Psychopharmacology (2004) 173:425–433
DOI 10.1007/s00213-003-1713-6

ORIGINAL INVESTIGATION

H. Valerie Curran · Huw Rees · Thomas Hoare · Rosa Hoshi · Alyson Bond

Empathy and aggression: two faces of ecstasy? A study of interpretative cognitive bias and mood change in ecstasy users

Received: 15 May 2003 / Accepted: 7 August 2003 / Published online: 20 January 2004

Abstract *Rationale:* As central 5-hydroxytryptamine (5-HT) is attenuated for a period following a single dose of MDMA ("ecstasy") and low 5-HT is associated with aggression, then MDMA users may be more aggressive in the days following an acute dose of the drug. *Objective:* This study therefore aimed to determine if acute use of MDMA is associated with aggression 4 and 7 days later. *Methods:* Twenty-nine MDMA users and 32 controls were compared on self-rated aggression and depression on the night of drug use (day 0), 4 and 7 days later. On day 4, participants performed an interpretative bias task in which they processed ambiguous sentences that could be interpreted in either an aggressive or neutral way (e.g. "The painter drew the knife"). *Results:* MDMA users had faster response times in completing ambiguous aggressive sentences than neutral sentences; controls showed the opposite pattern of performance. In a subsequent recognition task, MDMA users were more confident in judging, and responded faster to, aggressive than neutral sentences; controls again showed the opposite pattern of effects. The level of aggressive interpretative bias positively correlated with extent of MDMA use. Midweek, MDMA users had higher self-rated aggression and depression scores than controls; on day 7, scores of both groups were similar. *Conclusions:* MDMA users display a cognitive bias towards interpreting ambiguous information in an aggressive way a few days after taking the drug. Self-rated mid-week low mood and mid-week aggression do not persist 7 days after use of the drug. This pattern of results is consistent both with the acute and residual effects of MDMA on central 5-HT and with the notion that 5-HT plays a role in modulating human aggression.

Keywords MDMA · Ecstasy · Aggression · Depression · Cognitive bias · Interpretative bias

H. V. Curran (✉) · H. Rees · T. Hoare · R. Hoshi
Clinical Psychopharmacology Unit,
University College London,
Gower Street, London, WC1 6BT, UK
e-mail: v.curran@ucl.ac.uk
Tel.: +44-207-6791898
Fax: +44-207-9161989

A. Bond
National Addiction Centre,
Institute of Psychiatry,
London, UK

Introduction

MDMA (±3,4-methylenedioxymethamphetamine, "ecstasy") is a popular recreational drug taken for its acute effects that include increased euphoria, energy and empathy (Vollenweider et al. 1998; Cami et al. 2000). Acutely, MDMA releases serotonin (5-HT), dopamine and norepinephrine. However, its main action is on 5-HT: acutely, it causes an efflux of stored 5-HT from nerve terminals, prevents reuptake of 5-HT from the synaptic cleft and inhibits tryptophan hydroxylase, thereby inhibiting the synthesis of new 5-HT (Schmidt et al. 1986; McKenna and Peroutka 1990). An acute dose of MDMA can release around 80% of central serotonin stores (Green et al 1995) and this, combined with inhibition of tryptophan hydroxylase activity, means that the attenuation of central 5-HT may persist for days. This attenuation may have implications for the functioning of MDMA users for a period after an acute dose as depletion of brain 5-HT may mean that functions modulated by 5-HT are compromised.

5-HT is thought to be involved in the modulation of a wide variety of functions, including the regulation of mood and aggression (Young and Leyton 2002). Low 5-HT has been implicated in the aetiology of depression. For example, rapid depletion of central 5-HT by tryptophan depletion causes relapse of depression in women who had previously recovered from clinical depression (Smith et al. 1997) and the mechanism of action of antidepressants may involve increasing the availability of central 5-HT (Goodwin et al. 1985; Cowen 1991). Thus, the depletion of 5-HT for a period following ingestion of MDMA may be associated with depressed mood. Indeed,

three studies to date have reported low mood in recreational users of MDMA a few days after an acute dose (Curran and Travill 1997; Parrott and Lasky 1998; Verheyden et al. 2002).

Aggression in humans has also been linked to deficits in 5-HT (Brown et al. 1979, Coccaro et al. 1989; Linnoila and Virkkunen 1992, 1993; Cleare and Bond 1997). A few studies have compared a group of MDMA users with controls on measures of aggression. Gerra et al. (1998) found that male MDMA users who had not used MDMA for 3 weeks scored higher than MDMA-naive controls on measures of direct aggressiveness. More recently, Gerra et al (2001) assessed 12 MDMA users (abstinent for 3 weeks) with healthy controls (hospital staff) on the "point subtraction aggression paradigm", a behavioural provocation task in which participants are led to believe that they and an apparent "competitor" can deduct money from each other. They found significantly higher aggressive responses in MDMA users and level of aggressive responses correlated highly with estimated lifetime consumption of ecstasy. Curran and Verheyden (2003) found that 32 men who had stopped using MDMA for at least a year (mean 2.4 years) scored significantly higher on the Aggression Questionnaire (Buss and Perry 1992) than either 32 matched current users of the drug or 32 MDMA naive controls. However, results of these cross-sectional studies have not always been consistent. For example, McCann et al. (1994) reported that MDMA users had lower hostility scores than non-user controls.

