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ORIGINAL INVESTIGATION

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Gender differences in the subjective effects of MDMA

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Abstract *Rationale:* 3,4-Methylenedioxymethamphetamine (MDMA) mainly releases serotonin (5-HT) and is contained in the recreational drug Ecstasy. 5-HT is known to play an important role in mood and anxiety disorders, for which there is a female preponderance. To date, there are no systematic data on gender differences in the subjective effects of MDMA. *Objectives:* The present work analyzed the pooled data from three controlled studies on the psychological and physiological effects of MDMA in healthy volunteers with no or minimal MDMA experience. A particular focus of the analyses were possible gender differences. *Methods:* A total of 74 subjects (54 male, 20 female) participated in all three studies. MDMA in oral doses ranging from 70–150 mg (1.35–1.8 mg/kg) was administered under double-blind placebo-controlled conditions. Subjective peak changes were assessed by standardized psychometric rating scales. Physiological measures were blood pressure, heart rate, and peripheral body temperature. Adverse drug effects were assessed during the experimental session and after 24 h. *Results:* Psychoactive effects of MDMA were more intense in women than in men. Women especially had higher scores for MDMA-induced perceptual changes, thought disturbances, and fear of loss of body control. The dose of MDMA positively correlated with the intensity of perceptual changes in women. Acute adverse effects and sequelae were also more frequent in female than in male subjects. In contrast, men showed higher increases in blood pressure than woman. *Conclusions:* The fact that equal doses of MDMA per kilogram body weight produce stronger responses in women compared to men is consistent with an increased susceptibility of women to the 5-HT-releasing effects of MDMA. Our results also indicate that increasing doses of MDMA produce more hallucinogen-like perceptual alterations, particularly in women.

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Introduction

3,4-Methylenedioxymethamphetamine (MDMA) is an amphetamine derivative that produces an affective state of well-being and happiness associated with increased extroversion and sociability. During the late 1970s and early 1980s, MDMA has been examined as an adjunct in psychotherapy (Greer and Tolbert 1986, 1998; Shulgin 1986). Due to its apparent unique psychological effects, MDMA has been suggested belonging to a new class of compounds termed "entactogens" (from Greek: "touching within"; Nichols 1986), differentiating it from classic stimulants and hallucinogens. For more than a decade, MDMA has been widely used as a recreational drug called "Ecstasy". However, pills sold under this name show a large variability in composition and often contain other psychoactive substances such as 3,4-methylenedioxyethylamphetamine (MDE), *N*-methyl-1,3-benzodioxolbutanamine, *d*-amphetamine, methamphetamine, paramethamphetamine, dextromethorphan, ketamine, and cocaine (Milroy et al. 1996; Giroud et al. 1997; Sondermann and Kovar 1999; Baggott et al. 2000; Curran 2000).

Despite its widespread use as a recreational drug, systematic data on the phenomenology of the psychotropic effects of MDMA are scant. While there are several studies describing the effects of Ecstasy in recreational drug users (Peroutka et al. 1988; Solowij et al. 1992; Davison and Parrott 1997; Parrott and Lasky 1998), these reports are of only limited value since most of them are retrospective and lack drug identification. Furthermore, reports of recreational Ecstasy users and prospective placebo-controlled studies using MDMA in subjects with regular Ecstasy consumption (Grob et al. 1996; Grob 1998; Mas et al. 1999; Cami et al. 2000) are likely to be biased by the extensive previous drug experiences. There

are only a few non-placebo-controlled prospective (Greer and Tolbert 1986) or placebo-controlled studies assessing the effects of MDMA (Vollenweider et al. 1998a) or its congener MDE (Gouzoulis et al. 1993; Hermle et al. 1993; Gouzoulis-Mayfrank et al. 1999) in healthy MDMA/MDE-na subjects.

In animals, MDMA mainly releases serotonin (5-HT) via interaction with the 5-HT transporter (Rudnick and Wall 1992) and, to a lesser extent, also dopamine and norepinephrine (Schmidt 1987; Yamamoto and Spanos 1988; Berger et al. 1992). Recent studies in our laboratory indicate that 5-HT activation is also an important mechanism of action of MDMA in humans as most of the psychological and physiological effects of MDMA were greatly reduced after pretreatment with the selective 5-HT reuptake inhibitor citalopram (Liechti and Vollenweider 2000a; Liechti et al. 2000a, 2001). 5-HT is involved in the modulation of a variety of functions, particularly in the regulation of mood, and has been implicated in the pathophysiology of endogenous depression and anxiety disorders, in which there is a female-over-male preponderance. Interestingly, there are also gender differences in markers for serotonergic integrity in Ecstasy users, indicating relatively impaired serotonergic function in women compared to men (McCann et al. 1994). To date there are no investigations into possible gender differences in the acute psychoactive effects of MDMA. The present work summarizes three controlled studies of the acute effects of MDMA in healthy subjects with no or only a single previous MDMA experience. The analysis was focused on the hypothesis that women may show stronger psychological responses to the 5-HT releaser MDMA, consistent with an increased female susceptibility to mood disorders.

