), were used to assess drug effects under placebo and drug conditions (Dittrich 1994, 1996). The EWL mood-rating scale consists of six scales (factors) measuring efficiency, inactivation, extraversion–introversion, feelings of well-being, emotional excitability, and anxiety. The well-being scale yields the two subscale scores "self-confidence" and "heightened mood." The anxiety scale consists of the three subscales "thoughtfulness-contemplativeness," "apprehension-anxiety," and "dejection" (Janke and Debus).

The APZ-OAV rating scale reliably measures shifts in mood, thought disorder, and changes in the experience of the self/ego and of the environment in drug- and nondrug-induced altered states of consciousness (ASC). The APZ-OAV yields three dimensions (factors) consisting of several item clusters. The first subscale, OSE ("oceanic boundlessness"), measures derealization and depersonalization phenomena associated with a positive basic mood, ranging from heightened feelings to sublime happiness. The corresponding item clusters were "derealization," "depersonalization," "alterations of the sense of space and time," "positive basic mood," and "mania-like experience." The second subscale, VUS ("visionary restructuralization"), includes illusions, (pseudo-) hallucinations, synesthetic phenomena, as well as changes in the meaning and interpretation of various percepts. Item clusters were labeled "illusions," "hallucinations," "synesthesias," "changed meaning of percepts," "facilitated recollection of memories," and "facilitated imagination." The third subscale, AIA ("dread of ego dissolution"), measures thought disorder, anxious ego disintegration, loss of control over body and thought, and derealization phenomena associated with arousal and anxiety. The item clusters are "frightening derealization," "thought disorder," "delusion," "loss of thought control," and "loss of body control." The APZ-OAV dimensions OSE,

AIA, and VUS have been shown to be independent of etiology, for example, the inducing factor(s) of ASC (Dittrich et al. 1985; Dittrich 1994).

STROOP TEST

A trial-by-trial computerized version of the Stroop test was used. Stimuli were presented using MEL Professional 2.0 software (PST Pittsburgh, PA, USA) and an IBM-compatible 386 PC with a VGA color monitor (IBM PS/2). The latencies of subjects' spoken responses were collected with millisecond accuracy through a microphone (Labtec AM-22) connected to a PST Standard Serial Response Box (model 200A). Subjects sat 50 cm in front of the monitor, with the microphone 10 cm from their faces. The word stimuli were formed from capital letters of the Chicago font (30 points). Characters were 8 × 5 mm wide. The stimulus set consisted of the German words OBEN (above), UND (and), WENN (if), KAUM (hardly), BLAU (blue), GRÜN (green), ROT (red), GELB (yellow), and the nonword XXXX presented in the colors blue, red, green, or yellow. Four conditions, corresponding to four types of trials, were included: On congruent trials, words matched colors (e.g., the word BLAU written in blue); on conflict trials, words mismatched colors (e.g., BLAU written in red); on control X trials, the nonword sequence XXXX was presented in one of the four colors; and on control W trials, one of the neutral words (OBEN, UND, WENN, KAUM) was presented in one of the four colors (Carter et al. 1996). Forty-eight trials were assigned to each condition, yielding a total of 192 trials. Trial types were presented in random order to minimize strategy effects. Stimuli were given one at a time, and the task was to name the colors of the stimuli as quickly and accurately as possible. Subjects' spoken responses were coded by the experimenter pressing one of four color keys on the serial response box (or a fifth skip key if the response was ambiguous). A second monitor was viewed by the experimenter and displayed the number of the actual trial to enable potential coding mistakes to be corrected by noting the trial number. The monitors were placed so that both experimenter and subject could see only their respective screens. Before each stimulus, a fixation cross appeared in the center of the screen for 400 ms, followed by the stimulus itself, which remained on the screen until the subject made a verbal response. The experimenter's key press on the response box then triggered the next stimulus. Completion of the entire task took between 5 and 7 minutes.

Facilitation was defined as the percent reduction in response time in the congruent condition compared to either the control X or control W condition [(control − congruent)/control × 100]. Interference was defined as the percent increase in response time in the conflict condition compared to either the control X or control W condition [(conflict − control)/control × 100].