Studies which have manipulated brain 5-HT using rapid tryptophan depletion have shown depletion to increase aggression relative to an enhancement or control condition (Cleare and Bond 1995; Bond et al. 2001). Thus, acute release of 5-HT by MDMA would be associated with the opposite of aggression (empathy and pro-social behaviour) but several days later, depletion of 5-HT may be associated with antipathy and aggression. We recently confirmed this prediction in a comparison of 40 MDMA users with 40 non-MDMA, polydrug using controls (Verheyden et al. 2002). MDMA users on the night of MDMA use displayed lower self-rated aggression than controls but much higher levels 4 days after consuming the drug. This pattern of effects accords with increased release of 5-HT on the night of MDMA use and low 5-HT a few days later.

Self-report measures of aggression may be contaminated by social desirability effects. More convincing evidence of mid-week aggression in MDMA users would derive from an objective measure of aggression. Behavioural provocation tasks are impracticable in natural environments where people take recreational drugs. An alternative approach to objective measurement of aggression would be to use a cognitive bias assessment.

Based on Novaco's (1978) cognitive model of anger arousal, Copello and Tata (1990) developed a computer task to assess cognitive biases in the interpretation of sentences that were ambiguous for aggressive or neutral meanings (e.g. "The painter drew the knife"). They assessed three groups of participants: violent offenders, non-violent offenders and non-offending controls. Both offender groups were more likely to interpret ambiguous sentences in an aggressive manner whilst non-offenders showed the opposite pattern. Further, the tendency to infer aggression positively correlated with self-rated hostility. Copello and Tata's task also included ambiguous sentences concerned with general anxiety. Recently, the ambiguous sentences task has been further extended and developed (by A.J.B.) to exclude general anxiety items and focus specifically on aggressive versus neutral material. This version also provides more detailed measures of performance in requiring confidence ratings in recognition and automatically recording response times in each stage of the task. A pilot study using this task with 40 healthy volunteers found that hostility correlated positively with measures of aggressive interpretative bias.

The present study therefore aimed to determine whether our previous findings of increased subjective aggression 4 days after MDMA use (Verheyden et al. 2002) would be replicated using the objective cognitive measures deriving from the recently developed ambiguous sentences task. A second aim was to monitor changes in self-rated aggression and depression from acute MDMA use through to 7 days later. This is because no study to date has assessed residual effects of MDMA beyond 4 days and evidence from research with rodents suggests that low 5-HT may persist as long as 3 weeks following an acute dose (Rattray 1991). We reasoned that if depressed or aggressive mood persisted until the weekend following MDMA use, it might lead to "self-medication" with another dose of MDMA.

Materials and methods

Design and participants

An independent group, repeated measures design was used to compare MDMA users with controls on 3 days: the night of drug use (day 0), 4 and 7 days later. All participants were recruited using the snowball technique (Solowij et al. 1992) in parties and clubs. The MDMA users had all consumed the drug on the first test night (day 0). Controls were either MDMA naive or had tried the drug once but used other recreational drugs such as cannabis on a regular basis. The study was approved by the institutional ethics committee and all participants gave written informed consent on day 0 and again on day 4.

Procedure

Participants were assessed on the evening of day 0 and then again on days 4 and 7. On day 0 volunteers were taken individually to a quiet area, given an information sheet and asked for written consent. They then completed the assessments detailed below. Participants were asked to abstain from taking illicit drugs for the next 7 days and arrangements were made to meet up 4 days later. Follow-up testing on subsequent days was generally in the participant's home. On day 4 they were again asked for informed consent and then completed the day 0 assessments along with the ambiguous sentences task, trait measures of mood and a history of drug use. On day 7, the initial day 0 assessments were repeated.

Mood assessments on days 0, 4 and 7

To assess current mood state the following visual analogue scales were used: the Aggression Rating Scale (ARS; Bond and Lader 1986), Mood Rating Scale (MRS; Bond and Lader 1974) and a 'subjective effects scale'. Two additional visual analogue scales were given on days 4 and 7 only to assess disturbances of sleep patterns and loss of appetite over the previous 3-day period.

The standard 21-item Beck Depression Inventory (BDI; Beck 1978) was modified by changing the instructions at the top of the inventory to request participants to rate how they had been feeling over the last 3 days (Curran and Travill 1997). Pulse rate was taken on each of the 3 days.

Interpretative bias task

The extended version (Bond et al., unpublished data) of the ambiguous sentences task initially designed by Copello and Tata (1990) was used. The stimulus materials consisted of 36 unambiguous neutral filler sentences interspersed with 24 ambiguous sentences, which could be interpreted as either aggressive or neutral (e.g. "The painter drew the knife."). For the subsequent recognition task, 72 sentences were prepared of which 48 sentences were presented to any given subject. For the aggressive ambiguous sentences, 24 disambiguated versions were presented: 12 consistent with an aggressive interpretation (e.g. "The painter pulled out the knife") and 12 consistent with a neutral interpretation (e.g. "The painter sketched the knife"). The remaining 24 sentences consisted of 12 neutral filler sentences with the same meanings as those presented previously but with minor word changes and 12 new unambiguous neutral sentences.

Half the participants in each group were presented one set of disambiguated sentences and the other half the opposite set. The neutral sentences and 12 of the ambiguous aggressive sentences were obtained from Copello and Tata (1990). The additional 12 ambiguous sentences were selected from a pool for plausibility then rated and agreed upon by six independent judges (Bond et al., unpublished data).

Sentence completion

In the first part of the task, participants read the following instructions on the screen of a laptop computer: "A sentence will appear on the screen for a few seconds. The last word will be missing and instead you will see a dotted line –. Following this, two words will appear: one on the upper part of the screen and one on the upper part of the screen. If you think the word on the lower part of the screen completes the sentence then press the top button. If you think that the word on the lower part of the screen completes the sentence then press the lower button". Participants were then presented with 60 sentences in pseudo-random order, (24 aggressive ambiguous; 36 neutral). The sentence with the last word missing was displayed for 4 s, followed by two words, only one of which could logically complete the sentence. Once the participant responded, the next sentence appeared. Reaction time to each sentence was recorded. On completion of this part of the task, participants read aloud the numbers from 100 through to 1, which were displayed on the screen.