Materials and methods

Study description

This analysis summarizes data from three published double-blind, placebo-controlled within-subject studies performed in our laboratory between 1996 and 2000. Study 1 (Vollenweider et al. 1998a, 1999a) was conducted in a calm and comfortable laboratory environment at the University Hospital of Psychiatry. Prepulse inhibition of the acoustic startle reflex and psychological state were measured after placebo or MDMA (mean ± SD: 1.7±0.06 mg/kg, 120±19 mg; range: 1.64–1.8 mg/kg, 90–150 mg) administration in 13 healthy subjects (ten males, three females; age 29±7.5 years, range 23–49 years). Study 2 (Gamma et al. 2000) was conducted at the Department of Nuclear Medicine of the University Hospital Zurich. Regional cerebral blood flow, as measured by [$H_2{}^{15}O$]-positron emission tomography, and psychological state were assessed in 16 subjects (ten males, six females; age 26±2.5 years, range 22–30 years) after placebo or MDMA administration (mean ± SD: 1.7±0.05 mg/kg, 113±15 mg; range: 1.64–1.8 mg/kg, 90–140 mg). Setting and measurements of study 3 were identical to those of study 1, however, three different pretreatments were used in addition to MDMA (mean ± SD: 1.5±0.09 mg/kg, 102±12 mg; range: 1.37–1.77 mg/kg, 70–120 mg) and placebo (Liechti and Vollenweider 2000a, b; Liechti et al. 2000a, b, 2001). For the present analysis only the placebo and MDMA alone conditions were used. Study 3 included 45 subjects (34 males, 11 females; age 27±5.5 years, range 20–41 years). In all studies participants were told not to eat 2 h prior to each session. Subjective experience during the peak drug effect (105 and 120 min after MDMA or placebo intake) was assessed by psychometric ratings. Blood pressure, heart rate, and peripheral body temperature were measured before and throughout the session (0, 60, 90, 120, and 150 min after MDMA or placebo intake). Side effects were assessed by the List of Complaints (LC; Von Zerssen 1976) both during the session and after 24 h. The LC consists of 66 items yielding a global score measuring physical and general discomfort. Since psychometric ratings were identical and rating procedures were standardized across all three studies, data were pooled for the purposes of the present analysis. There were no correlations for age with any dependent measure of the present analysis and no group differences between the three studies.

All three studies were approved by the Ethics Committee of the University Hospital of Psychiatry, Zurich. The use of MDMA, specifically the administration of moderate single doses to MDMA-na healthy subjects under controlled conditions, was authorized by the Swiss Federal Health Office, Department of Pharmacology and Narcotics, Bern. While there is valid concern about the neurotoxicity of high and repeated doses of MDMA in humans (McCann et al. 1998, 2000), available evidence suggests that the doses used in the present studies are very unlikely to produce neurotoxicity or lasting behavioral or functional consequences (Vollenweider et al. 1999b). Also, written and oral comprehensive information on the possible adverse as well as positive effects of MDMA administration, according to the literature and our experience in controlled settings, and descriptions of the aim of the study and of the procedures involved was provided to the subjects, on the basis of which all participants gave their written informed consent.

Participants

All 74 subjects (54 male, 20 female; age 27±5.5 years, range 20–49 years) included in the analysis were recruited from the University hospital staff and at the Medical School of Zurich. Most participants were university students or physicians who had a personal scientific interest in the study. All subjects were screened by a semi-structured psychiatric interview, the Freiburg Personality Inventory (FPI; Fahrenberg et al. 1984), and by clinical examination. Exclusion criteria were personal or family history of mood disorders, schizophrenia, or other axis I disorders according to DSM-IV, scores exceeding two standard deviations from the mean values of normative data in the "neuroticism" scale of the FPI, regular present or past alcohol or substance abuse, and somatic illness. All subjects were healthy according to medical history, physical examination, electrocardiogram, and blood analysis. Sixty-nine subjects were MDMA-na, while 5 had one or two previous experiences with Ecstasy/MDMA in non-research settings. Furthermore, half of the subjects of study 3 (n=22) had received MDMA in combination with a pretreatment prior to the MDMA-alone session that was entered into the present analysis. These two MDMA sessions were separated by at least 2 weeks, and there was no difference in the psychological effects of MDMA alone between those subjects receiving MDMA alone first and those receiving MDMA plus pretreatment first. In addition, 13 subjects had once tried an hallucinogen and 39 had used cannabis. In sum, none of the subjects met DSM-IV criteria for substance abuse or dependence, except for 13 subjects with nicotine dependence. No drug screenings were performed during the study.

