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Experimentally induced aggressive behavior in subjects with 3,4-methylenedioxy-methamphetamine (“Ecstasy”) use history

Psychobiological correlates

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Abstract

Purpose: Objective measures of experimentally induced aggressiveness were evaluated in 12 male 3,4-methylenedioxy-methamphetamine (MDMA, “Ecstasy”) users, in comparison with 20 healthy male subjects. **Methods:** All the subjects were preliminarily submitted to DSM-IV interviews and Buss–Durkee Hostility Inventory (BDHI). During a laboratory task, the Point Subtraction Aggression Paradigm (PSAP), subjects earned monetary reinforcers with repeated button presses, and were provoked by the subtraction of money that was attributed to a fictitious other participant. Subjects could respond by ostensibly subtracting money from the fictitious subject (the aggressive response). Escape responses were also possible protecting the counter from monetary subtractions. **Results:** Money-earning responses were not different in Ecstasy users and controls; aggressive responses were significantly higher in Ecstasy users in comparison with control subjects ($F=20.74$, $P<.001$). Baseline adrenocorticotrophic hormone (ACTH) and cortisol (CORT) levels were higher in Ecstasy users than in controls. No difference was found in norepinephrine (NE) and epinephrine (EPI) basal levels of the two groups. During the experimentally induced aggressiveness, plasma ACTH concentrations increased significantly less and NE and EPI levels, together with heart rate (HR), increased significantly more in Ecstasy users than in healthy subjects. Despite ACTH-blunted

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responses, CORT did not increase differently from controls in Ecstasy users. PSAP aggressive responses positively correlated with catecholamines and CORT changes, BDHI Direct Aggression and Irritability scores, both in Ecstasy users and controls. A significant correlation was found between Ecstasy exposure extent and aggressive responses ($r=.78$, $P<.001$). **Implications:** Our findings suggest that Ecstasy users have higher outward-directed aggressiveness than healthy subjects. Aggressiveness in MDMA subjects seems to be associated more with MDMA pharmacological effects than with personality traits: Nevertheless, a premorbid psychobiological proneness to aggressive behavior cannot be excluded. Increased catecholamines reactivity, basal hypothalamus–pituitary–adrenal (HPA) axis hyperactivity, and blunted ACTH responses could be due to MDMA action on monoaminergic pathways and adrenal function. © 2001 Elsevier Science Inc. All rights reserved.

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1. Introduction

A variety of studies investigated aggressive/impulsive behavior in 3,4-methylenedioxy-methamphetamine (MDMA, “Ecstasy”) users, with unclear and contrasting results. Increased levels of aggressiveness and impulsiveness in association with long-lasting use of Ecstasy have been repeatedly evidenced (Gerra et al., 1998; Morgan, 1998b; Schifano, Di-Furia, Forza, Municuci, & Bricolo, 1998; Tuchtenhagen et al., 2000). Sudden aggressiveness has been also reported in humans among acute effects of similar amphetamine derivatives such as 3,4-methyl-enedioxy-*N*-ethylamphetamine (MDEA; Weinmann & Bohnert, 1998). Parrott, Sisk, and Turner (2000) reported recently that heavy Ecstasy users had higher hostility scores than controls at a psychometric evaluation. Parrott and Lasky (1998) previously found that Ecstasy users feel significantly more unsociable than control subjects during midweek, after a Saturday night dance with Ecstasy.

In contrast, McCann, Ridenour, Shaham, and Ricaurte’s (1994) findings evidenced lower levels of impulsiveness in heavy Ecstasy users and lower scores than controls on the Buss–Durkee Hostility Inventory (BDHI; Buss & Durkee, 1957): This finding is unexpected in subjects with an impairment of serotonin system (McCann, Eligulashvili, Mertl, Murphy, & Ricaurte, 1999; McCann, Szabo, Scheffel, Dannals, & Ricaurte, 1998), since blunted serotonergic function is normally associated with elevated levels of aggressiveness and impulsiveness (Brown et al., 1982; Coccaro, 1989; Virkkunen & Linnoila, 1993), but this is in agreement with reports in experimental animals that showed a reduction of aggression (threat and attack) among MDMA effects (Navarro & Maldonado, 1999).

No significant differences have been found on the State/Trait Anger Expression Inventory (Spielberger, 1988) and in hostility factor score at SCL-90 between light Ecstasy users and healthy subjects (Morgan, 1998a; Parrott et al., 2000), suggesting that the extent of exposure to Ecstasy may significantly influence the changes in aggressive behavior. Accordingly, Morgan (1998b) observed that the recreational users who had consumed the most Ecstasy in their lives had the most elevated trait impulsiveness scores.

Moreover, our previous studies on Ecstasy users after 12 months of abstinence showed a significant reduction of Direct Aggressiveness subscale scores at BDHI, compared with the scores after 3 weeks of abstinence (Gerra et al., 2000), with the evidence of a possible remission of this affective state, which could be attributed to the direct pharmacological effect of MDMA.

On the other hand, some studies indicate that people who used drugs may be more likely to engage in aggressive behaviors than those who do not use drugs (Kingery, Pruitt, & Hurley, 1992; Muntaner et al., 1990), independently from the specificity of substance abuse history (Kellam, Stevenson, & Rubin, 1982; Kofoed & MacMillan, 1986; Miller, 1991; Stabeneau, 1988; Tarter, Blackson, Brigham, Moss, & Caprara, 1995) and the direct action of the drugs. The finding of greater aggression in a group of abstinent individuals with a drug dependence history (Allen, Moeller, Rhoades, & Cherek, 1997) also supports the hypothesis about a preexisting proneness to aggressiveness, which might also characterize Ecstasy users' personality.

Therefore, with the present study, we decided to investigate abstinent Ecstasy users' responses to a laboratory method that has been developed to elicit aggression, so that it can be objectively quantified (Cherek, 1992) and the possible correlations of aggressive responses with psychometric personality features and Ecstasy exposure extent be known. We expected that 3 weeks after Ecstasy discontinuation, experimentally induced aggressiveness was elevated in MDMA users, in comparison with normal controls, and that the users who had consumed Ecstasy for a longer period of time showed more consistent aggressive responses, as a consequence of long-lasting Ecstasy neurotoxicity.

In addition, since our previous findings showed hypothalamus–pituitary–adrenal (HPA) axis function and catecholamine changes in association with aggressive behavior both in healthy subjects (Gerra et al., 1997) and methadone patients (Gerra et al., in press) submitted to the same laboratory procedure, we decided to investigate HPA axis and catecholamine responses during aggression paradigm (Point Subtraction Aggression Paradigm, PSAP), when Ecstasy users are systematically provoked while given the opportunity of aggressive responses. Similar to what was expected for behavioral findings, the aim of the study was to evaluate the possible neuroendocrine changes persistent after drug discontinuation and their hypothetical correlation with the aggressive responses and the extent of MDMA exposure.