Interpretative bias in recognition

For the second stage of the task, the following instructions were read to the participants: "You will now be presented with a series of sentences on the screen. Some of these sentences will have the same meaning as some you saw while carrying out the previous task. I want you to read the sentence carefully and decide whether it is similar in meaning to one that you have previously seen. Press 1 for NO, DEFINITELY NOT. You are certain you did not see a sentence with similar meaning before. Press 2 for NO, PROBABLY NOT. You think you probably did not see a sentence with similar meaning before. Press 3 for YES, PROBABLY DID. You think you probably did see a sentence with similar meaning before. Press 4 for YES, DEFINITELY DID. You are certain you did see a sentence with similar meaning before". The ratings were displayed at the top of the screen throughout. Reaction time to each sentence was recorded. Forty-eight sentences were presented at the rate of one every 10 s.

Other assessments on day 4

Trait measures

The aggression questionnaire (AQ; Buss and Perry 1992) was used to index trait aggression, and the Hospital Anxiety and Depression scale (HADS; Zigmond and Snaith 1983) was used to index trait anxiety and depression.

Drug history

Amount, frequency and duration of use of all psychotropic drugs was recorded as were details of drugs used on day 0. Demographic information (age, gender, height, weight, educational background and employment) was also recorded on day 4.

Statistical analyses

A repeated measures analysis of variance (ANOVA) with group (MDMA users versus controls) as a between subjects factor and day as a within-subjects factor was used on self-rating scores data assessed each day. The 13 variables comprising the ARS showed a high internal consistency on day 0 (Cronbach's α=0.85), 4 (α=0.95) and 7 (α=0.96) and so a mean aggression score for each participant was calculated and used in subsequent analysis. Repeated measures ANOVA was also used for the ambiguous sentences task with group as the between-subjects factor and sentence type (Aggressive versus Neutral) as the within-subjects factor. Pearson product-moment correlations were used to examine relationships between aggression, depression and drug use. All data were analysed using SPSS for Windows version 11.0.

Results

Demographics

In total there were 61 participants aged 19–24 years: 29 ecstasy users (20 males, 9 females) and 32 controls (18 males, 14 females). There were no group differences in age, body mass index, trait aggression (AQ), anxiety or depression (HADS) (Table 1). Highest educational level achieved also revealed no group differences and the majority of participants (22/29 MDMA users; 27/32 controls) were undergraduate or graduate students.

Participants in the MDMA group reported using MDMA a mean of 2.35 (±0.86) days a month, taking 2.71 (±1.50) tablets in a typical session and having used MDMA for 2.72 (±1.42) years. There were no significant group differences in use of cannabis or alcohol (Table 2). All the participants were regular alcohol users and most (20/29 MDMA users; 25/32 controls) were regular cannabis users. Other drug use reported by participants included amphetamines (one MDMA and one control

Table 1 Group means (SD) for age, body mass index (*BMI*), Aggression Questionnaire (*AQ*) score, HADS-A (anxiety) and HADS-D (depression)

	Age	BMI	AQ	HADS-A	HADS-D
MDMA users	21.52 (1.30)	21.3 (1.83)	67.35 (13.56)	5.72 (3.40)	2.48 (2.03)
Controls	21.41 (1.19)	21.6 (2.08)	68.06 (17.62)	5.84 (3.93)	2.38 (2.28)

Table 2 Alcohol and cannabis use by MDMA users and controls: means (SD)

	Controls	MDMA users
Alcohol frequency (days per month)	12.25 (7.39)	9.31 (4.34)
Alcohol typical dose (units per session)	5.69 (3.78)	5.26 (2.41)
Alcohol length of use (years)	5.34 (1.52)	5.57 (1.89)
Cannabis frequency (days per month)	11.16 (8.48)	12.20 (8.90)
Cannabis monthly use (ounces)	0.23 (0.24)	0.50 (0.66)
Cannabis length of use (years)	3.68 (2.02)	3.80 (1.73)

participant), ketamine (one MDMA and one control) and cocaine (eight MDMA and one control).

In terms of drugs used on day 0, 26 participants in each group had drunk alcohol, 11 MDMA users and 19 controls had used cannabis, one in each group had used cocaine and another one per group had used ketamine. Between day 0 and day 4, eight MDMA users and ten controls had used cannabis and 19 participants in each group had used alcohol.

Beck Depression Inventory (BDI)

BDI scores showed a significant group×time interaction [$F(2,58)=38.36$, $P<0.001$], a main effect of time [$F(2,58)=26.01$, $P<0.001$] but not of group ($F<1$). As seen in Fig. 1, MDMA users had lower BDI scores than controls on day 0, higher scores on day 4 and on day 7, scores of the two groups were similar. Covarying gender did not affect the pattern or level of significance of findings.