Psychometric ratings

The Adjective Mood rating scale (AM; Janke and Debus 1978) and the Altered State of Consciousness rating scale (OAV; Dittrich et al. 1985; Dittrich 1998) were used to assess the psychological effects of MDMA. The AM questionnaire consists of 14 scales measuring efficiency-activation, self-confidence, heightened mood, apprehension-anxiety, depressiveness, thoughtfulness-contempla-

tiveness, extroversion, introversion, inactivation, dazed state, tiredness, sensitivity, aggression-anger, and emotional excitation. The OAV rating is a visual analogue scale (66 items) that measures alterations in waking consciousness, including changes in mood, perception, experience of the self and of the environment, as well as thought disorder. The OAV yields three dimensions comprised of several clusters of items:

1. "Oceanic boundlessness" (OB) measures derealization and depersonalization associated with positive mood. The corresponding clusters of items are "derealization", "depersonalization", "altered perception of space and time", "positive basic mood", and "mania-like experience".
2. "Anxious ego dissolution" (AED) measures ego-disintegration and loss of autonomy and self-control associated with arousal and anxiety. The item clusters are "thought disorder", "fear of loss of thought control", "fear of loss of body control", "anxious derealization", and "delusion".
3. "Visionary restructuralization" (VR) includes the item clusters "elementary visual hallucinations", "visual (pseudo-)hallucinations", "synesthesia", "changed meaning of percepts", "facilitated recollection", and "facilitated imagination".

Drug and dosing

Pure racemic MDMA was obtained through the Swiss Federal Health Office, Department of Pharmacology and Narcotics, Bern, and prepared as gelatin capsules of 10 and 50 mg. Subjects received a single oral dose of MDMA [mean ± SD: 108±16 mg (1.6±0.12 mg/kg), range: 70–150 mg (1.35–1.8 mg/kg)] which is a typical single dose taken for research or recreational use (Greer and Tolbert 1986; Giroud et al. 1997; Curran 2000).

Data analysis

Data were analyzed using Statistica 5.5 for Windows (StatSoft, Tulsa, Okla., USA). Peak scores of all dependent measures were analyzed by 2×2 analyses of variance (ANOVAs) with drug (placebo versus MDMA) as within-subjects factor and gender (male versus female) as between-subject factor. Tukey's *post hoc* tests were performed based on significant main effects or interactions. Spearman's rank order correlations were used to assess the relationship between the dose of MDMA (mg/kg) and psychological or physiological peak effects of MDMA.

Results

Psychological effects of MDMA

F and *P* values for significant main effects and interactions are presented in Table 1. Subjective effects of MDMA began 30–60 min after MDMA administration, peaked at 75–120 min, and lasted for a mean duration of 3.5 h.

Altered state of consciousness rating scale

As shown in Fig. 1, MDMA produced significantly higher increases in all three dimensions of the OAV in female compared to male subjects. In the OB dimension, women showed significantly higher increases in positive basic mood, depersonalization, and altered perception of space and time (Table 1). Item-based analysis for OB revealed that more female than male subjects felt "care-

