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An investigation into the sub-acute effects of ecstasy on aggressive interpretative bias and aggressive mood – are there gender differences?

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Abstract

The lowering of serotonin for a period following MDMA use could account for the increases in both self-rated and objective measures of aggression previously found in ecstasy users several days after taking the drug. There is some evidence of gender differences in the acute, sub-acute and long-term effects of MDMA use, and given that gender differences have been found in aggression, it is possible that men may experience more aggression mid-week than women.

The aim of this study was to attempt to replicate findings showing increased bias towards aggressive material in ecstasy users several days after using the drug. In addition, to investigate possible gender differences in mid-week aggression.

A total of 46 participants were tested: 19 ecstasy users and 27 controls were compared on the night of drug use and 4 days later. On day 4, a task designed to tap cognitive bias toward material with aggressive content was administered. Participants were required to process sentences that could be interpreted as either aggressive or neutral and subsequently remember them in a recognition test. This data set was then combined with the data from Curran *et al.*'s (2004) study that employed exactly the same procedure. Thus, the data from 107 participants was analysed to investigate gender differences.

Ecstasy users recognized more aggressive sentences than controls and tended to react slower to neutral sentences than controls. Ecstasy users also rated themselves as being more aggressive and depressed than controls on day 4. No gender differences were found on any measure of aggression in the combined data set.

Both male and female ecstasy users show a bias toward interpretation of ambiguous material in an aggressive manner when compared to controls 4 days after ecstasy use.

Keywords
ecstasy, MDMA, gender, aggression, interpretative bias, cognitive bias

Introduction

Acutely ±3,4-methylenedioxymethamphetamine (MDMA, ecstasy) induces feelings of euphoria, energy and empathy (Vollenweider *et al.*, 1998; Harris *et al.*, 2002). Its recreational use is widespread, particularly within the dance scene (Riley *et al.*, 2001).

Preclinical research has repeatedly demonstrated that MDMA causes the release of serotonin (5-HT), dopamine and norepinephrine. Its main action, however, is the release of 5-HT and the prevention of its reuptake (Green *et al.*, 1995). This efflux of stored 5-HT, combined with the inhibition of tryptophan hydroxylase (TPH) means that levels of brain 5-HT could be depleted for a period of time following acute MDMA administration.

Low 5-HT is known to be associated with depression (e.g. Delgado *et al.*, 1991; Salomon *et al.*, 2003). Increasingly, research evidence supports the existence of the 'mid-week blues', a lowering of mood several days after ecstasy use (Curran and Travill, 1997; Parrott and Lasky, 1998; Verheyden *et al.*, 2002; Curran *et al.*, 2004) which may reflect MDMA-induced depletion of 5-HT and inhibition of TPH.

Serotonin has also been implicated in the modulation of

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aggression in humans: tryptophan depletion has been found to increase aggressive responses in both women (Bond *et al.*, 2001; Marsh *et al.*, 2002) and men (Cleare and Bond, 1995; Dougherty *et al.*, 1999). Two recent club-based studies have demonstrated that self-rated aggression follows the same pattern as had been demonstrated with depression scores: ecstasy users rated themselves as being less aggressive shortly after taking the drug but more aggressive a few days later compared to non-using controls (Verheyden *et al.*, 2002; Hoshi *et al.*, 2004). However, demand characteristics associated with using self-rating scales may influence the pattern of results. Ecstasy users' preconceptions about the 'mid-week blues', or 'moody Tuesday' phenomena (that are well known among ecstasy users) may affect their responses when presented with scales that make no attempt to disguise what they are tapping.

Previously we aimed to overcome these problems by using an objective information processing approach to assessing aggressive bias (Curran *et al.*, 2004). Participants were presented with ambiguous sentences that could be interpreted in either a neutral or an aggressive manner (e.g. 'the painter drew the knife'). After processing a series of ambiguous sentences the participants completed a recognition test where they were presented with previously seen sentences now made unambiguous (either 'the painter sketched the knife' or 'the painter pulled out the knife'), as well as new unseen sentences. Ecstasy users and controls carried out the task 4 days after an initial test session in which the ecstasy users had taken the drug in clubs or parties. The pattern of results on this task showed that a few days after ecstasy use, ecstasy users were cognitively biased towards interpreting ambiguous information in an aggressive way. They processed possibly aggressive sentences quicker than neutral ones and were more confident in recognizing aggressive interpretations. In contrast, the controls were cognitively biased towards neutral interpretations in both their response times and recognition confidence ratings. Given that controls were also recreational drug users, the increased aggressive bias of ecstasy users appeared to relate to their ecstasy use specifically rather than general club drug use. Indeed, frequency of ecstasy use was positively correlated with degree of aggressive cognitive bias.