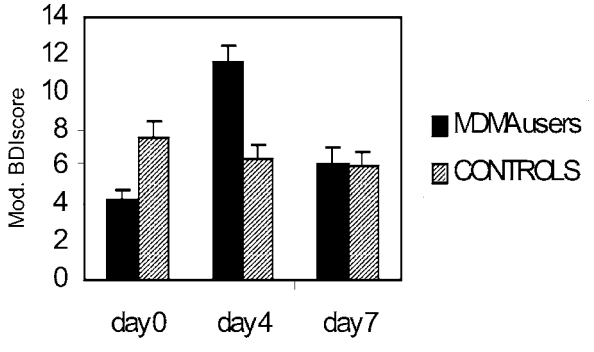

Fig. 1 Mean depression scores on day 0, 4 and 7 for the MDMA group and the control group

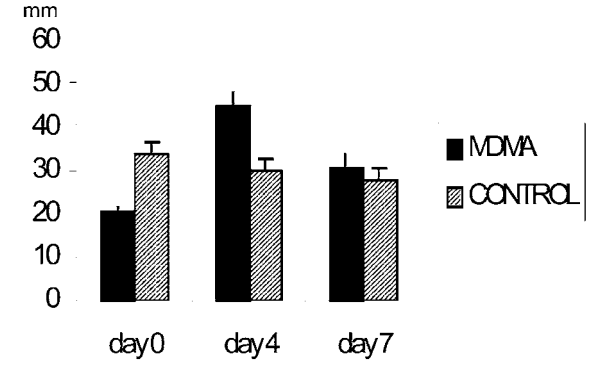

Fig. 2 Mean aggression (*ARS*) scores in mm on day 0, day 4 and day 7 for the MDMA group and the control group

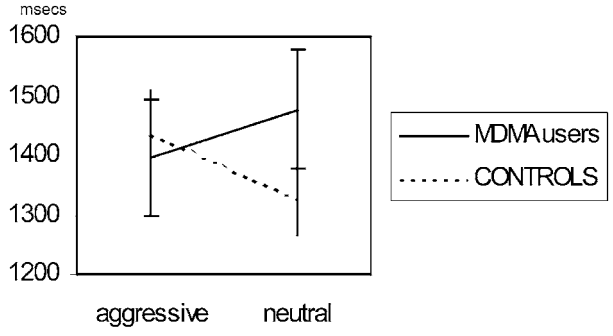

Fig. 3 Mean RTs to aggressive and neutral sentences for the MDMA group and the control group

Aggression rating scale (ARS)

A significant group×time interaction emerged on state aggression ratings [$F(2,58)=20.88$, $P<0.001$], a main effect of time [$F(2,58)=14.77$, $P<0.001$] but not of group ($F<1$) (Fig. 2). MDMA users' ratings were lower than controls on day 0, relatively higher on day 4 and similar on day 7. Covarying gender did not affect the pattern or level of significance of findings.

Ambiguous sentences task

Part 1: sentence completion

There was a significant group×sentence interaction [$F(1,59)=11.85$, $P<0.001$] on reaction times (RTs) in the first part of the task, in which participants completed sentences (Fig. 3). Controls took longer to complete ambiguous aggressive sentences than neutral sentences whilst the MDMA group showed the opposite pattern of

responding faster to ambiguous aggressive than neutral sentences.

Part 2: recognition bias

On the second part of the task, participants judged whether a sentence of similar meaning had been presented in part 1 of the task. There was no difference between the groups' recognition of the sentences, both groups recognising similar numbers of neutral (MDMA 8.1±1.9; control 8.0±1.9) and aggressive (MDMA 5.2±2.3; control 5.0±2.5) sentences.

RTs to sentences which participants endorsed as recognised showed a group×sentence interaction [$F(1,59)=8.20$, $P=0.006$] and a main effect of group [$F(1,59)=10.88$, $P=0.002$] but not of sentence. Controls took longer to recognise aggressive than neutral sentences; MDMA users showed the opposite pattern with faster RTs to aggressive sentences (Fig. 4a). MDMA users were also faster generally than controls. Confidence ratings (how sure they were that they had seen the sentence previously) showed a significant group×sentence interaction [$F(1,59)=5.20$, $P=0.026$] and a trend towards a group effect [$F(1,59)=3.97$, $P=0.052$]. Controls made more confident ratings than MDMA users for neutral sentences; ratings for aggressive sentences were similar in each group (Fig. 4b).

RTs to sentences which participants endorsed as *not* previously been presented also showed a significant sentence×group interaction [$F(1,59)=18.05$, $P<0.001$], a main effect of sentence [$F(1,59)=14.54$, $P<0.001$] and of group [$F(1,59)=10.10$, $P=0.002$]. Controls' RTs were similar for both types of sentence, whilst MDMA participants responded faster to aggressive sentences (Fig. 4c). Confidence ratings as to how sure they were that they had not seen the sentence previously showed no significant sentence or group differences.

When all the data from the ambiguous sentences was re-analysed with gender as a covariate, this had no effect on the pattern or level of significant findings.