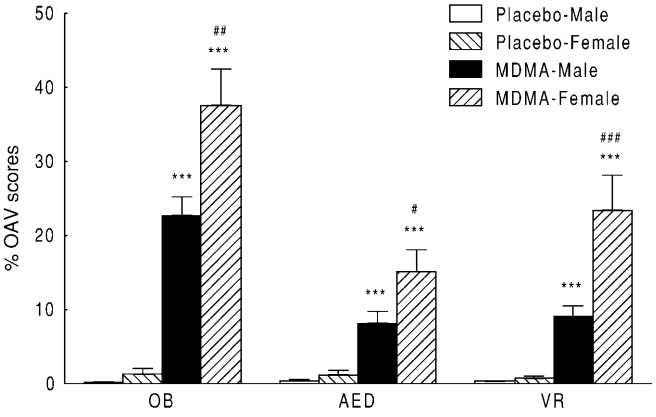

Fig. 1 Mean and SE scores of the Altered States of Consciousness rating scale (*OAV*), *n*=74; 54 males, 20 females. Levels of oceanic boundlessness (*OB*), anxious ego-dissolution (*AED*), and visionary restructuralization (*VR*) during the peak drug effect. 3,4-Methylenedioxymethamphetamine (MDMA) increased scores in all scales as indicated by *** for $P<0.001$ compared to placebo (ANOVA; drug main effect). Women scored significantly higher than men in all dimensions of the OAV. Significant gender differences are indicated by # for $P<0.05$, ## for $P<0.01$, and ### for $P<0.001$ (two-way ANOVA; drug × gender interaction). %OAV scores indicate percent of maximal absolute OAV scores for each scale

free", "free of worries and obligations", and experienced "boundless joy" and "comprehensive love". They felt "as if in a wonderful other world" and at the same time "at one with their surroundings". Subjects reported a "dream-like change of the perception of space and time " and that "physical sensations were more pleasurable".

Analysis of the MDMA-induced increases in AED scores revealed that women showed a significantly more pronounced increase in thought disturbances than men, including impaired decision making, accelerated thinking, and losing track of one's thoughts. In addition, female subjects also had significantly more fear of loss of body control than men.

Gender differences were most pronounced in the VR dimension, which indicates that female subjects experienced considerably more perceptual changes than men. More female than male subjects reported that "objects had a new and unfamiliar meaning" and that "minor things carried a particular meaning". Recollection and imagination were facilitated. Subjects "recalled long-forgotten things" and reported an "extraordinarily vivid imagination". Elementary hallucinations were reported by both genders, with a higher frequency in female subjects. Subjects reported seeing flashes of light, colors, and simple patterns. Objects appeared smaller, bigger, or slightly distorted and colors were more vivid. While tactile awareness was intensified, the sensation of pain was attenuated. Sounds appeared closer or farther away. Interestingly, women also had significantly increased scores on "visual (pseudo)-hallucinations" while there was no increase in men. In general, there were no complex hallucinations, however, a few subjects reported "seeing scenes with closed eyes". We found highly significant correlations between the dose of MDMA

Table 1 *F* and *P* values for main effects and interactions of drug (placebo vs MDMA) and gender, and post hoc results; *n*=74, 54 male and 20 female subjects. *MDMA* 3,4-Methylenedioxymethamphetamine, *OAV* Altered States of Consciousness rating scale, *OB* oceanic boundlessness, *AED* anxious ego-dissolution, *VR* visionary restructuralization

Psychometric ratings	MDMA	Gender	MDMA × gender[a]	Tukey's post hoc tests	
OAV scale	*F*(1,72)	*F*(1,72)	*F*(1,72)	Male[b]	Female[c]
OB	145.23***	9.5**	7.94**	***	***
Derealization	57.56***	NS	NS	***	***
Depersonalization	71.08***	7.26**	7.42**	***	***
Altered perception of space and time	96.31***	11.37***	8.54**	***	***
Positive basic mood	203.1***	11.21***	9.2**	***	***
Mania-like experience	66.15***	NS	NS	***	***
AED	52.37***	5.22*	4.22*	***	***
Anxious derealization	8.97***	NS	NS	NS	NS
Thought disorder	65.79***	10.09**	9.9**	***	***
Delusion	NS	NS	NS	NS	NS
Fear of loss of thought control	19.62***	NS	NS	**	**
Fear of loss of body control	28.47***	9.45**	4.89*	*	***
VR	76.74***	15.17***	15.04***	***	***
Elementary visual hallucinations	43.09***	11.3***	11.04***	**	***
Visual (pseudo-)hallucinations	22.7***	9.49**	8.96**	NS	***
Synesthesia	26.38***	7.55**	7.26**	NS	***
Changed meaning of percepts	88.03***	8.31**	10.3**	***	***
Facilitated recollection	23.96***	NS	NS	**	**
Facilitated imagination	33.21***	NS	NS	***	***
Adjective mood scale	*F*(1,71)	*F*(1,71)	*F*(1,71)		
Efficiency-activation	NS	NS	NS	†	NS
Self-confidence	35.81***	NS	NS	***	**
Heightened mood	44.45***	NS	NS	***	**
Apprehension-anxiety	18.98***	16.46***	NS	NS	***
Depressiveness	10.3**	5.12*	NS	NS	**
Thoughtfulness-contemplativeness	54.49***	4.35*	NS	***	***
Extroversion	42.33***	NS	NS	***	***
Introversion	8.51**	NS	NS	*	NS
Inactivation	7.49**	NS	NS	NS	NS
Dazed state	39.19***	NS	NS	***	**
Tiredness	7.93**	NS	NS	NS	NS
Sensitivity	17.32***	9.36**	NS	*	**
Aggression-anger	NS	NS	NS	NS	NS
Emotional excitation	39.63***	NS	NS	***	**
Physiological measures	*F*(1,72)	*F*(1,72)	*F*(1,72)		
Systolic blood pressure	148.1***	8.46**	4.49*	***	***
Diastolic blood pressure	81.02***	8.79**	NS	***	***
Heart rate	22.48***	4.8*	NS	***	NS
Body temperature [*F*(1,56)]	22.24***	NS	NS	***	NS
List of complaints (global score)	*F*(1,72)	*F*(1,72)	*F*(1,72)		
Acute side effects	131.79***	7.06**	4.89*	***	***
Sequelae after 24 h	46.14***	5.94*	3.59*	***	***