The main aim of the present study was to determine the robustness of these intriguing findings by attempting to replicate Curran *et al.* (2004). A new sample of ecstasy users and controls were therefore recruited and assessed following procedures identical to Curran *et al.* (2004). A subsidiary aim was to explore the possibility of gender differences in the relationship between aggressive interpretative bias and ecstasy use, as the predominance of males in our previous study did not allow for gender comparisons. There are gender differences in the expression of aggression (Nunn and Thomas, 1999; Newman *et al.*, 1999). Further, there is some preliminary evidence that women may be more sensitive to acute MDMA effects (Leichti *et al.*, 2001) and to the neurobiological effects of MDMA as measured by serotonin transporter densities (Reneman *et al.*, 2001; Buchert *et al.*, 2004). We took advantage of the opportunity to combine our new data set with that of Curran *et al.* (2004), which could allow sufficient power to explore gender differences.

Materials and methods

Design and participants

Ecstasy users were compared to controls on the night of drug use (day 0) and 4 days later using an independent groups, repeated measures design. Participants were recruited using the 'snowball technique' (Solowij *et al.*, 1992). To ensure that the participants' judgement was not impaired following drug use with regards to consenting to take part in the study, written, informed consent was obtained on both day 0 and day 4. Participants were tested following an identical procedure to that described in Curran *et al.* (2004). The study was approved by the institutional ethics committee.

Procedure

On the first night of the study (day 0) participants were tested in clubs or parties. After agreeing to take part they were taken individually to a quiet area where they read the volunteer information sheet and gave written consent. After completing the self-rating assessments of mood states outlined below, a time was arranged to follow up the participant on day 4. This usually took place at the participants' homes, where once again written informed consent was obtained. The same set of self-rated mood assessments was completed as on day 0, as well as assessments of trait mood and an interpretative bias computer task, all described below. The participants' pulses were taken on both days 0 and 4.

State mood assessments – days 0 and 4

Visual analogue scales were used to assess current (or state) mood on both days of the study: the Aggression Rating Scale (ARS; Bond and Lader, 1986), the Mood Rating Scale (MRS; Bond and Lader, 1974) and a subjective effects scale (SES) tailored to include typical subjective effects experienced after ecstasy use. This scale included additional items added following Curran *et al.* (2004) designed to tap more of the known empathic effects of MDMA. A modified Beck Depression Inventory (BDI; Beck, 1978) designed to tap how the participants had been feeling over the last 3 days (Curran and Travill, 1997) was also administered at both test sessions.

Interpretative bias task – day 4

The task, procedure and instructions followed exactly those used by Curran *et al.* (2004). The stimuli for the first part of the task consisted of 36 unambiguous neutral sentences interspersed with 24 ambiguous sentences, which could be interpreted as either aggressive or neutral (e.g. 'The painter drew the knife'). For the recognition task, 72 sentences were prepared, 48 of which were presented to any given subject. For the 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 sentences with the same meanings (but slightly different

wording) to those presented previously and 12 new unambiguous neutral sentences. Half of the participants in each group were presented with one set of disambiguated sentences and the other half the opposite set.

Part 1: Sentence processing In the first part of the task the participants were presented with the 24 ambiguous and 36 neutral sentences on a laptop computer, one at a time for 4 s. The last word of the sentence was missing. After each incomplete sentence two words appeared simultaneously on the screen and participants were required to choose the word that meaningfully completed the sentence (only one of the words could do this). Reaction time was recorded. Immediately after completing this part of the task, a filler task was given whereby the participants were required to read aloud the numbers 100–0 which were displayed on the screen.

Part 2: Recognition memory In the second part of the task 48 sentences were presented at the rate of one every 10 s. Participants were asked to rate how confident they were about whether they had seen a sentence with a similar meaning in the first part of the task or not. They responded on a four-point scale: 1 = definitely not, 2 = probably not, 3 = probably yes and 4 = definitely yes. Both the ratings and reaction times to each sentence were recorded automatically.

Other assessments on day 4

The Hospital Anxiety and Depression scale (HADs; Zigmond and Snaith, 1983) was used to index trait anxiety and depression, and trait aggression was indexed using the Aggression Questionnaire (AQ; Buss and Perry, 1992). A drug use history interview was carried out to assess amount, frequency and duration of use of other psychotropic drugs, and details of drugs used on day 0 and on days 1–3 (if any) were also recorded. Demographic information (age, educational background and employment) was also collected on day 4.