STATISTICAL ANALYSIS

All analyses were performed by computer using STATISTICA/w™, version 5.1 (StatSoft™, 1995). In this study, each subject served as his or her own control to minimize the effect of interindividual variation in psychological and physical scores. To examine the time course of blood pressure and body temperature, as well as differences in psychological scores (EWL, APZ-OAV) between placebo and MDMA, a two-way analysis of variance (ANOVA) was performed with drug (placebo or MDMA) and psychological or physical scores (EWL, APZ-OAV, blood pressure or body temperature) as repeated measures. A two-way ANOVA was also used to assess differences in Stroop performance with drug (placebo or MDMA) and Stroop conditions (XXXX, neutrals, conflict or congruent) as repeated measures. When significant main effects or interactions were revealed in the ANOVA, *post hoc* comparisons were done with LSD tests. The significance level of the main factors are cited in the text, and those for LSD *post hoc* tests of individual measures are given in the figures. Probability values of .05 or less were considered statistically significant.

RESULTS

Acute Psychological Effects of MDMA

All psychological measures (EWL , APZ-OAV) were obtained during the peak effects of MDMA, between 75 to 120 minutes post drug ingestion. Data for the EWL mood rating scale and the APZ-OAV questionnaire are given in Figure 1 and Figure 2. A two-way ANOVA revealed a significant EWL x MDMA interaction [$F(5,60) = 3.16$; $p < .013$]. *Post hoc* analysis showed significant increases in the EWL scores extraversion/introversion ($p < .01$), well-being ($p < .001$), emotional excitability ($p < .00001$), and state anxiety ($p < .01$). Analysis of the anxiety subscales revealed that the overall increase in state anxiety was caused by a significant increase ($p < .001$) in the thoughtfulness-contemplativeness subscale; whereas, the apprehension-anxiety and dejection subscales were not significantly changed. The subscale scores self-confidence ($p < .01$) and heightened mood ($p < .001$) of the well-being scale were also significantly increased. Although subjects seemed alert and aroused, no significant increases in the EWL score for efficiency was found (Figure 1).

MDMA produced a significant APZ-OAV x MDMA interaction [$F(2,24) = 32.98$; $p < .00001$] and significant increases in the OSE ($p < .00002$; *post hoc*), VUS ($p < .0002$; *post hoc*), and AIA ($p < .02$; *post hoc*) scores (Figure 2).