*$P<0.05$
**$P<0.01$
***$P<0.001$
†Significant main effect of drug for men alone ($P<0.01$)

[a] Gender difference during MDMA
[b] Difference between placebo and MDMA for male subjects
[c] Difference between placebo and MDMA for female subjects

(mg/kg) and VR scores after MDMA administration in all subjects (r=0.36; n=74, $P<0.001$), in female subjects (r=0.68; n=20, $P<0.001$), but not in male subjects (r=0.23; n=54, P=0.09). There were no significant correlations between dose of MDMA and OB or AED scores. Thus, higher doses of MDMA in the range of 1.35–1.8 mg/kg (70–150 mg) produced more hallucinogen-like perceptual changes particularly in women. In contrast, increasing doses of MDMA did not produce increases in OB and AED.

There were no gender differences in the OAV in the placebo condition.

Adjective mood rating scale

Figure 2 shows peak scores of all scales of the AM. *F* and *P* values are presented in Table 1. MDMA mainly elicited an increase in heightened mood, self-confidence, and extroversion in both genders. Item-based analysis revealed that subjects were mainly happier, more relaxed, carefree, open, sociable and talkative. There was also a significant increase in thoughtfulness-contemplativeness, with subjects being in a state of dreaminess and lost in thought. MDMA-induced increases in emotional excitation were due to increased restlessness, with a third of

Table 2 Physiological effects of MDMA

		n	Placebo		MDMA	
			Baseline	Peak	Baseline	Peak
Systolic blood pressure (mm Hg)	Male	54	125±12	124±13	123±12	157±21*, **
	Female	20	114±8	112±10	116±12	138±14*, **
Diastolic blood pressure (mm Hg)	Male	54	78±11	80±12	77±11	95±14*
	Female	20	75±8	75±10	76±10	86±11*
Heart rate (beats/min)	Male	34	64±10	60±8	64±11	73±14*
	Female	11	67±11	70±9	70±14	83±15
Body temperature (°C)	Male	44	36.6±0.3	36.5±0.3	36.6±0.4	36.9±0.4*
	Female	14	36.7±0.3	36.8±0.4	36.7±0.4	37±0.4

*P<0.001, post hoc test for MDMA versus placebo based on significant drug main effect
**P<0.05, significant drug × gender interaction