Statistical analysis

Repeated measures analysis of variance (ANOVA) with group (ecstasy versus controls) as a between-subjects factor and sentence type (aggressive versus neutral) as a within-subjects factor were used to analyse the interpretative bias task. Repeated measures ANOVA was also used on self-rating scores obtained on both days (BDI, ARS, MRS and SES), with group as a between-subjects variable and day (day 0 versus day 4) as a within-subjects variable. The ARS is comprised of 13 variables that showed high internal consistency both on day 0 (Cronbach's $\propto = 0.92$) and day 4 ($\propto = 0.95$). Thus, a mean aggression score was calculated and used in subsequent analyses. Univariate ANOVAs were used to compare groups and genders on aggression (AQ), depression (Had-D), anxiety (Had-A), age and drug use apart from some measures of drug use where Mann-Whitney U-tests (two-tailed) were used due to non-parametric data. Chi-square was used to assess if there was a gender imbalance between the groups. Pearson product–moment correlations were used to examine the relationship between aggression (both self-rated and measures from the computer task) and drug use. For the analysis of the combined data set, gender was included as an additional between-subjects factor in order to investigate the possibility of gender differences. Further correlations between ecstasy use and aggression measures were carried out separately for males and females on the basis that in a previous study (Verheyden *et al.*, 2002) the correlations varied by gender. All data were analysed using SPSS for Windows version 11.0.

Results

Results are reported in 2 parts: first, the results from the new data set (1a), and second the results from the new data set combined with Curran *et al.* (2004) (1b).

Part 1a: Replication study

Demographics In total 46 participants aged between 18 and 23 years completed the study on both test days: 19 ecstasy users (11 males and eight females) and 27 controls (17 males and ten females). The control group were mainly ecstasy-naive, although 2 had previously tried the drug once. The majority of the participants were undergraduate students. There were no group differences in gender, age, trait aggression (AQ), depression (Had-D) or anxiety (Had-A) (Table 1).

Table 1 Group means (SD) of aggression (AQ), anxiety (Had-A), depression (Had-D) and age, and of frequency, dose and length of ecstasy, cannabis and alcohol use

	Ecstasy users	Controls
Aggression, anxiety, depression, age		
AQ	73.84 (18.19)	70.30 (12.31)
HAD-A	7.84 (4.06)	7.37 (3.53)
HAD-D	3.42 (2.46)	3.33 (2.37)
Age	20.21 (1.55)	20.63 (0.79)
Drug use		
Ecstasy frequency (days per month)	2.53 (1.31)	–
Ecstasy typical dose (tablets)	3.05 (0.96)	–
Ecstasy length of use (years)	2.47 (1.67)	–
Ecstasy use day 0 (tablets)	2.45 (0.78)	–
Alcohol frequency (days per month)	11.58 (3.86)	11.11 (4.34)
Alcohol typical dose (units)	7.79 (3.68)	9.48 (4.15)
Alcohol length of use (years)	5.16 (2.32)	5.52 (1.78)
Alcohol day 0 (units)	5.47 (4.97)	9.44 (6.74)
Alcohol days 1–3 (units)	3.37 (3.39)	3.44 (4.77)
Alcohol day 4 (units)	0.53 (1.31)	0.15 (0.53)
Cannabis frequency (days per month)	9.74 (8.01)	3.67 (4.49)
Cannabis monthly use (oz)	1.66 (1.23)	1.22 (1.01)
Cannabis length of use (years)	3.32 (2.69)	2.52 (2.17)
Cannabis day 0 (joints)	1.47 (1.58)	0.26 (0.59)
Cannabis days 1–3 (joints)	1.42 (1.61)	0.37 (0.79)
Cannabis day 4 (joints)	0.58 (0.96)	0.04 (0.19)

Levels of use of ecstasy, alcohol and cannabis are given in Table 1. All participants drank alcohol regularly. Cannabis was used ≥1 day per month by 15/19 ecstasy users and 17/27 controls. There was a group difference in frequency of cannabis use ($U = 142.00$, $p = 009$, two-tailed) showing that ecstasy users smoked cannabis on more days per month than controls (9.73 ± 8.01 vs. 3.67 ± 4.49). Four ecstasy users and one control used cocaine, five ecstasy users and four controls used amphetamines and two ecstasy users used ketamine occasionally. A significant group difference in the amount of alcohol that was consumed on day 0 ($U = 160.50$, $p = 0.031$, two-tailed) indicated that the control group drank more units of alcohol on day 0 than ecstasy users (9.44 ± 6.74 vs. 5.47 ± 4.97). Other drug use on day 0 included 11 ecstasy users and five controls smoking cannabis and cocaine was used by two ecstasy users. There were no significant differences in amount of cannabis or alcohol consumed in the days between the test sessions (days 1–3). Despite having been asked to refrain from alcohol and drug use on day 4, three ecstasy users and two controls had drunk alcohol (2–4 units) and six ecstasy users and one control had smoked cannabis (sharing one to three joints) prior to testing (Table 1).

Interpretative Bias Task

Part 1: sentence processing

No group or sentence type differences emerged in the time to complete ambiguously aggressive and neutral sentences.