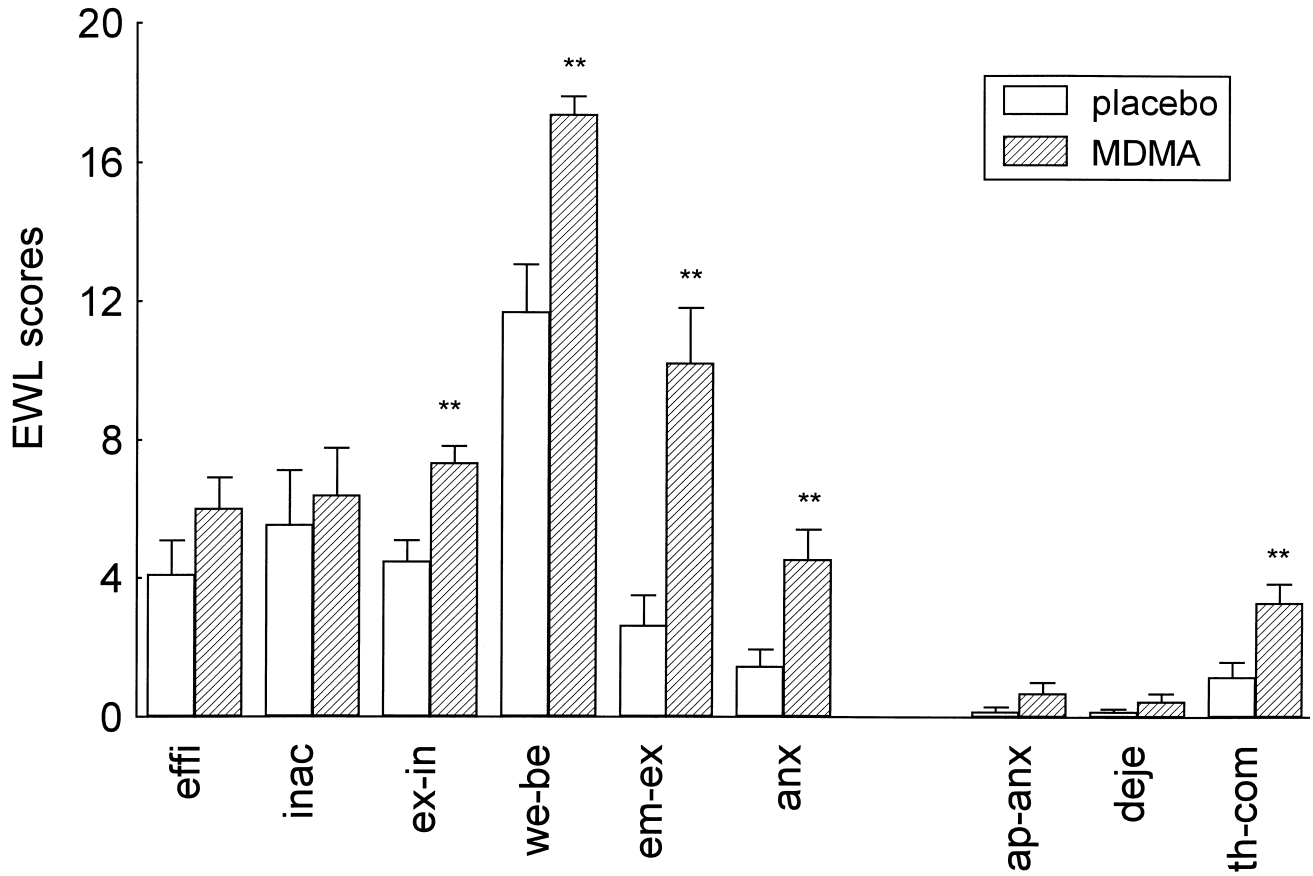

Figure 1. EWL mood rating scores during placebo and MDMA (mean ± SE, $n = 13$); effi = efficiency, inac = inactivation, ex-in = extroversion-introversion, we-be = well being, em-ex = emotional excitability, anx = anxiety; subscale scores of the anxiety factor include ap-anx = apprehension-anxiety, deje = dejection, and th-com = thoughtfulness-comtemplativeness; significant changes are indicated by asterisks: ** for $p < .01$; *** for $p < .001$ (LSD *post hoc* test).

Post hoc analysis revealed that there were moderate increases in the OSE clusters for derealization ($p < .001$), depersonalization ($p < .001$), alterations in the sense of space and time ($p < .001$) and mania-like experience ($p < .001$). The most pronounced increase was seen in the OSE cluster for positive basic mood ($p < .001$). In the VUS dimension, scores for changed meaning of percepts ($p < .0001$), illusions ($p < .05$), facilitated recollection ($p < .01$) and imagination ($p < .05$) were significantly increased, whereas scores for hallucinations and synesthesias were not significantly altered. Analysis of AIA clusters revealed significant increases for thought disorder ($p < .0001$) and loss of body control ($p < .03$). Scores for frightening derealization, delusion and loss of thought control were not significantly changed by MDMA.

Stroop

MDMA produced no significant change in either reaction time or error rate compared to placebo. The mean values of reaction times and error rates for XXXX, neutrals, conflict, and congruent conditions of the Stroop test, as well as percentage interference and percentage facilitation for placebo and MDMA conditions are seen in Table 1. A two-way ANOVA of reaction time revealed a significant main effect of condition [XXXX, neutrals, conflict, congruent; $F(3,33) = 40.43$; $p < .00001$], confirming the expected Stroop effect. Most importantly, there was neither a significant main effect of drug nor a significant condition × drug interaction, indicating that MDMA had no influence on Stroop performance. The same pattern of significance was found for error rates: a significant condition effect [$F(3,33) = 13.57$; $p < .00001$], but no significant main effect of drug, and no significant condition x drug interaction. Interference for conflict vs. XXXX and conflict vs. neutral words was significant for both MDMA and placebo (all $p < .0001$); whereas, facilitation was significant only for congruent vs. neutral words ($p < .0002$). ANOVAs for interference and facilitation, however, revealed no significant differences between MDMA and placebo.