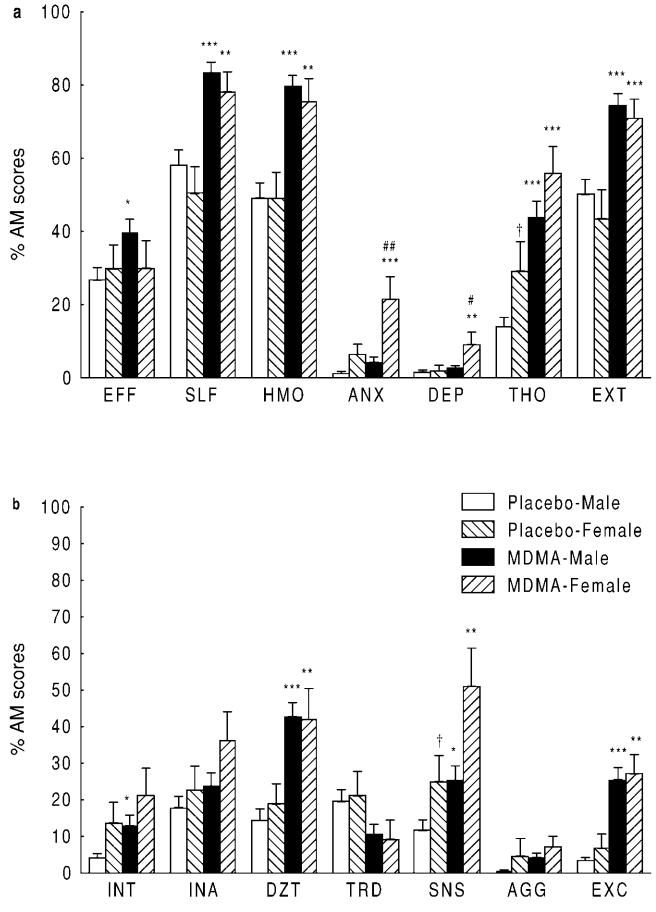

Fig. 2a, b Mean and SE scores of the Adjective Mood rating scale (*AM*), *n*=72; 52 males, 20 females. *EFF* Efficiency-activation, *SLF* self-confidence, *HMO* heightened mood, *ANX* apprehension-anxiety, *DEP* depressiveness, *THO* thoughtfulness-contemplativeness, *EXT* extroversion, *INT* introversion, *INA* inactivation, *DZT* dazed state, *TRD* tiredness, *SNS* sensitivity, *AGG* aggression-anger, *EXC* emotional excitability. Significant changes induced by MDMA compared to placebo are indicated by * for P<0.05, ** for P<0.01, *** for P<0.001 (ANOVA; drug main effect). MDMA produced anxiety and depressiveness in females but not in males, as indicated by # for P<0.05 and ## for P<0.01 (two-way ANOVA; drug × gender interaction). † for P<0.05 indicates gender differences under placebo condition (main effect of gender). %AM scores indicate percent of maximal absolute AM scores for each scale

the subjects feeling fidgety. While tiredness was reduced there was an increase in dazed state that was due to half of the subjects feeling intoxicated. In contrast to women, men were slightly activated by MDMA and reported being more active and energetic (significant main effect of drug for men alone [F(1,40)=7.1; P=0.01]. Interestingly, only women had increased scores for anxiety and depression. Item-based analysis showed that these changes were mainly attributable to feelings of helplessness, defenselessness, and an increased need for protection. Dysphoric reactions associated with anxiety were observed at drug onset in a few subjects. These uncomfortable, dysphoric states of mood were transient and passed with subjects becoming acquainted with the drug effect and being reassured by the investigator. We found a significant correlation between the dose of MDMA (range 1.35–1.85 mg/kg) and MDMA-induced anxiety scores in women (r=0.5; n=20, P<0.03) but not in men.

There were no gender differences in the placebo condition in any rating except for sensitivity and thoughtfulness which were both higher in women.

Physiological effects of MDMA

Effects of MDMA on blood pressure, heart rate, and body temperature are summarized in Table 2. *F* and *P* values are presented in Table 1. MDMA significantly increased both diastolic and systolic blood pressure in both genders. There was a significant drug × gender interaction for systolic blood pressure, indicating that the MDMA-induced increase in blood pressure was more pronounced in men. In male subjects the peak difference between MDMA and placebo was 33 mmHg for systolic blood pressure and 15 mmHg for diastolic blood pressure. In female subjects the peak difference between MDMA and placebo was 26 mmHg for systolic blood pressure and 11 mmHg for diastolic blood pressure. In sum, 24 of 74 subjects had systolic blood pressure values of more than 160 mmHg, 7 reached values above 180 mmHg, and one 49-year-old man (baseline blood pressure: 140/95) had a hypertensive reaction (240/145 mmHg) without other signs of hypertensive

Table 3 Acute and short-term adverse effects of MDMA. Numbers indicate percentage of all subjects under MDMA reporting a specific complaint. Numbers in *parentheses* indicate percentage of all subjects under placebo reporting a specific complaint