Part 2: recognition memory

A significant group × sentence type interaction [$F(1,44) = 6.24$, $p = 0.016$] and a main effect of sentence type [$F(1,44) = 10.25$,

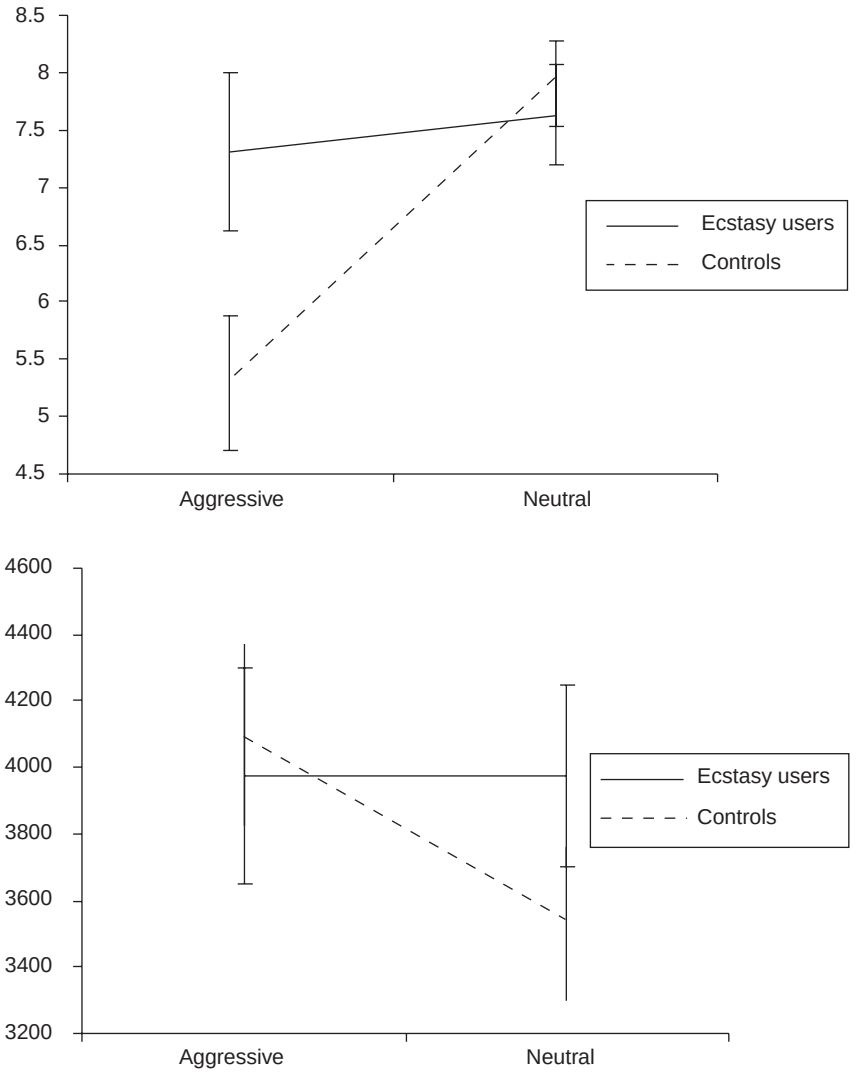

Figure 1 Mean (SE) (a) number of sentences correctly recognized by ecstasy users and controls (b) reaction times for recognition of aggressive and neutral sentences

$p = 0.003$] was found for the number of sentences correctly identified as being seen in the first part of the task (Fig. 1a). Ecstasy users recognized more disambiguated aggressive sentences than controls; both groups recognized similar amounts of neutral sentences. No significant group or sentence type differences were found in how confident the participants were in recognizing previously seen sentences. In addition, the speed of judging whether sentences with a similar meaning had been seen in the first part of the task showed a trend towards a significant group × sentence type interaction [$F(1,44) = 2.27$, $p = 0.078$]. Ecstasy users tended to react slower to neutral sentences than controls, whereas both groups showed similar reaction times to aggressive sentences (Fig. 1b). No significant differences were found in the recognition of previously seen, unambiguously neutral sentences.

Aggression Rating Scale

Self-rated aggression showed a significant group × day interaction [$F(1,44) = 15.13$, $p < 0.001$] and a main effect of day [$F(1,44) = 17.34$, $p < 0.001$]. Ecstasy users rated themselves as less aggressive than controls on day 0 and more aggressive than them on day 4 (Fig. 2a).

Beck Depression Inventory

Self-rated depression also showed a group × day interaction [$F(1,44) = 31.36$, $p < 0.001$] and a main effect of day [$F(1,44) = 4.28$, $p = 0.044$]. Ecstasy users rated themselves as less depressed than controls on day 0 and more depressed on day 4 (Fig. 2b).

Mood rating scale

The MRS is condensed into three factors: sedation, discontentedness and anxiety.

Sedation: A main effect of day was found [$F(1,44) = 10.28$, $p = 0.003$] showing that both groups rated themselves as more sedated on day 4 than on day 0.