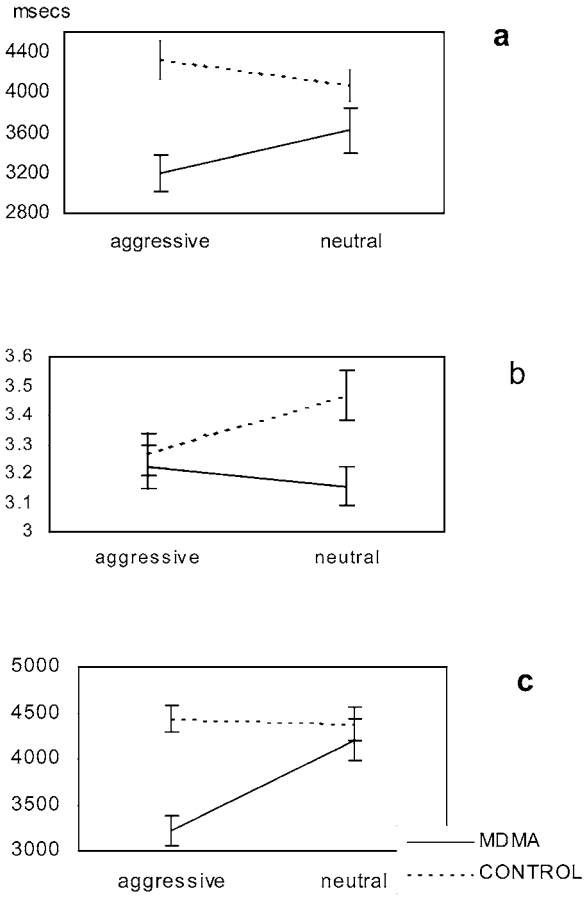

Fig. 4 Recognition bias results showing means for MDMA users and controls for **a** RTs to sentences endorsed as seen previously; **b** confidence ratings to sentences endorsed as seen previously; **c** RTs to sentences endorsed as not seen previously

Pulse rate

A significant group×time interaction [$F(2,58)=70.22$, $P<0.001$] reflected the much higher pulse rate of MDMA users only on day 0 compared to the controls (Table 3).

Table 3 Group means (SD) on days 0, 4 and 7 for pulse rate, mood factors and subjective effects

	MDMA			Control		
	Day 0	Day 4	Day 7	Day 0	Day 4	Day 7
Pulse rate	93.52 (10.51)	71.79 (10.54)	71.07 (9.95)	75.25 (9.18)	72.31 (8.21)	71.88 (8.38)
Alert/drowsy	40.93 (11.62)	46.04 (10.09)	36.76 (13.28)	49.52 (15.73)	36.41 (15.89)	36.32 (14.67)
Contented/discontented	15.73 (11.02)	51.59 (15.36)	37.41 (16.80)	29.73 (13.12)	31.01 (12.65)	31.69 (13.63)
Calm/anxious	54.69 (18.97)	37.93 (13.05)	33.22 (14.75)	39.64 (23.52)	34.38 (21.88)	37.12 (19.16)
Irritability	8.52 (9.87)	46.07 (22.65)	28.31 (21.08)	29.76 (22.95)	28.75 (18.47)	27.78 (17.15)
Physical tiredness	23.90 (18.25)	47.97 (16.71)	29.86 (15.18)	55.72 (22.03)	49.25 (18.92)	40.81 (15.98)
Lack energy	15.72 (15.36)	49.62 (18.35)	32.83 (18.97)	48.28 (26.06)	46.81 (19.57)	42.40 (18.50)
Headache	11.14 (13.65)	18.80 (18.32)	8.62 (7.43)	20.53 (25.98)	13.91 (17.96)	20.97 (24.53)
Sweating	63.79 (24.11)	17.14 (15.44)	12.72 (14.11)	25.16 (24.57)	13.97 (18.93)	17.09 (18.67)
Blurred vision	42.97 (19.97)	10.31 (12.33)	6.69 (7.97)	26.13 (22.49)	12.97 (19.70)	11.69 (19.28)
Depression	12.93 (12.68)	43.00 (17.65)	27.45 (15.91)	24.06 (19.27)	27.97 (19.82)	26.72 (20.35)
Anxiety	19.31 (13.83)	44.52 (22.46)	30.10 (17.83)	35.81 (26.84)	33.84 (22.79)	28.44 (16.31)
Disturbed sleep	–	41.3 (23.4)	15.4 (16.39)	–	26.84 (25.35)	18.44 (23.80)
Loss of appetite	–	36.59 (28.42)	13.86 (13.19)	–	14.81 (21.69)	15.09 (23.54)

Mood rating scale (MRS)

Three factors were computed: alert/drowsy, contented/discontented and calm/anxious. A group×time interaction was found for alert/drowsy [$F(2,58)=7.68$, $P=0.001$] as well as a main effect of time [$F(2,58)=7.39$, $P=0.001$] with MDMA users being more alert on day 0 and more drowsy than controls on day 4 (Table 3). A group×time interaction [$F(2,58)=58.77$, $P<0.001$] and a main effect of time [$F(2,58)=44.92$, $P<0.001$] emerged on contented/discontented whereby MDMA users showed comparatively high contentment on day 0, greater discontentment on day 4 and a similar levels to controls on day 7. On calm/anxious, a group×time interaction [$F(2,58)=4.82$, $P=0.012$] and a main effect of time [$F(2,58)=7.65$, $P=0.001$] reflected MDMA users being more anxious than controls on day 0 but having similar scores on days 4 and 7.

Subjective effects scale (SES)

As the SES comprises 13 scales, an alpha level of 0.01 was adopted to reduce type I errors. Five somatic items showed group×time interactions: physical tiredness [$F(2,58)=10.68$, $P<0.001$], lack of energy [$F(2,58)=13.23$, $P<0.001$], headache [$F(2,58)=5.13$, $P=0.009$], sweating [$F(2,58)=20.43$, $P<0.001$] and blurred vision [$F(2,58)=8.17$, $P=0.001$] (Table 3). The pattern of effects for blurred vision and sweating was the same: MDMA users scored higher than controls on day 0, but there was little difference on days 4 and 7. Similarly, MDMA users reported much less tiredness and lack of energy than controls only on day 0. Group×time interactions on anxiety [$F(2,58)=8.17$, $P=0.001$], depression [$F(2,58)=12.99$, $P=0.001$] and irritability [$F(2,58)=20.99$, $P<0.001$] reflected MDMA users' lower scores than controls on day 0, higher scores on day 4 but similar scores on day 7. Group×time interactions on disturbed sleep [$F(1,59)=10.85$, $P=0.002$] and loss of appetite [$F(1,59)=20.43$, $P<0.001$] reflected higher ratings by MDMA users than controls on day 4 and similar ratings on day 7.