For these reasons, behavioral responses and neuroendocrine measures including cortisol (CORT), adrenocorticotropic hormone (ACTH), norepinephrine (NE), and epinephrine (EPI) plasma levels were investigated during aggression paradigm (PSAP), at 3 weeks after Ecstasy discontinuation, in subjects who were exposed to Ecstasy for different periods of time.

2. Material and methods

2.1. Subjects

Twelve male MDMA users, aged 18–29 years (mean \pm S.D. = 24 ± 3.55 years), with a history of at least 50 occasions of drug use (mean \pm S.D. = 77.9 ± 23.51 ; range: 50–150) prior

to drug interruption entered the study (Group A). All the subjects gave informed consent. The subjects included in the study used MDMA only during the weekend nights, one to two pills every night. In the Italian illicit market, the variability of MDMA concentration is from 25 to 125 mg (Bellomo, 1995). The duration of MDMA use was from 12 to 36 months (mean \pm S.D. = 15.9 ± 22.1). Demographic data and characteristics of MDMA use are included in Table 1.

All the subjects were studied 3 weeks after their last dose of Ecstasy. In the last month before and after MDMA discontinuation, the urine controls for amphetamines, methamphetamines, morphine, methadone, cannabis, cocaine, barbiturates, and alcohol were performed three times a week. The urine controls were positive for MDMA only, before discontinuation, in eight subjects among MDMA users, and for cannabis and MDMA in four subjects (cannabis was found only in 4 out of 12 urine controls in two subjects and in three urine controls in the other two subjects).

Previous prolonged consumption and/or dependence on other drugs of abuse and psychotropic agents or continuous excessive alcohol intake were anamnestically excluded, utilizing a structured interview. Many subjects were excluded after the first contact because most MDMA users had also used other drugs for long time. All the subjects included in the study reported episodic use of cannabis or abuse of alcohol (beer), short-term use of heroin was reported by three subjects (some months, 2–3 years before the study), and episodic use of cocaine was reported by other two subjects.

Information about MDMA and/or other drugs use were obtained in several ways including: self-report during a first clinical evaluation; an MDMA questionnaire that asked about duration, frequency, doses, and time of last dose; a questionnaire concerning other drugs and alcohol; a double interview with the family to correct for possible denial; and urine controls during the last month before discontinuation. The subjects were requested to report the number of tablets of Ecstasy used in their life, the number of opportunities, and months of continuous drug exposure.

The subjects had contacted one of the investigators at the Drug Addiction Service in Parma (AUSL) seeking initial information about MDMA ($n=2$) or treatment ($n=4$) and the other subjects ($n=6$) contacted the center through a teacher or one of the parents. Three subjects were students, five subjects were workers, and four were unemployed. Two of the three students showed academic underachievement. They were still living in their parents' home, and their socioeconomic status was medium or high. Six subjects did not report

Table 1

HR and SBP before and after three different experimental sessions a PSAP in Ecstasy users (Group A) and controls (Group B)

	Before first sessions		After first session		After second session		After third session	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
HR	73.1 \pm 2.6	68.1 \pm 4.2	87.4 \pm 2.5	80.9 \pm 2.1	92.33 \pm 3.5	83.4 \pm 2.7	90.4 \pm 3.6	81.1 \pm 2.4
					$t=2.43, P<.05$		$t=2.56, P<.02$	
SBP	122.3 \pm 3.1	115.6 \pm 5.5	143.2 \pm 4.2	127.3 \pm 2.6	145.8 \pm 4.5	133.5 \pm 3.1	151.6 \pm 4.2	135.3 \pm 4.1
					$t=2.14, P<.05$		$t=2.16, P<.05$	

relationship problems in the family and six (50%) had relationship conflicts with family members. All MDMA users in the study spent their weekend nights in disco clubs and manifested a preference for techno music. Seven subjects among the MDMA users showed a weight lost within 10% of their ideal weight that was recovered in the 3 weeks after MDMA discontinuation.

Subjects were admitted to a long-term psychosocial rehabilitation program, and if two-times-a-week analyses for urine metabolites of the main substances of abuse excluded their consumption in the first 3 weeks after admission, they were included in the study. The episodic use of cannabis or alcohol during the 3 weeks of the study (one to two positive urine controls for 3 weeks) did not result in dismissal from the study. Rather, relapse in MDMA use, or continuous use, with dependence and abuse of drugs other than MDMA and alcohol, were grounds for dismissal.

Criteria for exclusion also included severe chronic liver (transaminases < 50 U/l and gamma-globulins $< 20\%$ g/dl) or renal (creatinine clearance: 100–120 mg/l/min) diseases or other chronic physical disorders, significant weight loss ($> 10\%$) or obesity, endocrinopathies, and immunodeficiencies (the subjects were HIV negative).

Twenty healthy male volunteers, recruited from the hospital staff and matched for age (19–32 years: mean \pm S.D. = 26.4 + 6.5 years), were used as controls (Group B). Subjects were defined healthy by physical examination and routine biochemical tests. Exclusion criteria from the study were the same as those used for the patients. Socioeconomic and educational background of healthy volunteers were not significantly different from patients' background. Volunteers were also controlled by urinary drug screening for 4 weeks before the study. Four subjects, among healthy controls, reported no current alcohol use, while the other subjects reported weekly alcoholic drinking ranging from 2 to 18 per week. Age and years of education were similar to those of methadone patients.

Although the normal subjects included as controls were all hospital staff, they did not work in the same building and in substance abuse field, excluding the possibility of prior knowledge regarding the experiment.

2.2. Personality assessment

DSM-IV clinical evaluation and psychometric measures were performed 3 weeks after MDMA discontinuation. Axis I and II disorders were evaluated by a trained psychiatrist utilizing the Structured Clinical Interview according to DSM-III-R (SCID) for Axis I disorders (Spitzer, Williams, Gibbon, & First, 1990) (Italian version: *Intervista Clinica Strutturata per il DSM-III-R*; Fava, Guaraldi, Mazzi, & Rigatelli, 1993) and the Structured Interview for DSM-IV Personality Disorders (SIDP) for Axis II disorders (Pfohl, Blum, Zimmerman, & Stangl, 1989) (Italian version: Maggini & Piccini, Draft Ed., 1994)

The SCID excluded Axis I disorders among MDMA users and controls. The evaluation with SIDP for Axis II disorders found two subjects with open personality disorders out of 12, one subject had borderline personality disorder, and one had avoidant personality disorder. Other three subjects showed symptoms partially corresponding to avoidant and antisocial personality disorder criteria, but not the complete clinical picture of this Axis II disorder. No

Axis II disorders were in evidence among control subjects. Although major depression was not diagnosed among MDMA users, seven subjects showed dysphoria and mood changes in the weeks following MDMA discontinuation and two subjects had subtle cognitive impairment and confusion episodes.