Vital signs

MDMA produced a significant increase of diastolic and systolic blood pressure, as shown in Table 2. A two-way

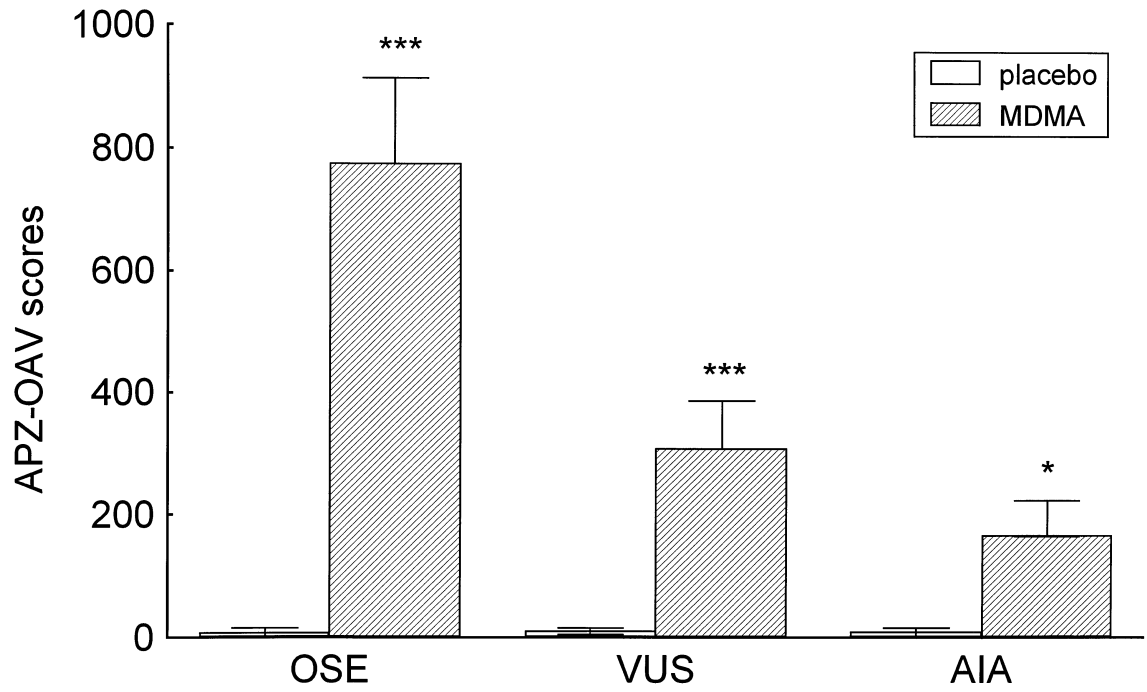

Figure 2. APZ-OAV scores OSE (oceanic boundlessness), VUS (visionary restructuralization), and AIA (dread of ego-dissolution) during the peak effects of MDMA (1.7 mg/kg PO) or placebo. *Post hoc* analysis revealed significant differences in the APZ-OAV scores between MDMA and placebo as indicated by asterisks: * for $p < .05$; *** for $p < .001$ (LSD *post hoc* test).

ANOVA for systolic blood pressure revealed a significant main effect of drug [F(1,2) = 41.09; $p < .02$] and a significant drug x time interaction [F(3,6) = 11.31; $p < .007$]. Significant changes occurred in the 0 to 75 minutes and 75 to 150 minutes interval (one-way ANOVAs). Two-way ANOVA for diastolic blood pressure was not significant, but one-way ANOVAs showed significant changes in the 75 to 150 minutes and the 150 to 300 minutes interval. Increases were in the range of 10 to 30 mm Hg for systolic blood pressure and 5 to 10 mm Hg for diastolic blood pressure. The hypertensive effect of MDMA peaked about 2 h after drug administration. Twelve of 13 subjects peaked at 160/100 mm Hg. One subject (49 years old) reached peak values of 240/145 mm Hg without any other signs of hypertensive crisis lasting for about 20 minutes, thus no pharmacological intervention was necessary. All subjects showed an elevation of pulse rate, but this was not analyzed in detail. One-third of the subjects reported palpitations, but no other signs of hypertension or discomfort were noted.