Correlations

Differences in responses to aggressive and neutral sentences (aggressive minus neutral) were calculated and then correlated with drug use and self-ratings of aggression and depression within the MDMA group. The difference between the number of aggressive and neutral sentences endorsed as recognised correlated with frequency of MDMA use ($r=0.45$, $P=0.014$). The difference between confidence ratings for recognising aggressive and neutral sentences correlated with number of MDMA tablets taken in a typical session ($r=-0.41$, $P=0.029$), amount of cannabis used in a month ($r=-0.52$, $P=0.004$), frequency of cannabis use ($r=-0.44$, $P=0.018$) and frequency of alcohol use ($r=-0.43$, $P=0.021$). These inter-correlations with different drug use should be considered in the context of correlations between use of MDMA and use of other drugs (e.g. frequency of cannabis and of alcohol use ($r=0.62$, $P<0.001$); years of alcohol and of MDMA use ($r=0.73$, $P<0.001$); amount of MDMA per session and frequency of cannabis use ($r=0.68$, $P<0.001$). Differences in confidence ratings in recognising aggressive and neutral sentences correlated positively with ARS scores on day 7 ($r=0.44$, $P=0.017$).

Self-ratings of aggression and depression were also correlated with drug use. Within the MDMA group, there was a positive correlation between how many times MDMA was taken a month and ARS scores both on day 4 ($r=0.43$, $P=0.02$) and day 7 ($r=0.50$, $P<0.006$). Frequency of MDMA use correlated with BDI scores on day 7 ($r=0.38$, $P<0.05$). Years of MDMA use correlated with ARS scores on day 4 ($r=0.41$, $P=0.03$) and day 7 ($r=0.67$, $P<0.001$) and BDI scores on day 7 ($r=0.41$, $P=0.03$). There were no significant correlations between self-ratings of aggression or depression and use of cannabis or alcohol.

The same correlations were carried out within the control group. The difference in RT for completing aggressive and neutral sentences correlated negatively with ARS scores on day 4 ($r=-0.37$, $P=0.04$). The difference in confidence ratings for recognising aggressive and neutral sentences correlated negatively with ARS scores on day 4 ($r=-0.37$, $P=0.04$) and positively with typical amount of alcohol consumed on a session ($r=0.36$, $P=0.04$).

Discussion

This study has generated two main findings. Firstly, ecstasy users show increased aggression mid-week on objective measures of interpretative bias as well as on self-ratings. Second, increased mid-week aggression and depression observed on self-rating measures does not persist 7 days to the weekend following acute drug use.

Aggressive interpretative bias

The ecstasy and control groups were well matched for age, education, trait aggression, and trait depression. Importantly, the two groups did not differ significantly in their reported use of drugs other than MDMA. The interpretive bias task showed a distinctly different pattern of performance by ecstasy users compared with controls. In the initial part of the task, ecstasy users were faster in completing sentences that could be interpreted aggressively compared with those which had only neutral interpretations. The control group showed the exact opposite pattern of being slower to complete aggressive than neutral sentences. This suggests that ecstasy users had enhanced sensitivity to the potentially aggressive content of the ambiguous sentences, processing these

significantly faster than they processed the neutral content of other sentences.

In the second phase of the task participants were asked if they recognised sentences as having a similar meaning to ones they previously completed in the first phase of the task. There was no difference between the groups' actual recognition of the sentences. However, their confidence ratings did differ. Ambiguous aggressive sentences (e.g. "The painter drew the knife") were recognised more confidently by controls when they were re-presented as neutral ("The painter sketched the knife") than when they were re-presented as aggressive ("The painter pulled out the knife"). The ecstasy users, in contrast, were rather more confident when the aggressive rather than neutral version of the sentence was re-presented. Response times in recognition also showed marked group differences. Ecstasy users were much faster to respond to sentences that were re-presented in an aggressive than in a neutral form whilst again, the controls showed precisely the opposite pattern of performance. This finding was the case for sentences rated as seen before and those rated as not seen before.

Taken together, this pattern of results on the interpretative bias task provides very strong evidence that a few days after ecstasy use, participants were cognitively biased towards interpreting ambiguous information in an aggressive way. They processed aggressive interpretations faster than neutral ones and they were rather more confident in recognising aggressive interpretations. In contrast, the controls can be seen to cognitively biased towards neutral interpretations (or away from aggressive interpretations) in both their response times and confidence ratings. Given that the controls were also recreational drug users, the increased aggressive bias of MDMA users appears to relate to their use of MDMA specifically rather than reflecting any general aggressive bias of recreational drug users.

This is further supported by the positive association between extent of ecstasy use and measures of aggressive interpretational bias in this task. More frequent use of ecstasy was positively correlated with the difference between the number of aggressive and neutral sentences recognised. Thus the more often the drug was used each month, the greater the aggressive-neutral difference and so the bigger the bias towards aggressive interpretation of ambiguous sentences. A related measure, the difference between confidence ratings for aggressive minus neutral sentences, was positively correlated with the number of tablets taken in a typical ecstasy using occasion. However, unlike numbers of sentences recognised, this measure also correlated with the frequency of use of both cannabis and alcohol and with amount of cannabis used. It is difficult to attribute causation to any one drug when the population studied is typified by poly-drug use. Not surprisingly, frequency of use of cannabis and of alcohol were strongly correlated and, although frequency of ecstasy use was not correlated with those measures, there was an association between other measures of ecstasy use (years of use and number of tablets per session) and use of alcohol and cannabis. At the same time, the major difference between our groups was in use of MDMA and the aggressive interpretative bias shown so clearly in MDMA users seems more likely to relate to the action of this drug on 5-HT.