Discontentedness: There was a significant group × day interaction [$F(1,44) = 4.65$, $p = 0.036$] and a main effect of day was found [$F(1,44) = 7.49$, $p = 0.009$]. While both groups rated themselves as more discontented on day 4, the controls were less contented than the ecstasy users on day 0 and more contented than them on day 4.

Anxiety: A group × day interaction was found [$F(1,44) = 11.25$, $p = 0.002$] as well as a main effect of day [$F(1,44) = 21.33$,

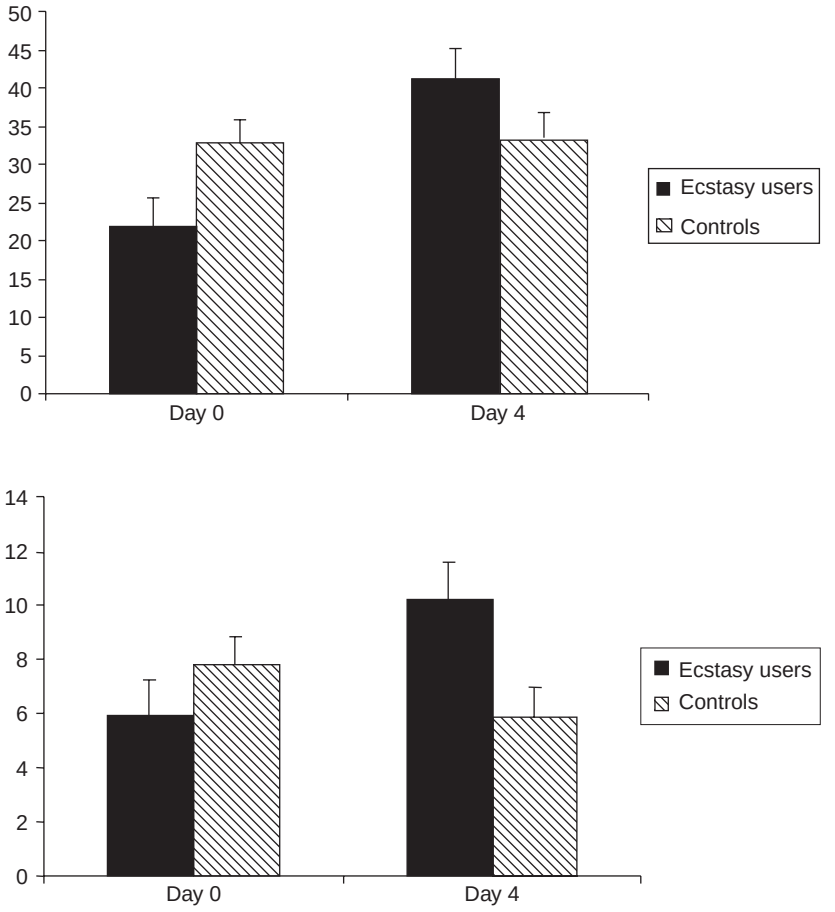

Figure 2 Mean and SEM (a) aggression (ARS) scores and (b) depression (BDI) scores for ecstasy users and controls on day 0 and day 4

$p < 0.001$]. Ecstasy users rated themselves as more anxious than controls on day 0, while the 2 groups had similar levels on day 4.

Pulse

A significant day × group interaction [$F(1,44) = 26.51$, $p < 0.001$] and a main effect of day [$F(1,44) = 41.34$, $p < 0.001$] were found reflecting much faster pulse rate in ecstasy users than in controls on day 0 (95.5 ± 13.7 vs. 75.0 ± 10.3) and similar rates in both groups on day 4 (76.1 ± 8.3 vs. 72.8 ± 9.4).

Subjective effects scales (SES)

As the SES comprises 26 sub-scales a more stringent alpha level of 0.01 was adopted to reduce the likelihood of type I errors. Fifteen items showed a significant day × group interaction, all reflecting ecstasy users rating themselves as higher than controls on day 0 but similar on day 4. These scales included affective items [euphoria ($p < 0.001$); closeness to others ($p < 0.001$); openness to others ($p = 0.001$)], somatic items [teeth clenching ($p < 0.001$); dry mouth ($p < 0.001$); blurred vision ($p = 0.001$); jaw clenching ($p < 0.001$); thirsty ($p < 0.001$); loss of appetite ($p = 0.007$)] and cognitive items [lack of concentration ($p = 0.004$); memory problems ($p = 0.004$); sensitive to colour ($p < 0.001$)].