	Acute adverse effects of MDMA (placebo)			Sequelae 24 h after MDMA (placebo)		
	All *n*=74	Female *n*=20	Male *n*=54	All *n*=74	Female *n*=20	Male *n*=54
Difficulty concentrating	59 (15)	75 (15)	54 (15)	28 (8)	30 (10)	28 (7)
Jaw clenching	58 (0)	65 (0)	56 (0)	20 (0)	25 (0)	19 (0)
Lack of appetite	54 (4)	75 (5)	46 (4)	39 (3)	50 (0)	35 (4)
Dry mouth/thirst	53 (3)	65 (5)	48 (2)	34 (4)	60 (10)	24 (2)
Impaired balance	49 (0)	50 (0)	48 (0)	7 (0)	5 (0)	7 (0)
Restless legs	41 (1)	40 (0)	41 (2)	11 (1)	5 (0)	13 (2)
Sensitivity to cold	41 (11)	50 (15)	37 (9)	12 (3)	10 (10)	13 (0)
Dizziness	38 (1)	40 (0)	37 (2)	7 (0)	10 (0)	6 (0)
Palpitations	35 (1)	50 (0)	30 (2)	7 (0)	15 (0)	4 (0)
Restlessness	34 (1)	35 (0)	33 (2)	12 (1)	15 (5)	11 (0)
Being cold	34 (7)	45 (15)	30 (4)	9 (3)	20 (10)	6 (0)
Sweating/sweaty palms	31 (0)	20 (0)	35 (0)	12 (0)	5 (0)	15 (0)
Forgetfulness	28 (1)	40 (5)	24 (0)	11 (1)	10 (0)	11 (2)
Heavy legs	27 (1)	50 (0)	19 (2)	12 (0)	20 (0)	9 (0)
Fatigue	26 (47)	35 (45)	22 (48)	41 (26)	55 (25)	35 (26)
Weakness	26 (1)	35 (5)	22 (0)	24 (1)	35 (5)	20 (0)
Hot flushes	24 (3)	40 (5)	19 (2)	15 (1)	20 (5)	13 (0)
Tremor	23 (0)	25 (0)	22 (0)	8 (0)	10 (0)	7 (0)
Paresthesia	22 (9)	25 (15)	20 (7)	1 (8)	5 (10)	0 (7)
Inner tension	20 (5)	15 (5)	22 (6)	8 (5)	10 (5)	7 (6)
Brooding	16 (3)	20 (0)	15 (4)	18 (1)	20 (0)	17 (2)
Nausea	15 (3)	10 (5)	17 (2)	1 (0)	0 (0)	2 (0)
Lack of energy	15 (8)	25 (10)	11 (7)	24 (4)	40 (5)	19 (4)
Exhaustibility	15 (4)	15 (10)	15 (2)	19 (1)	30 (0)	15 (2)
Frequent urge to urinate	14 (5)	10 (10)	15 (4)	15 (5)	15 (10)	15 (4)
Headache	12 (12)	15 (20)	11 (9)	27 (7)	35 (10)	24 (6)
Insomnia	–	–	–	24 (0)	30 (0)	22 (0)
Anxiety	11 (1)	15 (5)	9 (0)	1 (1)	5 (0)	0 (2)
Irritability	8 (1)	15 (5)	6 (0)	5 (0)	15 (0)	2 (0)
Increased appetite	4 (7)	0 (5)	6 (7)	1 (3)	0 (0)	2 (4)
Muscle aches	1 (3)	5 (5)	0 (2)	3 (3)	5 (0)	2 (4)
Bad dreams	–	–	–	7 (3)	15 (5)	4 (2)

crisis. MDMA increased heart rate in both genders by 13 beats/min compared to placebo, however, this was only significant in men. Similarly, peripheral body temperature was increased significantly by 0.4°C compared to placebo in male subjects while MDMA-induced increases in body temperature did not reach statistical significance in female subjects. All body temperatures remained below 38°C. There were no correlations between the dose per kilogram body weight and blood pressure or body temperature values.

MDMA produced a series of acute adverse effects as shown in Table 3. Adverse effects were more frequently reported by women compared to men and mainly included jaw clenching or increased tension in maxillary muscles, dry mouth, and lack or loss of appetite. Sweating and nausea were more frequent in men. At the onset of the MDMA effect some subjects reported nausea, hot flushes, paresthesia, and dizziness. Tremor and increased restlessness were observed in about one-third of the subjects. Side effects were generally considered mild and were similar to those reported in previous controlled studies (Vollenweider et al. 1998a) or by Ecstasy users (Peroutka et al. 1988; Solowij et al. 1992). There were no complications requiring medical intervention.

Short-term sequelae registered 24 h after MDMA administration are summarized in Table 3. Some acute effects of MDMA lasted up to the next day such as lack of appetite, dry mouth, and increased jaw muscle tension. Newly occurring after effects were fatigue, muscle ache, and headache in about half of the subjects. Up to one-third of the subjects reported slightly depressed mood including emotional irritability, lack of energy, brooding and bad dreams. These sequelae lasted up to 3 days in a few subjects. Women reported significantly more of these adverse after effects than men.