Character and quantification of aggressiveness (defined as direct, indirect, or verbal; irritability; negativism; resentment; suspiciousness; guilt; and total score) were analyzed by the BDHI (Buss & Durkee, 1957) in the Italian version, *Questionario per la Tipizzazione della Aggressività* (QTA; Castrogiovanni, Maremmani, & Di Muro, 1993). QTA raw scores, in accordance with Castrogiovanni et al. (1993), have been used for the total score and for the single subscale scores.

2.3. Apparatus

During experimental sessions of PSAP, subjects sat in a $4.5 \times 4.0\text{-m}^2$ sound-attenuated chamber. The chamber contained a monochrome monitor and a $10 \times 43 \times 25\text{-cm}^3$ response panel. Three Microswitch push buttons labeled “A,” “B,” and “C” were mounted on the top of the response panel in straight line 10 cm apart. The cable coming into the back of the response panel was of sufficient length to allow subjects to place the response panel on their lap during sessions. The monitor and response panels were linked to a Pentium-based computer outside the chamber using an interface card (Med Associates, Georgia, VT, USA) and a customized hardware system. This computer and interface controlled and recorded all experimental events. PSAP license was obtained from the University of Texas (1992).

2.4. Instructions for PSAP

Prior to participation subjects were provided with information about the test. Subjects were told that they could expect to earn from £6000 to 9000 per session.

Prior to the first session, subjects were shown a diagram of the computer monitor and response panel and read the following instructions: “Today, you will be able to earn money by working at the response console. This is a drawing of the response panel and computer monitor. You will be participating with another person in this study. These other people will have similar response panels and monitors. These other people are located at another facility. As the drawing illustrates, the response panel contains three buttons labeled A, B, and C. When each session starts, the letters A, B, and C and a counter will appear on the computer screen. The counter will be at zero. Pushing the A button will cause the B and C letters to go off the screen. Pushing the A button approximately 100 times will cause the A letter to go off the screen, and add £200 to the counter. After about 1 second, the A, B, and C letters will come back on the computer screen. At that time, you can continue to press Button A or switch to Button B or C. During the session, the counter on your computer screen may become larger and £200 will be subtracted. After the £200 is subtracted, the counter will return to its normal size. This means that one of the other persons has subtracted £200 from your counter by pushing Button B on his response panel. The money that this person subtracts from your counter is added to his counter. If you push Button B on your response

panel, the A and C letters will go off the screen. After you have pushed Button B approximately 10 times, the letter B will go off the screen and £200 will be subtracted from the other person's counter. After about 1 second, the B, A, and C letters will come back on the computer screen. You can continue to press Button B and subtract additional money from the other person or switch to Button A or C. If you subtract money from the other person, it will not be added to your counter. Remember, money subtracted from your counter by the other person is added to that person's counter. If you push Button C on your response panel, the A and B letters will go off the screen. After you have pushed Button C approximately 10 times, the letter C will go off the screen and your earnings displayed on the counter will be protected from subtractions initiated by the other person for some period of time. After about 1 second, the A, B, and C letters will come back on the computer screen. You can continue to press Button C or switch to Button A or B." No additional information regarding the procedure was provided. Portions of the instructions were repeated if the subjects asked questions.

2.5. Point Subtraction Aggression Paradigm

The PSAP software program was used to measure aggressive, escape, and non-aggressive responding.

2.6. Response options

During experimental sessions subjects were provided with three response options: (1) a monetary reinforced response, (2) an aggressive response, and (3) an escape response. Pressing Button A was maintained by a fixed ratio (FR) 100, i.e., 100 consecutive responses, schedule of monetary reinforcement. Completion of the FR 100 on Button A incremented the counter by £200. Subjects were paid the amount shown on their counter at the end of the session. Ten consecutive presses on Button B (FR 10) ostensibly resulted in the subtraction of £200 from another fictitious person paired with the subject during the session. Responding on Button B was defined as aggressive, since such responding ostensibly resulted in the presentation of an aversive stimulus, i.e., loss of money, to another person. The Button C was used to make escape responses. Subjects were told that 10 Button C presses (FR 10) would protect their counter from monetary subtractions for a variable period of time. The protection lasted 250 s. Once a subject selected Button A, B, or C, then only that response option was available until the required ratio of 10 or 100 responses was completed, and then all three response options were available.

2.7. Provocation

Subtracting money from the subjects occasioned aggressive responding. Monetary subtractions were presented randomly via a computer program, which selected intervals between 6 and 120 s for successive subtractions. These monetary subtractions were attributed to the fictitious other person paired with the subject.

2.8. *Consequences of aggressive and escape responding*

Aggressive and escape responding were maintained by the initiation of provocation-free intervals during which no money was subtracted from the subjects. Besides ostensibly subtracting money from the other person (Option B) or protecting their earnings (Option C), completing an FR 10 on either Button B or C also initiated a 200-s interval during which no additional subtractions occurred. After the 250-s interval elapsed, monetary subtractions were again presented. At least one £200 subtraction had to occur before each 250-s provocation-free interval could be initiated. These contingencies ensured that subjects could not avoid monetary subtractions, but they could reduce the number of subtractions occurring in each session by responding on Button B and/or Button C. Thus, subjects were periodically provoked throughout the session and in the absence of aggressive or escape responding, 20–25 subtractions were presented in a session.

2.9. *Procedure*

Subjects participated in three PSAP sessions 25 min each, conducted at 2:30, 3:30, and 4:30 p.m. Subjects were given a 30-min break outside the testing chamber between each PSAP session. Between sessions, subjects waited in a common area containing magazines. All the subjects fasted from food and drink at least 3 h before the time of the study. Subjects did not receive any information regarding session duration or the number of sessions.

2.10. *Evaluation of instructional deception for PSAP sessions*

Subjects were given a questionnaire at the end of the day that asked them: (1) to describe the other subject and (2) to estimate whether they had subtracted more or less money than the other subject. This questionnaire is used routinely to assess whether or not the instructional deception regarding the other person had been established and maintained throughout the experiment.

2.11. *Cardiovascular measures*

Heart rate (HR) and systolic and diastolic blood pressure (SBP and DBP, respectively) were measured before starting the three sessions and after their completion.