Correlations In the ecstasy group a negative correlation was found between frequency of ecstasy use and total number of neutral sentences recognized in the second part of the interpretative bias task ($r = -0.47$, $p = 0.043$). Again within the ecstasy group a correlation was found between the 'anger' sub-scale of the AQ and the total number of aggressive sentences recognized in the second part of the task ($r = 0.512$, $p = 0.025$). This scale of the AQ also correlated with response time to neutral sentences in the control group ($r = 0.394$, $p = 0.042$). In the control group years of alcohol use was correlated with response time to recognizing aggressive sentences ($r = 0.556$, $p = 0.003$), frequency of alcohol use was correlated with total scores on the AQ ($r = 0.397$, $p = 0.04$).

Part 1b: Combined data set exploring gender differences

Demographics The combined data set produced a total of 107 participants aged between 19 and 24 years who completed the study on both test days: 48 ecstasy users (31 males and 17 females) and 59 controls (35 males and 24 females). The control group was made up mainly of those who were ecstasy-naive, although two had previously tried the drug once. Four participants in the ecstasy group were starting university courses the following term and two were in full-time employment. All other participants were undergraduate or postgraduate students. There were no group differences in gender, age, trait aggression (AQ), depression (Had-D) or anxiety (Had-A) and no group × gender interactions, although there was a main effect of gender [$F(1,103) = 6.24$, $p = 0.014$] whereby females self-rated higher anxiety levels than males (7.63 ± 3.69 vs. 5.88 ± 3.60) (Table 2). There were no significant differences when comparing gender in each group (i.e. female ecstasy users vs. female controls and male ecstasy users vs. male controls).

Ecstasy use by males and females is given in Table 2. Males reported using significantly more tablets in a typical session than females ([$F(1,46) = 5.04$, $p = 0.03$]; there were no differences in frequency (days per month) or years of use. There were no group differences or group × gender interactions in the use of cannabis or alcohol (Table 2). All participants drank alcohol regularly and 35/48 ecstasy users and 42/59 controls regularly smoked cannabis. There was a main effect of gender showing that males drank more units of alcohol per session (7.75 ± 4.37 vs. 5.54 ± 2.50) [$F(1,103) = 8.56$, $p = 0.004$], on more days per month

Table 2 Group means (SD) of aggression (AQ), anxiety (Had-A), depression (Had-D) and age, and of frequency, dose, length of use of ecstasy, alcohol and cannabis for the two combined data sets

	Ecstasy users			Controls		
Aggression, anxiety, depression, age	Male	Female	Total	Male	Female	Total
AQ	70.90 (15.19)	68.12 (16.92)	69.92 (15.70)	72.26 (14.18)	64.46 (16.07)	69.08 (15.33)
Had-A	5.71 (3.50)	8.12 (3.1)	6.56 (3.78)	6.03 (3.65)	7.29 (3.72)	6.54 (3.70)
Had-D	2.81 (2.41)	2.94 (1.92)	2.85 (2.23)	2.91 (2.39)	2.67 (2.33)	2.81 (2.35)
Age	21.19 (1.70)	20.65 (1.11)	21.00 (1.53)	21.23 (1.03)	20.79 (1.14)	21.05 (1.09)
Drug use						
Ecstasy frequency (days per month)	2.48 (1.18)	2.29 (0.77)	2.42 (1.05)	–	–	–
Ecstasy typical dose (tablets)	3.15 (1.48)	2.29 (0.66)	2.84 (1.31)	–	–	–
Ecstasy length of use (years)	2.92 (1.70)	2.09 (0.92)	2.63 (1.51)	–	–	–
Alcohol frequency (days per month)	11.06 (4.46)	8.65 (3.50)	10.21 (4.27)	12.77 (6.44)	10.20 (5.52)	11.73 (6.16)
Alcohol typical dose (units)	6.79 (3.71)	5.29 (1.61)	6.26 (3.19)	8.60 (4.78)	5.71 (2.99)	7.42 (4.36)
Alcohol length of use (years)	6.06 (1.95)	4.21 (1.71)	5.41 (2.05)	5.86 (1.56)	4.79 (1.56)	5.42 (4.63)
Cannabis frequency (days per month)	10.87 (9.81)	5.14 (4.91)	8.94 (8.76)	7.29 (8.44)	5.12 (5.97)	6.41 (7.55)
Cannabis monthly use (oz)	0.95 (1.20)	0.70 (0.89)	0.86 (1.10)	0.69 (0.87)	0.60 (0.90)	0.66 (0.87)
Cannabis length of use (years)	3.15 (2.68)	2.44 (1.95)	2.90 (2.45)	2.79 (2.36)	2.60 (2.16)	2.71 (2.26)

(11.97 ± 5.62 vs. 9.56 ± 4.80) [F(1,103) = 5.46, $p = 0.021$] and had drunk for longer (5.85 ± 1.74 vs. 4.55 ± 1.63) [F(1,103) = 18.28, $p < 0.001$] than females. In addition, a significant main effect of gender was found for number of days per month cannabis was used: again, males used more frequently than females (8.97 ± 9.22 vs. 5.24 ± 5.49) [F(1,103) = 5.69, $p = 0.019$]. Eight males and four females in the ecstasy group, and two males in the control group used cocaine occasionally. One male ecstasy user and two male controls used amphetamines and three male ecstasy users used ketamine (all <1 day per month). On day 0, 44 ecstasy users and 52 controls drank alcohol, 30 ecstasy users and 16 controls smoked cannabis, four ecstasy users and one control used cocaine, two ecstasy users and one control used ketamine. In addition, between the two test sessions 31/48 ecstasy users and 34/59 controls consumed alcohol, and cannabis was used by 19/48 ecstasy users and 16/59 controls.