Table 1. Performance in the Stroop Test in Normals Under Placebo and MDMA ($n = 13$)

		Placebo		MDMA (1.7 mg/kg)		*p* values
	Condition	**Mean**	**SD**	**Mean**	**SD**	***post-hoc***
Reaction time (ms)	XXXX	581	70	586	77	ns
	Neutrals	593	76	609	96	ns
	Conflict	696	100	695	120	ns
	Congruent	560	82	565	100	ns
% Errors	XXXX	0.3	0.8	0.2	0.6	ns
	Neutrals	0.2	0.6	0.7	1.3	ns
	Conflict	2.9	4.9	5.6	12.2	ns
	Congruent	0.2	0.6	0.2	0.6	ns
% Interference	Conflict–XXXX	21.5	12.1	17.6	11.6	ns
	Conflict–neutrals	19.3	10.2	14.2	11.3	ns
% Facilitation	Congruent–XXXX	5.4	5.0	4.9	6.5	ns
	Congruent–neutrals	3.6	6.7	7.6	5.2	ns

Table 2. Effects of MDMA on Blood Pressure and Body Temperature

	Placebo		MDMA		
Time Intervals	**BD_{diast}**	**p^a**	**BD_{diast}**	**p^a**	**p^b**
predrug baseline	88	——	88	——	ns
0–75 min	88	ns	94	ns	ns
75–150 min	92	ns	101	0.05	0.05
150–300 min	92	ns	97	0.05	ns
	BD_{syst}	**p^a**	**BD_{syst}**	**p^a**	**p^b**
predrug baseline	130	——	128	——	ns
0–75 min	130	ns	148	0.03	(0.06)
75–150 min	132	ns	158	0.04	0.05
150–300 min	131	ns	151	ns	ns
	T(°C)	**p^a**	**T(°C)**	**p^a**	**p^b**
predrug baseline	36.6	——	36.7	——	ns
0–75 min	36.5	ns	36.7	ns	ns
75–150 min	36.7	ns	36.9	ns	ns
150–300 min	36.6	ns	37.2	ns	ns

BP = mean values of blood pressure (mm Hg), T = mean values of body temperature (°C, axillary).
[a] Significant changes for postdrug vs. predrug condition.
[b] Significant changes for placebo vs. MDMA (one-way ANOVAs).

MDMA seemed to produce a discrete increase of body temperature of about 0.2 to 0.5°C, which, however, did not reach statistical significance.

Acute Adverse Effects of MDMA and Short-Term Sequelae 24 h After Ingestion

Acute adverse effects of MDMA are listed in Table 3. Observed effects were comparable to those reported in previous studies or known from subjective reports from MDMA users (Peroutka et al. 1988; Liester et al. 1992). No unexpected or severe complications occurred. Most frequently reported (8/13) were bruxism (jaw clenching), lack of appetite, disturbance of balance, and difficulty in concentration. Stimulant effects and altered body sensations such as restless (6/13) or heavy (5/13) legs, paresthesias (4/13), increased sensitivity to cold (5/13), and hot flashes (3/13) were less frequent. Further acute symptoms were palpitations, sweating, and thirst. Interestingly, MDMA reduced fatigue and private and job-related worries.

Some of the symptoms present during the acute phase of the MDMA experience persisted up to 24 hours afterwards, including suppressed appetite (6/13), thirst (6/13), jaw clenching (4/13), feeling of restlessness (5/13), difficulty in concentration (4/13), and sweating (3/13). Newly occurring aftereffects included lack of energy (6/13), insomnia (5/13), and brooding (3/13). Fatigue was reported by five of the 13 subjects, but this was not an elevation compared to placebo. A summary of 24 h sequelae is shown in Table 4.