2.12. *Endocrine measures*

For the hormonal assays (ACTH and CORT), EDTA-decoagulated blood was drawn immediately before the first session (Time 0) and immediately after each session (Times 30, 90, and 150 min) through a catheter inserted in a vein 30 min before starting the test and kept patent by saline infusion. Blood samples were immediately centrifuged in the cold and the plasma was frozen at -80°C until assayed. Previous evaluations of two basal blood

samples, 30 min from one another, evidenced that the second baseline hormonal value was not influenced by intravenous insertion (Gerra et al., 1998; Kirschbaum, Pirke, & Hellhammer, 1993), suggesting that the emotional state was not significantly changed 30 min after the insertion: The catheter was not perceived as a stressful stimulus at Time 0 and did not consistently affect the behavioral measures.

CORT plasma concentrations were measured utilizing a competitive enzyme immunoassay by commercial kits (AIA-PACK, Eurogenetics Italy, Torino, Italy). ACTH was measured by commercial kits (Medical System DPC, Immulite, Los Angeles, CA, USA).

The determination of EPI and NE was carried out by means of high-performance liquid chromatography with electrochemical detection (Raggi et al., 1999). The mobile phase was composed of methanol (2.5%) and an aqueous solution of citric acid, EDTA, and sodium 1-octanesulfonate at pH 2.9 (97.5%); the stationary phase was a reversed phase C8 column (150 × 4.6 mm, id: 5 μm). An accurate solid-phase extraction procedure of the catecholamines from human plasma was carried out on Oasis HLB cartridges, after catecholamine complexation with diphenylborate.

The intraassay and interassay coefficients of variation were 3.7% and 7.5% for CORT, 6% and 10% for ACTH, 4% and 10% for NE, and 5% and 12% for EPI. Assay sensitivities were 0.3 nmol/l for CORT, 15 pg/ml for ACTH, and 1 pg/ml for NE and EPI.

2.13. Statistical analysis

A repeated-measures analysis of variance (ANOVA), with session (1–3) as the within-subject factor, and subject group (Ecstasy subjects vs. controls) as the between-subject factor, was used to compare aggressive, escape, and point-maintained responses (number of responses per minute) between Ecstasy users and healthy controls. Post hoc tests were used to determine individual data point differences.

Hormonal responses during the three sessions at Times 0, 30, 90, and 150 min, were measured as mean of the areas under the curves (mean AUCs ± S.E.) of CORT, ACTH, EPI, and NE plasma levels, and the AUCs were compared between Ecstasy users and controls with ANOVA. The differences in the hormonal AUCs represented the individual's endocrine pattern associated with aggressive responding.

Psychometric scores (BDHI) were compared between the two groups using independent *t* test.

Pearson analysis was used for the correlations between hormonal measures (mean AUCs) and aggressive, escape, and point-maintained responses (number of responses per minute), psychometric variables and aggressive behavioral responses, Ecstasy doses (or extent of Ecstasy exposure: number of tablets reported) and behavioral responses.

3. Results

The questionnaires revealed that all the Ecstasy users and subjects believed they were paired up with one opponent across their three PSAP sessions.

3.1. Cardiovascular measures

Mean basal values of HR, of SBP and DBP were not significantly different in the group of Ecstasy users (Group A) and controls (B subjects). HR and blood pressure changes during the three PSAP sessions are reported in Table 1. During the PSAP sessions, HR increased significantly in both groups, but more significantly in Group A. Repeated-measures ANOVA revealed a significant difference between Groups A and B HR increases ($F=7.4$, $df=76$, $P<.01$). The same was true for SBP increases. Repeated-measures ANOVA demonstrated a significant difference between Groups A and B for SBP increases ($F=8.99$, $df=76$, $P<.005$). Instead, DBP did not significantly change in either group.

3.2. Psychometric measures

Ecstasy subjects scored significantly higher on BDHI Direct Aggression and Irritability scales than did controls ($t=3.87$, $df=38$, $P<.001$; $t=3.51$, $df=38$, $P<.001$) (Table 2).

3.3. Point-maintained responses (PSAP)

Money-earning (point maintained) responses were lower, but not significantly, in Group A subjects (Ecstasy subjects) than in B subjects (controls), during the first session. No differences between A and B subjects point maintained responses were found in the following two sessions (Fig. 1).

3.4. Aggressive responding (PSAP)

The Ecstasy subjects emitted significantly more aggressive responses across all three PSAP sessions compared to control subjects (Fig. 2). Repeated-measures ANOVA revealed a significant main effect of group ($F=20.74$, $df=76$, $P<.001$) on aggressive responding and a significant effect of session ($F=8.02$, $df=76$, $P<.001$). Post hoc test determined that aggressive responses (individual data points) were significantly higher during the first session, in comparison with the second and the third sessions both in Ecstasy users (Group A: $F=4.9$, $P<.05$; $F=5.27$, $P<.01$) and in controls (Group B: $F=22.02$, $P<.001$; $F=20.12$, $P<.001$).

Table 2

Psychometric measures (mean±S.E.) in Ecstasy users (Group A) and controls (Group B)

BDHI Direct Aggressiveness		BDHI Irritability	
Group A	Group B	Group A	Group B
59.8±3.72	43.4±1.7	57.4±3.51	44.2±1.9
$t=3.87$, $P<.001$		$t=3.51$, $P<.002$	

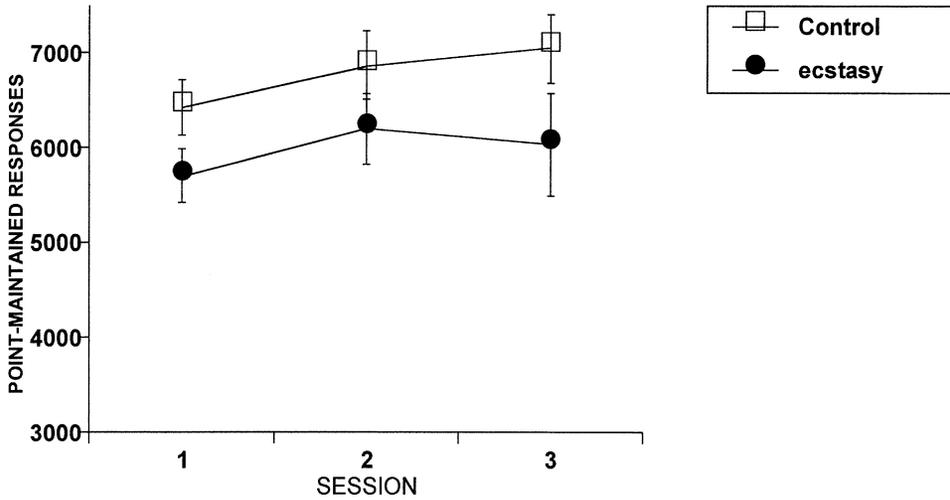


Fig. 1. Point-maintained responses (mean ± S.E.) at PSAP during first, second, and third sessions in Group A subjects (Ecstasy users, • - - - - •) and Group B subjects (controls, □ - - - - □).