In terms of relationship between self-rated aggression and interpretative bias, only one correlation emerged within the MDMA group and this was a *positive* correlation between state aggression scores on day 7 and differences in confidence ratings between aggressive and neutral sentences. Intriguingly, in the control group, there was a *negative* correlation between this same interpretative bias measure and state aggression scores on day 4. However, differences in confidence ratings between aggressive and neutral sentences correlated positively for controls with amount of alcohol consumed in a typical session. Clearly, these correlations should be interpreted with caution given the possibility of chance associations.

Low 5-HT has been implicated in impulsivity (poor response inhibition) as well as aggression. Users of illicit drugs are generally more impulsive than non-users, and ecstasy users have been shown to be more impulsive than non-using controls (e.g. Morgan 1998; Curran and Verheyden 2003). Although we did not assess response inhibition in this study, the generally faster response times of MDMA users than controls on both stages of the interpretative bias task may reflect their greater impulsivity. The task may thus differentially assess impulsivity (overall reaction speed) and aggression (differences in response and response times to aggressive versus neutral sentences). Indeed, it would be interesting to replicate this study using a cognitive assessment of response inhibition as well as subjective ratings of impulsivity.

Self-ratings of aggression and depression over 7 days

The second main finding of the present study was that self-rated aggression and depression was significantly increased mid-week in the ecstasy users but by the following weekend had decreased to the same level as controls. Mid-week depression replicated two previous studies (Curran and Travill 1997; Verheyden et al. 2002). Mid-week aggression replicated the findings of Verheyden et al. (2002). That both these effects no longer persisted on day 7 suggests that low mid-week serotonin has returned to normal a week after acute use of ecstasy. Although one might argue that mood at weekends is perhaps naturally more positive than mid-week because of the greater opportunity for leisure and pleasure, it is difficult to see why this would apply to the ecstasy users and not to the controls who use other recreational drugs. Recovered mood by day 7 would also suggest that ecstasy users do not self-medicate the following weekend to improve their mood. This would also accord with the pattern of use of MDMA being less than weekly—our participants, like the majority of ecstasy users, reported taking the drug roughly every 2 weeks.

There were clear associations between self-rated aggression and depression and level of use of MDMA. Aggression scores on day 4 and 7 correlated with both frequency of use per month and years of use. Depression scores on day 7 also correlated positively with monthly frequency and years of use. Interestingly there was no association between self-rated aggression or depression and any measure of cannabis or alcohol use.

The fact that the trait measure of aggression did not reveal any difference between the control and MDMA groups suggests that the midweek difference in state aggression is due to an acute MDMA dose and subsequent attenuation of 5-HT rather than any pre-existing differences between participants' levels of aggression. It is not the case that people who use MDMA are inherently more aggressive than people who do not use this drug. The lack of group differences in state aggression on day 7 also supports this.

Methodological considerations

Like virtually all studies of recreational drug users (Curran 2000), the present study has methodological limitations in that dose or purity of MDMA taken on day 0 was not verifiable and participants' drug history was not objectively confirmable. Nevertheless, MDMA users displayed an increased heart rate of about 20 beats per minute on day 0, their self-ratings the same day (increased sweating, energy, alertness, contentment) and subsequently on day 4 (disturbed sleep, suppressed appetite) all fit with the profile of MDMA's effects and suggest that MDMA had been taken.

Most of our participants were men and the relatively low numbers of women meant we could not compare gender across the drug groups. As there was some imbalance in the gender composition of the MDMA (69% male) and control (56% male) groups, gender was covaried in the analysis of the interpretative bias task and of depression and aggression scores over the week but this had no effect on any of the results. Previously we found that although women were more susceptible to mid-week depression than men, there was no gender difference in self-rated levels of mid-week aggression (Verheyden et al. 2002). However, given a controlled study showing a gender difference in subjective response to MDMA (Liechti et al. 2001), it would be helpful to use the interpretive bias task in a study with larger groups that were balanced for gender.

Summary

In summary, this study compared 29 MDMA users with 32 controls on the night of drug use, 4 and 7 days later. Mid-week, MDMA users showed increased levels of self-rated aggression and depression but at the end of the week did not differ from controls. On an objective task, MDMA users were more likely to infer aggression from ambiguous cues and were faster to respond to aggressive than neutral cues whereas controls showed the opposite pattern of effect. The degree of aggressive interpretative bias in MDMA users correlated with extent of use of MDMA. These findings are consistent with the acute and residual effects of MDMA on brain 5-HT and with the role of 5-HT in human aggression. The acute and residual effects of this drug reveal two faces of ecstasy, the residual (mid-week aggression and depression) being a mirror image of the acute (empathy and high).

Acknowledgements None of the authors have any interest, financial or otherwise, that might potentially bias their work. We thank Dr. Suzanne Verheyden for comments on an earlier draft of this article.