Table 3. Acute Sequelae of MDMA

Subjective Sensation	Placebo Number of Subjects (Total $n = 13$)	MDMA Number of Subjects (Total $n = 13$)
Jaw clenching (bruxism)	0	8
Lack of appetite	0	8
Difficulty concentrating	1	8
Impaired balance/gain	0	8
Restless legs	0	6
Perspiration	0	5
Heavy legs	0	5
Increased sensitivity to cold	1	5
Thirst	0	5
Forgetfulness	0	5
Palpitations	0	4
Feelings of restlessness	0	4
Insomnia	0	4
Dizziness or vertigo	0	4
Tremor	0	4
Paresthesias	0	4
Weakness	0	3
Hot flashes	1	3
Being cold	0	3
Inner tension	0	3
Frequent urge to urinate	1	2
Fatigue	5	1
Nausea	0	1
Private or job-related worries	3	0

DISCUSSION

This study investigated the acute psychological and adverse effects of MDMA in MDMA-naive healthy volunteers using a double-blind placebo-controlled study design. This agent has been suggested to represent a new class of psychotropics named entactogens. The major finding was that MDMA, at a typical recreational dose (1.7 mg/kg PO), produced a state of enhanced mood and well-being associated with moderate derealization and depersonalization, thought disorder, anxiety, and without marked increases in psychomotor drive.

Affective changes, both measured and subjectively reported, were of a generally positive nature. Subjects reported experiencing an increased responsiveness to emotions, a heightened openness, and a sense of closeness to other people. The subjects' experience of enhanced susceptibility to emotional and sensory stimuli is reflected by the significantly increased score for emotional excitability of the EWL rating scale. Most of the subjects were more verbal and wanted to talk about their "new" experience, whereas, few responded with withdrawal and wanted to focus on their inner experiences. Similar affective responses were described in experienced MDMA users (Downing 1986; Greer and Tolbert 1986; Peroutka et al. 1988; Solowij et al. 1992) and in a study by Hermle et al. (1993), who investigated the psychological effects of 3,4-methylenedioxyethamphet-

Table 4. Short-Term Sequelae 24 Hours After Ingestion of MDMA

Subjective Sensation	Placebo Number of Subjects (Total $n = 13$)	MDMA Number of Subjects (Total $n = 13$)
Lack of appetite	0	6
Lack of energy	1	6
Thirst	0	6
Fatigue	5	5
Feeling of restlessness	0	5
Heavy legs	0	5
Insomnia	0	5
Feeling of weakness	0	4
Frequent urge to urinate	1	4
Difficulty concentrating	1	4
Decreased libido	0	4
Jaw clenching (bruxism)	0	4
Perspiration	0	3
Increased sensitivity to cold	1	3
Brooding	0	3
Private or job-related worries	3	3
Headache	0	2
Increased need to sleep	1	2
Forgetfulness	0	1

amine (MDE) in healthy volunteers. In contrast to Hermle et al. (1993), who observed both euphoric and depressive reactions to MDE, none of our subjects showed depressive reactions under MDMA.

The apparent discrepancy between the lack of subjectively reported anxiety and the increase in state anxiety as measured by the EWL rating scale is attributable solely to an increase in the "thoughtfulness-contemplativeness" subscale, whereas, the "apprehension-anxiety" and "dejection" subscales were not significantly elevated. The increase in the "thoughtfulness-contemplativeness" subscale, which consists of items describing a state of feeling "profound," "thoughtful," "dreamy," "lost in thought," and "contemplative," probably reflects more the pensive "inward-turning" observed in some subjects than an actual increase in anxiety. Similarly, feelings of calmness and relaxation, but no change in anxiety scores were reported in recreational MDMA users (Davison and Parrott 1997).

However, although subjects did not explicitly report anxious feelings, a certain degree of anxiety may have been associated with first signs of loss of body control, as indicated by the significant increase in the "loss of body control" item cluster of the AIA dimension. In fact, several subjects showed transient concern that the beginning loss of control might progress further. Thus, it is possible that outside of controlled settings or with higher doses, anxiety regarding loss of control could develop to a degree where it could lead to panic attacks. There are, indeed, case reports describing panic attacks in individuals under the acute influence of MDMA (Whitaker Azmitia and Aronson 1989). Also, enduring panic attacks have been reported in individuals after repeated MDMA use (McCann and Ricaurte 1991; Pallanti and Mazzi 1992), and in one case, even after a single dose (McCann and Ricaurte 1992). On the other hand, it is well known that the effects of psychoactive drugs are highly dependent upon setting, set (personality traits, vulnerability, educational level), as well as dose and purity of ingested substances. The fact that, in contrast to situations of illegal MDMA use, these factors were controlled in our study may explain the minimal anxiety experienced by our subjects.