3.5. Escape responding (PSAP)

Escape responses were slightly, but not significantly, higher in Ecstasy users than in normal controls across the three PSAP sessions: There was no significant main effect of group, session, or Session × Group interaction in escape responding. Group A subjects

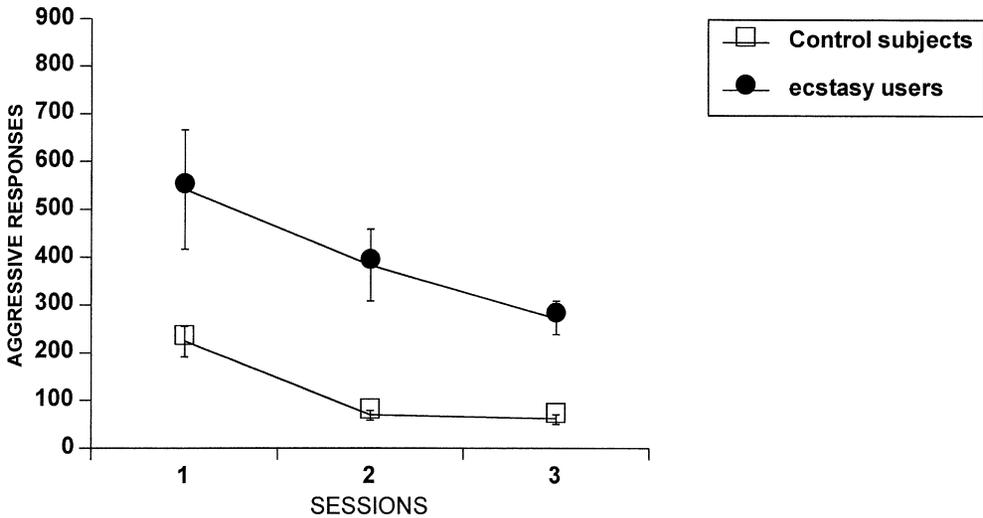


Fig. 2. Aggressive responses (mean ± S.E.) during first, second, and third sessions in Group A subjects (Ecstasy users, • - - - - •) and Group B subjects (controls, □ - - - - □).

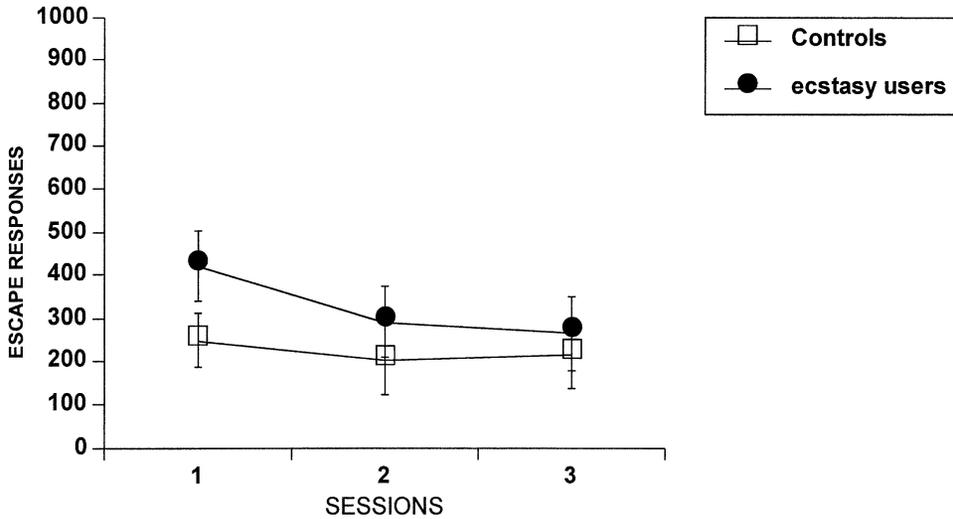


Fig. 3. Escape responses (mean \pm S.E.) at PSAP during first, second, and third sessions in Group A subjects (Ecstasy users, \bullet - - - - \bullet) and Group B subjects (controls, \square - - - - \square).

showed higher escape responses during the first session, in comparison with Group B subjects ($F=6.5$, $df=38$, $P<.05$), at the post hoc test (Fig. 3).

3.6. Hormonal findings

Mean basal values of plasma concentrations of NE and EPI were not significantly different in the two groups of subjects (NE: Group A—Ecstasy users: 0.713 ± 0.1 pg/ml vs. Group B—controls: 0.54 ± 0.084 pg/ml; EPI: Group A—Ecstasy users: 0.63 ± 0.07 pg/ml vs. Group B—controls: 0.54 ± 0.084 pg/ml). Basal levels of ACTH and CORT were significantly higher in Group A than in Group B (ACTH: Group A—Ecstasy users: 20.27 ± 1.83 pg/ml vs. Group B—controls: 13.15 ± 0.59 pg/ml; CORT: Group A—Ecstasy users: 351.09 ± 28.51 pg/ml vs. Group B—controls: 229.03 ± 28.99 pg/ml) ($F=13.73$, $df=38$, $P<.001$; $F=9.51$, $df=38$, $P<.005$).

Across the three PSAP sessions, NE concentrations (Fig. 4) were more significantly increased in Group A than in Group B. Repeated-measures ANOVA revealed significant effects of group ($F=10.34$, $df=38$, $P<.001$), session ($F=13.83$, $df=3$, $P<.001$), and Session \times Group interaction ($F=5.43$, $df=114$, $P<.05$). Post hoc test determined that NE values (individual data points) were significantly higher after the first, second, and third sessions, in comparison to baseline values, in Ecstasy users ($F=6.5$, $P<.01$; $F=8.5$, $P<.005$; $F=25.93$, $P<.001$, respectively), and after the third session in Group B ($F=6.79$, $P<.01$; $F=24.28$, $P<.001$). NE AUCs were significantly larger in Group A than in Group B (Group A = 85.5 ± 5.6 vs. Group B = 35.67 ± 5.19 , $t=3.21$, $df=38$, $P<.005$).