Because of gender differences, alcohol use was covaried in the analysis of all measures reported below. However, no effect of this covariance was found on any measure, and no significant interactions were found between alcohol use and group or gender.

Interpretative Bias Task (Table 3)

Part 1: sentence processing

A significant group × sentence type interaction [F(1,102) = 9.90, $p = 0.002$] and a main effect of sentence type [F(1,102) = 11.35, $p = 0.001$] were found; there was no main effect or interactions with gender. As seen in Table 3, controls were faster to complete neutral than potentially aggressive sentences; ecstasy users showed similar reaction times to both. As expected, nearly all of the participants completed all of the sentences correctly. No gender differences were found.

Part 2: recognition memory

Recognition accuracy showed a main effect of sentence type [F(1,102) = 44.10, $p < 0.0001$] indicating that both groups recognized more neutral than aggressive sentences. There were no group differences in recognition, with both groups recognizing a similar number of aggressive (ecstasy users 6.06 ± 2.55, controls 5.19 ± 2.81) and neutral (ecstasy users 7.90 ± 1.69, controls 7.95 ± 2.06) sentences.

Reaction time to sentences that participants correctly identified

Table 3 Performance on the cognitive bias task of the two combined data sets: group means (SD) of reaction time to sentences completion, response times and confidence ratings of sentences endorsed as seen and reaction times to sentences endorsed as not seen

		Part 1: reaction time to completion of sentences	
		Aggressive	Neutral
Ecstasy	Males	1313.18 (558.74)	1306.85 (543.19)
	Females	1324.15 (409.18)	1260.94 (412.86)
	Total	1317.06 (506.26)	1290.59 (496.84)
Controls	Males	1353.27 (427.00)	1188.41 (370.48)
	Females	1329.27 (460.82)	1144.77 (348.55)
	Total	1343.51 (437.31)	1170.66 (359.31)
		Part 2: response time to sentences endorsed as seen	
Ecstasy	Males	3400.61 (1090.2)	3739.35 (1335.94)
	Females	3695.94 (1157.4)	3794.76 (1116.38)
	Total	3505.21 (1111.32)	3758.98 (1250.67)
Controls	Males	4109.14 (1418.95)	3634.17 (1097.92)
	Females	4381.13 (1138.86)	4095.50 (844.50)
	Total	4219.78 (1308.73)	3821.83 (1002.63)
		Part 2: confidence ratings of sentences endorsed as seen	
Ecstasy	Males	3.39 (0.460)	3.35 (0.469)
	Females	3.44 (0.496)	3.38 (0.485)
	Total	3.41 (0.469)	3.37 (0.470)
Controls	Males	3.37 (0.459)	3.57 (0.472)
	Females	3.29 (0.464)	3.48 (0.500)
	Controls	3.34 (0.459)	3.53 (0.481)
		Part 2: response times to sentences endorsed as not seen	
Ecstasy	Males	3642.97 (1409.55)	4169.48 (1299.91)
	Females	3637.18 (1130.29)	4342.00 (903.61)
	Total	3640.92 (1305.04)	4230.58 (1167.69)
Controls	Males	4079.69 (1120.43)	4211.00 (1212.88)
	Females	4371.04 (850.95)	4496.63 (936.66)
	Total	4198.20 (1021.71)	4327.19 (1109.18)

Table 4 Group means (SD) for self-rated aggression and depression on day 0 and day 4

		Day 0		Day 4	
		Ecstasy users	Controls	Ecstasy users	Controls
Aggression (ARS)					
	Males	21.89 (10.83)	31.28 (14.94)	45.15 (18.62)	30.05 (15.15)
	Females	19.47 (10.86)	36.71 (16.07)	40.18 (17.96)	33.67 (17.96)
	Total	21.04 (10.79)	33.49 (16.07)	43.39 (17.82)	31.52 (16.30)
Depression (BDI)					
	Males	5.35 (4.14)	6.97 (5.22)	11.58 (5.78)	5.31 (4.14)
	Females	4.24 (2.91)	8.79 (5.47)	10.18 (3.45)	7.38 (6.05)
	Total	4.96 (3.76)	7.71 (5.35)	11.08 (5.09)	6.15 (5.06)

as having previously been seen showed a group × sentence type interaction [$F(1,102) = 6.60$, $p = 0.012$]. Ecstasy users were faster than controls at recognizing aggressive sentences, while both groups had similar reaction times to neutral sentences (Table 3). Confidence ratings for these sentences also showed a group × sentence type interaction [$F(1,102) = 8.85$, $p = 0.004$], indicating that the ecstasy users were more confident in their judgement when recognizing aggressive sentences than controls, whereas control participants were more confident than ecstasy users in their recognition of neutral sentences (Table 3). There was also a main effect of sentence type [$F(1,102) = 5.52$, $p = 0.021$]. There were no main effects or interactions with gender.