MDMA also produced slight-to-moderate depersonalization phenomena and perceptual changes as measured by the APZ-OAV rating scale. The unique pattern on the APZ-OAV scale of high OSE (oceanic boundlessness), low VUS (visionary restructuralization) and low AIA scores (dread of ego-dissolution) produced by MDMA discriminates it from hallucinogens and stimulants. Specifically, a comparison of the APZ-OAV scores of the present study with those from a similarly designed previous study with the hallucinogen psilocybin, revealed OSE scores in MDMA subjects approximately similar (80%) to those seen after psilocybin, but VUS and AIA scores only about 30 to 50% of the values seen in psilocybin subjects (Vollenweider et al. 1997b). MDMA produced mild depersonalization phenomena, which, in contrast to psilocybin, were not experienced as problematic or psychotic fusion, but as a pleasurable state of loosened ego boundaries. Moreover, unlike psilocybin, MDMA did not produce hallucinations, but, instead, its effects were typically described as an intensification of sensory perception ("colors were more intense," "objects appeared more detailed," etc.) and visual illusions (3-dimensional vision of flat objects, micropsia, and macropsia, etc.). With regard to psychostimulants, in a comparable study with healthy volunteers, euphorigenic doses of d-amphetamine produced similar AIA scores, but lower OSE and VUS scores than those seen in the present study with MDMA (Vollenweider et al. 1997a). These findings are suggestive of appreciable differences in the psychological profiles produced by MDMA relative to psilocybin or d-amphetamine, although a dose response study is needed to confirm these conclusions.

Nevertheless, this conclusion is in line with the observation that MDE, a structural analog of MDMA, produced a comparable profile of APZ-OAV scores to that seen in the present study, and that the effects of MDE could also be discriminated from the effects of hallucinogens and stimulants when the drugs were compared directly (Hermle et al. 1994; Gouzoulis et al. 1997). Similar distinctions between MDMA-like drugs and hallucinogens or stimulants have been made in animal studies examining both behavioral effects and mechanisms of action (Geyer and Callaway 1994). Finally, at the dose tested, MDMA did not affect Stroop performance, indi-

cating that MDMA does not produce attentional deficits. In contrast, psilocybin administration impaired Stroop performance in a comparison study with healthy volunteers (Vollenweider et al. 1997a). Because the psilocybin study used the same Stroop paradigm as used here and the anticipated Stroop interference effects were observed in the present subjects, the failure to detect an effect of MDMA on Stroop performance cannot be attributed to an insensitivity of the particular paradigm to the effects of psychoactive drugs. Hence, the present findings provide further support for the view that MDMA and MDE may constitute a new class of psychoactive substances (Nichols 1986).

MDMA-induced thought disorder was moderate, and there was no evidence of confused or delusional thinking or paranoid ideations. Thought disturbances included accelerated thinking, thought blocking, and impaired decision making. Difficulties in concentrating were reported by most subjects. Similarly, Downing (1986) reported difficulties in mathematical calculations and impaired judgment in a decision-making task, but no short-term memory impairment. Thus, it may seem surprising that, despite significant thought disturbance, no significant effects of MDMA on Stroop performance, a measure of selective attention, were detected in the present study. This discrepancy might be attributable to the fact that the time span during which attention is demanded in the Stroop task is relatively short, as compared to the time span involved in more complex cognitive tasks, such as mathematical calculation, where attention has to be sustained over a longer time period.

MDMA and related drugs have been considered safe by most, but not all, anecdotal reports. In our study, none of the subjects experienced psychosis. However, increased anxiety (Peroutka et al. 1988), dysphoric and psychotic reactions (Hermle et al. 1993), and risky behavior (Downing 1986) have been reported in individual case reports of entactogen users. Personality traits, set and setting, dose and quality of the substances used, as well as interactions with alcohol or other psychoactive drugs have been suggested to be critical factors contributing to the differences in psychological responses to MDMA seen between clinical settings and uncontrolled recreational use (Fischer 1954; Fischer et al. 1968; Hermle et al. 1993; Dittrich, 1994; Kemmerling et al. 1996). Moreover, a recent paper on MDMA-related psychiatric complications further indicates that subjects with a previous history of illicit drug abuse or psychiatric disorders are particularly at risk for short- and long-term MDMA-related sequelae, although in a few case reports, psychiatric complications were also noted in "normals" after a single dose of MDMA (Kemmerling et al.). Nevertheless, the present data suggest that the risk for MDMA-induced psychiatric complications can be minimized under clinical conditions by careful evaluation and preparation of volunteers.