Similarly, EPI concentrations (Fig. 5) were more significantly increased in Group A than in Group B. Repeated-measures ANOVA revealed significant effects of group ($F=6.3$, $df=38$,

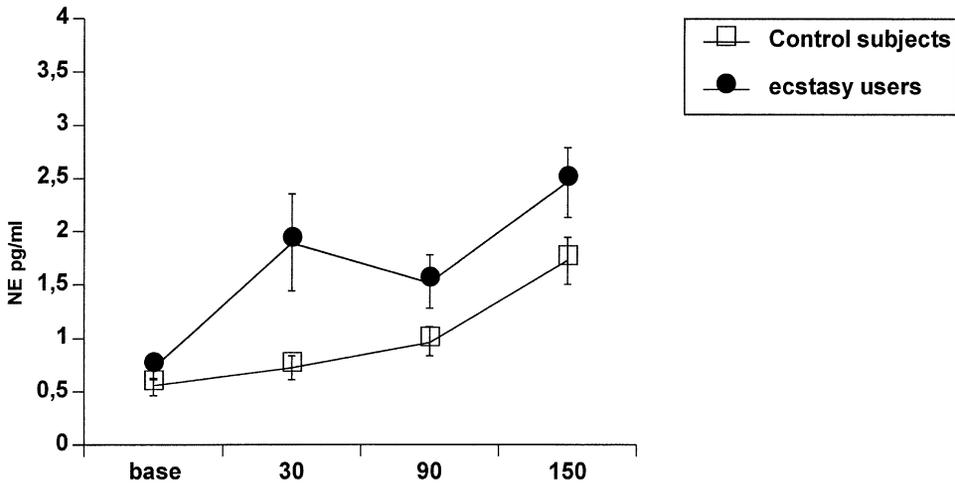


Fig. 4. NE (mean \pm S.E.) responses during PSAP before first session and after first, second, and third sessions in Group A subjects (Ecstasy users, • - - - •) and Group B subjects (controls, □ - - - □).

$P < .054$), session ($F = 11.97$, $df = 3$, $P < .001$), and Session \times Group interaction ($F = 4.56$, $df = 114$, $P < .01$). Post hoc test determined that EPI individual data points were significantly higher after the first, second, and third session, in comparison to baseline values, in Ecstasy users ($F = 14.13$, $P < .001$; $F = 12.2$, $P < .001$; $F = 11.63$, $P < .005$, respectively) and after the second and third sessions in Group B ($F = 6.03$, $P < .05$; $F = 6.65$, $P < .01$, respectively). EPI

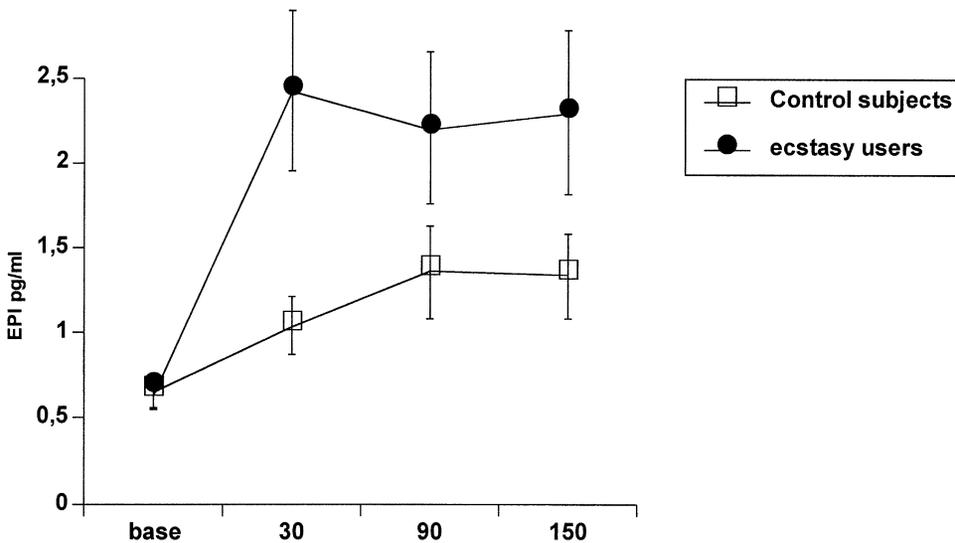


Fig. 5. EPI (mean \pm S.E.) responses during PSAP before first session and after first, second, and third sessions in Group A subjects (Ecstasy users, • - - - •) and Group B subjects (controls, □ - - - □).

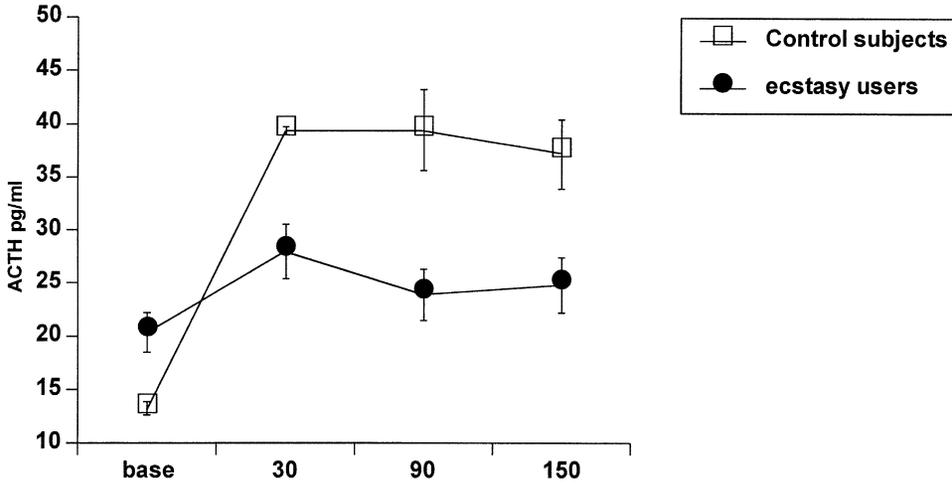


Fig. 6. ACTH (mean \pm S.E.) responses during PSAP before first session and after first, second, and third sessions in Group A subjects (Ecstasy users, \bullet - - - - \bullet) and Group B subjects (controls, \square - - - - \square).

AUCs were significantly larger in Group A than in Group B (Group A = 130.0 ± 17.62 vs. Group B = 43.00 ± 16.79 , $t = 2.48$, $df = 28$, $P < .05$).

In contrast with catecholamine responses, ACTH concentrations rose significantly after the stimulus (Fig. 6) more in Group B (control subjects) than in Group A. Repeated-measures ANOVA revealed a significant effect of group ($F = 5.74$, $df = 38$, $P < .05$), session ($F = 33.43$, $df = 3$, $P < .001$), and Session \times Group interaction ($F = 14.7$, $df = 114$, $P < .001$). Post hoc test determined that ACTH individual data points were significantly higher after the first, second, and third session, in comparison to baseline values, in normal subjects ($F = 37.25$, $P < .001$; $F = 45.38$, $P < .001$; $F = 52.55$, $P < .001$, respectively) and only after the first session ($F = 5.76$, $P < .05$) in Ecstasy users. ACTH AUCs were significantly larger in Group B than in Group A (Group A = 401.1 ± 87.61 vs. Group B = 1924.67 ± 245.79 , $t = 5.83$, $df = 38$, $P < .001$).