There were no significant or relevant differences in the outcome measures between student and non-student subjects, or between MDMA-na subjects and those who reported prior use of MDMA. No acute or subacute complications occurred during or after the experimental sessions, and after completing the study none of the participants expressed any interest in taking MDMA as a recreational drug (Liechti and Vollenweider 2000a, b).

Discussion

The present work analyzed psychological and physiological effects of MDMA in controlled settings in healthy

male and female subjects. Generally, subjective effects of MDMA were more intense in women than in men. Women especially had higher scores for MDMA-induced perceptual changes, anxiety, and adverse effects. Thus, it appears that women have a more hallucinogen-like experience associated with appreciable anxiety during MDMA. Men, in contrast, were slightly activated by MDMA, which was not the case in women, and also had significantly higher increases in systolic blood pressure than women. The finding that women experienced stronger psychological and adverse MDMA effects than men has not yet been reported and might indicate increased sensitivity in female subjects to the effects of MDMA. On the other hand, it could be argued that women have equally strong MDMA experiences to men but simply report higher scores in self-ratings. This view, however, is not consistent with the investigators' observations during the experimental sessions. Furthermore, placebo scores in women were not different from those of men in most scales, but clearly increased during MDMA. Finally, activation scores showed an opposite effect, with men scoring higher than women after MDMA.

Gender differences in markers for serotonergic activity have previously been reported in Ecstasy users, suggesting relatively impaired serotonergic function in women compared to men (McCann et al. 1994). Specifically, reductions in the concentrations of the monoamine metabolite 5-hydroxyindoleacetic acid in cerebrospinal fluid were greater in women than men (46% versus 20%) within the Ecstasy group. This finding together with the present observation raises the question whether women might be more susceptible to any MDMA-induced depletion of 5-HT. In the study of McCann and colleagues, however, reported absolute doses of MDMA were similar in both genders while women weighed less, resulting in relatively higher doses per kilogram body weight in women. Therefore, the greater reduction in serotonergic markers in women reported by McCann et al. could be dose related. In contrast, our study examined equal doses of MDMA per kilogram body weight in male and female subjects and considerably higher absolute doses in men compared to women. Yet, women experienced both stronger acute and subacute MDMA effects than men, suggesting pharmacodynamic gender differences. A weakness of the present work, however, is that blood levels of MDMA were not assessed. Therefore, we cannot exclude that women had higher blood levels compared to men due to pharmacokinetic gender differences. However, one would not expect greater blood pressure responses in men compared to women if plasma levels were lower in men. The possibility that the present gender differences in the acute response to MDMA may indicate a generally increased sensitivity of women to serotonergic alterations and, subsequently, a higher female susceptibility to mood disorders should be further investigated.

In the present study, the slight hallucinogen-like effects were positively correlated with the dose of MDMA per kilogram body weight in woman. Except for anxiety there were no other significant correlations between the dose of MDMA per kilogram and psychological effects of MDMA. The present finding indicates that hallucinogen-like effects of MDMA might be increasingly prominent at doses higher than 1.4 mg/kg, especially in women, and is consistent with Ecstasy users reporting hallucinogenic effects of MDMA at higher doses (Solowij et al. 1992). Similarly, anxiety might increase with higher doses, while positive effects of MDMA do not appear to correlate with dose, at least for the dose range used in the present studies. We have recently shown that perceptual effects of MDMA were significantly reduced after pretreatment with the 5-HT_2 antagonist ketanserin in healthy subjects (Liechti et al. 2000b). This result suggests a contributing role for 5-HT_2 receptors in the mediation of MDMA-induced perceptual changes. Since MDMA, besides its 5-HT-releasing properties, has moderate direct affinity for 5-HT_2 receptors (Battaglia et al. 1988) and hallucinogens are thought to act as 5-HT_{2A} agonists (Glennon et al. 1984; Sanders-Bush et al. 1988; Vollenweider et al. 1998b), the slight hallucinogen-like effects of MDMA, especially at higher doses, might be related to its direct action at 5-HT_{2A} sites.

In conclusion, equal doses of MDMA per kilogram body weight produced stronger subjective effects in women compared to men, consistent with an increased susceptibility of women to the 5-HT-releasing effects of MDMA. With increasing doses, MDMA produced more hallucinogen-like perceptual alterations, especially in women.

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