In the present study, MDMA at a typical recreational dose (1,7 mg/kg PO), also produced transient cardiovascular effects with moderate increases in both systolic and diastolic blood pressure. Consistent with previous reports (Downing 1986; Gouzoulis et al. 1993), most of the subjects were not aware of the changes in cardiovascular parameters and did not report unpleasant physical symptoms. Similar increases in blood pressure were observed in a pilot study after comparable doses of MDMA in experienced users (Downing, 1986) and in a prospective study with MDE in normals (Gouzoulis et al. 1993). In contrast, Grob et al. (1996) found no significant increases in blood pressure after administration of relatively low doses of MDMA (0.25–1.0 mg/kg PO). Thus, it seems that the increases in blood pressure seen after MDMA ingestion are dose dependent. On the other hand, it is of note that MDMA, even at lower doses, may well exacerbate latent cardiovascular problems, such as labile hypertonia, which possibly was the cause for the exaggerated hypertensive response seen in one of our volunteers. The observed rise in blood pressure and, particularly, the severe hypertensive response in one subject have implications for illicit MDMA use in uncontrolled settings. Higher or repeated amounts of MDMA, as often consumed at all-night dance sessions or "raves," might potentially lead to severe hypertensive reactions and arrhythmias. Hypertension in combination with coagulopathy might possibly be responsible for cerebral insults as reported in single case reports (Green et al. 1996).

As previously reported by Grob et al. (1996), we found a slight, but nonsignificant increase of body temperature (0.2 to 0.5 °C) in MDMA subjects at resting state. Although MDMA, at the dose tested, had virtually no hyperthermic effects, it is noteworthy that higher doses of MDMA (5 mg/kg) produced hyperthermia in rats and that this increase in body temperature depended upon both ambient temperature and water consumption (Dafters 1994). Given these findings, it is reasonable to assume that modest doses of MDMA (0.25-1.7 mg/kg) should not cause physical complications, but that higher doses, as often approached at "raves," in combination with high ambient temperature, physical strain, and dehydration might lead to a potentially dangerous hyperthermia.

The most frequently reported acute adverse effects resembled those of amphetamine and were usually not considered as severe by the subjects. These effects were jaw clenching (bruxism), anorexia, difficulties in concentration, and motor restlessness and occurred with similar incidence as previously seen in recreational users (Peroutka et al. 1988; Liester et al. 1992). Another important finding of this study is that several adverse effects, such as motor restlessness and difficulties in concentration, were still present in one-third of the subjects 24 hours after MDMA ingestion. This might be

attributable to interindividual differences in drug metabolism and/or excretion pattern or the sustained presence of active metabolites. In fact, individual differences in metabolism and excretion of MDMA in healthy volunteers have been reported by Helmlin et al. (1996). The same study also discovered several new metabolites of MDMA, which may contribute to the after effects of MDMA, although it is not known whether these metabolites are psychoactive. In three subjects, brooding newly appeared the following day, a finding that may reflect serotonin depletion subsequent to excessive serotonin release (Johnson et al. 1986).

In summary, the present data indicate that a moderate recreational dose of MDMA produces an affective state of enhanced mood associated with moderate derealization phenomena, mostly without anxiety or severe distortion of thought, and without marked stimulation of psychomotor drive. In contrast to the generally positive emotions, several somatic side effects, such as jaw clenching, suppressed appetite, restlessness, and insomnia, were experienced during and after the trial. Lack of energy, fatigue, feelings of restlessness, difficulty concentrating and brooding were noted the following day in some of the subjects. Hyperthermia reported in single cases of MDMA users seems to occur only with higher doses than those used in the present study and might be facilitated in settings with high ambient temperature and physical strain. Increases in blood pressure were generally moderate. The transient severe hypertensive reaction seen in one of our subjects demonstrates that the hypertensive effects of MDMA, even at moderate recreational doses, should not be underestimated, particularly in subjects with latent cardiovascular problems.

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