CORT concentrations rose significantly after the stimulus (Fig. 7) both in Ecstasy users and in control. Repeated-measures ANOVA did not reveal a significant effect of group, session, and Session \times Group interaction. Post hoc test determined that CORT individual data points were significantly higher after the first session, but not in the other two sessions, in comparison to baseline values, in Ecstasy users ($F = 6.1$, $P < .01$). In contrast, in control subjects, CORT individual data points were significantly higher after the first, second, and third sessions, in comparison to baseline values ($F = 31.70$, $P < .001$; $F = 14.57$, $P < .001$; $F = 12.42$, $P < .001$, respectively). CORT AUCs were not significantly different in the two groups.

3.7. Correlations between PSAP responding and psychometric instruments

Aggressive responding (mean of responses per minute) positively correlated with Buss–Durkee scores at Direct Aggressiveness subscale and at Irritability subscale, both in Ecstasy

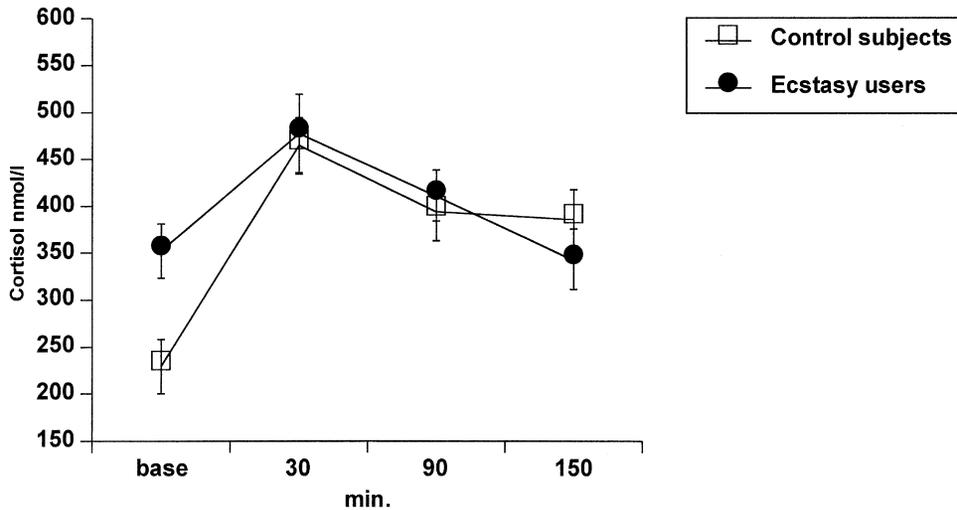


Fig. 7. CORT (mean \pm S.E.) responses during PSAP before first session and after first, second, and third sessions in Group A subjects (Ecstasy users, \bullet - - - \bullet) and Group B subjects (controls, \square - - - \square).

users and controls (Group A: $r = .63$, $P < .01$; $r = .56$, $P < .05$; Group B: $P < .001$, $r = .78$; $r = .64$, $P < .01$).

3.8. Correlations between PSAP responding and hormonal measures (AUCs)

NE, EPI, and CORT AUCs obtained during aggressive sessions correlated positively with PSAP aggressive responding measures both in Ecstasy patients and healthy controls (respectively, Group A: $r = .83$, $P < .001$; $r = .78$, $P < .005$; $r = .64$, $P < .01$; Group B: $r = .53$, $P < .05$; $r = .65$, $P < .01$; $r = .52$, $P < .05$). No other statistical correlation was found between hormonal findings and aggressiveness responding.

3.9. Correlations between PSAP responding and cardiovascular measures

HR and SBP changes obtained during aggressive sessions correlated positively with PSAP aggressive responding measures both in Ecstasy users and healthy controls (respectively, Group A: $r = .54$, $P < .05$; $r = .6$, $P < .01$; Group B: $r = .52$, $P < .05$; $r = .53$, $P < .05$).

3.10. Correlations between PSAP responding/hormonal measures (AUCs) and Ecstasy exposure extent

Aggressive responses to PSAP significantly correlated with the extent of exposure to Ecstasy (number of tablets, $r = .78$, $P < .001$).

No significant correlation was evidenced between psychometric measures (BDHI) and hormonal correlates of aggressive behavior.

4. Discussion

Our findings evidence increased levels of outward-directed aggressiveness in Ecstasy users: Aggressive responses to provocation were higher in the subjects exposed to MDMA than those of healthy subjects who have never used Ecstasy, during the entire laboratory procedure. In comparison with our data obtained with the same experimental paradigm in methadone patients, the subjects included in the present study who have taken Ecstasy showed during the first session even more aggressiveness than heroin addicts (Gerra et al., in press). These results are in agreement with the reports demonstrating more impulsiveness and hostility in heavy Ecstasy users (Morgan, 1998b; Parrott et al., 2000) and with our previous psychometric measures that evidenced high levels of aggressiveness 3 weeks after MDMA discontinuation (Gerra et al., 2000). The opposite findings reported by McCann et al. (1994), who observed reduced aggressiveness in Ecstasy users, may be due to the differences in the subjects samples included in these studies, in relationship to the history of substance abuse: In fact, our subjects, as opposed from those of McCann et al., did not report a long-lasting history of dependence or continuous abuse of many drugs other than Ecstasy. Another factor that could have influenced the evaluation of aggressive behavior in Ecstasy users is the time after drug discontinuation: In fact, our previous findings showed that aggressiveness scores decreased significantly after 12 months of abstinence from MDMA, in comparison with psychometric measures during early abstinence (Gerra et al., 2000).

The high levels of aggressiveness in response to provocative events was not unexpected in Ecstasy users, who showed in many studies a consistent impairment of serotonin function (Gerra et al., 1998; McCann et al., 1994, 1998; Ricaurte, McCann, Szabo, & Scheffel, 2000), which was found to be involved in aggressive behavior control (Brown et al., 1982; Coccaro, 1989; Virkkunen & Linnoila, 1993).

Although it is difficult to compare data obtained with the same method in different research centers, our Ecstasy users showed aggressive responses higher than those measured by Allen et al. (1997) in abstinent subjects with a history of substance abuse, supporting the hypothesis of a specific action of Ecstasy in influencing aggressive behavior.