References

Beck AT (1978) The Beck Depression Inventory (BDI). The Psychological Corporation, Harcourt Brace Jovanovitz

Bond AJ, Lader MH (1974) The use of analogue scales in rating subjective feelings. Br J Med Psychol 47:211–218

Bond AJ, Lader MH (1986) A method to elicit aggressive feelings and behaviour via provocation. Biol Psychol 22:69–79

Bond AJ, Wingrove J, Critchlow DG (2001) Tryptophan depletion increases aggression in women during the premenstrual phase. Psychopharmacology 156:477–480

Brown GL, Goodwin FK, Ballenger JC, Goyer PF, Major LF (1979) Aggression in humans correlates with cerebrospinal fluid amine metabolites. Psychiatry Res 1:131–139

Buss AH, Perry M (1992) The aggression questionnaire. J Person Soc Psychol 63:452–459

Cami J, Farre M, Mas M, Roset PN, Poudevida S, Mas A, San L, de la Torre R. (2000) Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. J Clin Psychopharmacol 20:455–466

Cleare AJ, Bond AJ (1995) The effect of tryptophan depletion and enhancement on subjective and behavioural aggression in normal male subjects. Psychopharmacology 118:72–81

Cleare AJ, Bond AJ (1997) Does central serotonergic function correlate inversely with aggression? A study using D-fenfluramine in healthy subjects. Psychiatry Res 69:89–95

Coccaro EF, Siever LJ, Klar HM, Maurer G, Cochrane K, Cooper TB, Mohs RC, Davis KL (1989) Serotonergic studies in patients with affective and personality disorders. Correlates with suicidal and impulsive aggressive behavior. Arch Gen Psychiatry 46:587–599

Copello AG, Tata PR (1990) Violent behaviour and interpretative bias: an experimental study of the resolution of ambiguity in violent offenders. Br J Clin Psychol 29:417–428

Cowen PJ (1991). Serotonin receptor subtypes: implications for psychopharmacology. Br J Psychiatry Suppl 12:7–14

Curran HV (2000) Is MDMA (ecstasy) neurotoxic in humans? An overview of evidence and of methodological problems in research. Neuropsychobiology 42:34–41

Curran HV, Travill RA (1997) Mood and cognitive effects of 3,4 methylenedioxymethamphetamine (MDMA, "ecstasy"): week-end "high" followed by midweek "low". Addiction 92:821–831

Curran HV, Verheyden SL (2003) Altered response to tryptophan supplementation after long-term abstention from MDMA ("ecstasy") is highly correlated with human memory function. Psychopharmacology 169:91–103

Gerra G, Zaimovic A, Giucastro G, Maestri D, Monica C, Sartori R, Caccavari R, Delssignore R (1998) Serotonergic function after 3,4 methylenedioxymethamphetamine ("ecstasy") in humans. Int Clin Pharmacol 13:1–9

Gerra G, Zaimovic A, Ampollinin R, Giusti F, Delsignore R, Raggi MA, Laviola G, Macchia T, Brambilla F (2001) Experimentally

induced aggressive behaviour in subjects with 3,4 methylenedioxymethamphetamine (“ecstasy”) use history. Psychobiological correlates. J Subst Misuse 13:471–491
Goodwin GM, DeSouza RJ, Green AR (1985) Presynaptic serotonin receptor-mediated response in mice attenuated by antidepressant drugs and electroconvulsive shock. Nature 317:531–533
Green AR, Cross AJ, Goodwin GM (1995) Review of the pharmacology and clinical pharmacology of 3,4 methylenedioxymethamphetamine (MDMA or ecstasy). Psychopharmacology 119:247–260
Liechti ME, Gamma A, Vollenweider FX (2001) Gender differences in the subjective effects of MDMA. Psychopharmacology 154:161–168
Linnoila M, Virkkunen M (1992) Biologic correlates of suicidal risk and aggressive behavioural traits. J Clin Psychopharmacol 12:19S–20S
Linnoila M, Virkkunen M, George T, Higley D (1993) Impulse control disorders. Int Clin Psychopharmacol 8:53–56
McCann UD, Ridenour A, Shaham Y, Ricaurte GA (1994) Serotonin neurotoxicity after (±)3,4-methylenedioxymethamphetamine (MDMA; “ecstasy”): a controlled study in humans Neuropsychopharmacology 10:129–138
McKenna DJ, Peroutka SJ (1990) Neurochemistry and neurotoxicity of 3,4-methylenedioxymethamphetamine (MDMA, “ecstasy”) J Neurochem 541:14–22
Morgan MJ (1998) Recreational use of ecstasy (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology 19:252–264
Novaco RW (1978) Anger and coping with stress: Cognitive behavioural intervention. In: Foreyt JP, Rathjen P (eds) Cognitive behavioural therapy: research and application. Plenum Press, New York/London
Parrott AC, Lasky J (1998) Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. Psychopharmacology 139:261–268
Rattray M (1991) Ecstasy: towards an understanding of the biochemical basis of the actions of MDMA. Essays Biochem 26:77–87
Schmidt C J, Wu L, Lovenberg W (1986) Methylenedioxymethamphetamine: a potentially neurotoxic amphetamine analogue. Eur J Pharmacol 124:175–178
Smith KA, Fairburn CG, Cowen PJ (1997) Relapse of depression after rapid depletion of tryptophan. Lancet 349:915–919
Solowij N, Hall W, Lee N (1992) Recreational MDMA use in Sydney: a profile of “ecstasy” users and their experiences with the drug. Br J Addict 87:1161–1172
Verheyden SL, Hadfield J, Calin T, Curran HV (2002) Sub-acute effects of MDMA (3,4 methylenedioxymethamphetamine, “ecstasy”) on mood: evidence of gender differences. Psychopharmacology 161:23–31
Vollenweider FX, Gamma A, Liechti M, Huber T (1998). Psychological and cardiovascular effects and short-term sequelae of MDMA (“ecstasy”) in MDMA-naive healthy volunteers. Neuropsychopharmacology 19:241–251
Young SN, Leyton M (2002) The role of serotonin in human mood and social interaction: insight from altered tryptophan levels. Pharmacol Biochem Behav 71:857–865
Zigmond AS, Snaith RP (1983) The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 67:361–370