The difference in aggressive behavior measured between MDMA users and control subjects could be due to reduced aggressiveness of the healthy subjects included in the study: Hospital staff members of control group, as in the case of health workers, could have been especially selected for low level of aggressiveness. Fortunately, our control subjects did not show significantly lower scores at BDHI, particularly for Irritability subscale, in comparison with the mean levels of control subjects evaluated by Castrogiovanni et al. (1993), utilizing the Italian version of the QTA. Ecstasy users of our study, on the other side, showed higher scores at BDHI than those reported as normal controls by Castrogiovanni et al.

Ecstasy seems to be unable to affect monetary-reinforced responses, expressed as the capacity to earn money during the experimental paradigm: The subjects showed a slight, but not significant, reduction of point-maintained responses in comparison with controls, suggesting that MDMA has not impaired, at least in these subjects, the ability to focus on a behavioral challenge and to fight for positive achievements. In contrast, prior findings obtained in methadone patients showed a reduced ability to earn money and focus on task

achievements (Gerra et al., in press), increasing the evidence on methadone maintenance about an inferior test performance (Darke, Sims, McDonald, & Wickes, 2000; Specka et al., 2000), which was not found in Ecstasy users.

Significantly higher levels of escape responses during the first session in Ecstasy users, in comparison with our control subjects and with Allen et al.'s subjects, who abused drugs other than Ecstasy, may suggest a tendency for behavioral inhibition in MDMA subjects in front of unknown and unexpected stimuli and could be related with depressive mood, inactivation, emotional excitability (Gamma et al., 2000), anxiety proneness (Parrott et al., 2000; Wareing, Fisk, & Murphy, 2000), and difficulties in social coping (Gerra et al., 1999) that were previously reported in association with Ecstasy use.

High basal levels of ACTH and CORT in Ecstasy users may be attributable to a variety of reasons: possibly increased worry and the perception of the challenge as more stressful could be revealed by more pronounced escape behavior in Ecstasy subjects, in comparison with controls, during the initial phase of the paradigm, and may explain the higher basal levels of stress hormones as an anticipatory reaction (Gerra et al., 1998). Higher CORT basal levels in Ecstasy users may represent the neuroendocrine pattern reported in depressed adolescents at risk for substance abuse: HPA axis was found active when the system is normally quiescent and unable to express any response during coping processes with stressful conditions (Rao et al., 1999). Ecstasy has been also demonstrated to directly increase CORT (Mas et al., 1999) and ACTH plasma levels in humans (Grob, Poland, Chang, & Ernst, 1996), possibly being responsible of changes in HPA axis function that were found involved in affective states of different psychopathologies (Boyer, 2000; King, Barkley, & Barrett, 1998).

NE and EPI hyperreactivity during experimental aggressiveness among Ecstasy subjects and a positive correlation between NE AUCs and PSAP aggressive responses in all participant might indirectly represent the involvement of central sympathetic system in the modulation of aggressive behavior (Netter, Henning, & Roed, 1996; Zuckerman, 1994). NE increased responses to stressful stimuli in more aggressive subjects have been previously observed in healthy subjects, utilizing a modified version of Cherek paradigm (Gerra et al., 1997) and in adolescents submitted to a mixed model of psychological stress (Gerra et al., 1998). However, there are many interpretative difficulties with such evidence. First, the association between NE–EPI and aggressiveness may indicate that catecholamines modulate the quantity and quality of aggressiveness through their neuroendocrine effects (Mayerhofer, Bartke, & Began, 1993). Secondly, aggressiveness, as an aspecific distress condition, could be a cause and not a consequence of increased NE and EPI (Wyatt, Portnoy, Kupfer, & Snyder, 1971). Moreover, MDMA action seems to specifically affect noradrenergic system influencing the monoamine transporter (Rothman et al., 2000, 2001). Thus, catecholamines more consistent rise in Ecstasy users could be partly attributed to a long-lasting direct pharmacological action of MDMA.

Since we found noradrenergic hyperresponsiveness during PSAP also in methadone patients (Gerra et al., in press), a possible psychobiological pattern, common to substance abusers and independent from the specificity of drug history, cannot be excluded: Both Ecstasy users and methadone patients showed higher reactivity to provocative events, with possible more emotional arousal and related sympathetic activation.

The impairment of ACTH responses in Ecstasy users, with a dissociation between catecholamines secretion and pituitary function, and a well-maintained CORT response to PSAP could reflect, on one side, a reduced reactivity of hypothalamus–pituitary axis in the presence of a persistent basal activation induced by MDMA (Grob et al., 1996). On the other hand, possible continuous stimulation exerted by MDMA on adrenals function (Mas et al., 1999) may have primarily induced a basal CORT hypersecretion with the consequent inhibition of ACTH release during stress exposure through a negative feedback mechanism (Williams, Wilson, & Foster, 1985).

In addition, a derangement in HPA axis function in Ecstasy users might be due to the serotonergic changes induced by prolonged exposure to Ecstasy: MDMA users showed significantly reduced CORT responses to serotonergic agonists (Gerra et al., 1998; McCann et al., 1999), and the striatal serotonin depletion in these subjects (Kish, Furukawa, Ang, Vorce, & Kalasinsky, 2000) could be responsible of a defective serotonergic control of the pituitary–adrenal axis that has been reported in other pathological conditions in humans (Volpi et al., 1997). Nevertheless, in experimental animals, the inhibition of the 5HT pathway significantly reduces ACTH release in response to experimental stimuli (Giovambattista, Chisari, & Spinedi, 1997).

Furthermore, experimental evidence has shown a “cross-talk” between the noradrenergic and serotonergic systems (Leonard, 2000) suggesting that also the sympathetic pattern of our Ecstasy users may have been influenced by the deficit of serotonin function.

The correlation of behavioral aggressive responses with the extent of the exposure to Ecstasy, although obtained in a small sample of subjects, again seems to indicate that aggressiveness higher levels may be caused by the Ecstasy pharmacological action, persisting after 3 weeks of abstinence. Probably due to the small number of subjects included in our study, a correlation between neuroendocrine findings and the extent of exposure to Ecstasy was not evidenced, suggesting that the psychobiological condition associated with Ecstasy use reflects a more complex monoaminergic imbalance. In any case, aggressive responses in Ecstasy users, significantly higher than those observed in the same experimental condition in methadone users, suggest that these behavioral characteristics are specific to MDMA users and not just drug users in general.

Otherwise, the hypothesis of psychobiological changes preexisting to Ecstasy intake, associated with personality traits and affecting aggressive behavior (Kelly & Cherek, 1993), cannot be completely excluded by our findings. Authors using the PSAP to investigate substance abusers evidenced that aggression is most dependent on the individual’s previous aggressive behavior (Moeller et al., 1997). Following this second hypothesis, the extent of the exposure to Ecstasy may be interpreted not simply as the cause of behavioral changes, but also as an increased proneness to use Ecstasy characterizing more aggressive individuals.

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