Reaction times for those sentences that participants endorsed as *not* previously seen showed a significant group × sentence type interaction [$F(1,102) = 8.17$, $p = 0.005$], as well as a main effect of sentence type [$F(1,102) = 8.17$, $p = 0.005$]. While control participants showed similar reaction times to both types of sentences, ecstasy users reacted faster to aggressive sentences (Table 3). There were no significant group, gender or sentence type differences in the number of sentences participants incorrectly rejected or in how confident they were in their judgement that they had not seen the sentences previously.

Self-ratings

As the subjective effects (ARS, BDI, MRS, SES) showed the same pattern of group differences in Curran *et al.* and the new sample reported here, it is not surprising that the combined data set replicated the findings of each data set. Thus, the results are not reported separately here. The re-analysis with gender showed only one significant difference: the anxiety subscale of the MRS showed a day × gender interaction [$F(1,102) = 5.73$, $p = 0.018$] whereby females in both groups rated themselves as more anxious than males on day 0. The means (SD) for self-rated aggression and depression for males and females in both groups are shown in Table 4.

Pulse rate

A significant group × day interaction was found [$F(1,102) = 101.82$, $p < 0.0001$], with ecstasy users having a much higher pulse rate than controls on day 0 (94.3 ± 11.8 vs. 75.1 ± 9.6) but similar on day 4 (73.5 ± 9.9 vs. 72.5 ± 8.7). There was no effect of gender.

Correlations

Correlations were carried out separately for males and females to explore the relationship between performance on the interpretative bias task, drug use and self-report measures of aggression. Due to the number of correlations carried out an alpha level of 0.01 was adopted. In female ecstasy users the number of ecstasy tablets taken in a typical session correlated negatively with reaction time of completing both neutral sentences ($r = -0.63$, $p = 0.007$) and aggressive sentences ($r = -0.58$, $p = 0.01$) in the first part of the task. No correlations were found between number of ecstasy tablets used on day 0 and any measure of aggression. In female ecstasy users amount of cannabis used per month also correlated negatively with the number of neutral sentences recognized in the second part of the task ($r = -0.75$, $p = 0.001$). In male ecstasy users a correlation was also found between units of alcohol consumed in a typical session and the reaction time to neutral sentences recognized in the second part of the task ($r = 0.48$, $p = 0.007$). There were no correlations within the control group.

Discussion

Part 1 – new data set

The main finding from the analysis of the new data set is that ecstasy users show a bias toward material with an aggressive content when recognizing previously ambiguous material 4 days after ecstasy use. Ecstasy users recognized more aggressive sentences than controls, whereas both groups recognized a similar number of neutral sentences. In addition, ecstasy users tended to react more slowly than controls when recognizing neutral sentences, while both groups showed similar reaction times to aggressive sentences. There appeared to be an association between frequency of ecstasy use and performance on the task: the more frequently ecstasy was used the fewer neutral sentences were correctly identified. Although bias toward recognition of aggressive material in the sample tested by Curran *et al.* (2004) manifested

itself in reaction times and confidence in recognition, rather than in the number of sentences recognized, both ecstasy using groups demonstrated aggressive cognitive bias using an objective task 4 days after ecstasy use. Thus, both studies showed an association between ecstasy use and performance of the interpretative bias task. That the reaction time effect was not observed in the new sample may reflect various factors, conceivably including the somewhat lower participant number in the present study or other sample variations.

The results on self-rated aggression replicated the findings of three previous studies (Verheyden *et al.*, 2002; Curran *et al.*, 2004; Hoshi *et al.*, 2004), showing that ecstasy users rated themselves as being less aggressive than controls on day 0 and more so on day 4. The results on self-rated depression also replicated three previous studies (Curran and Travill, 1997; Verheyden *et al.*, 2002; Curran *et al.*, 2004), with ecstasy users reporting lower levels of depression than controls on day 0 and higher levels on day 4. Ecstasy users also rated themselves as being less discontented than controls on day 0 while the opposite pattern of group differences was observed on day 4. These findings and the results from the interpretative bias task, add to the growing body of evidence of increased aggression and a lowering of mood mid-week following weekend ecstasy use. The evidence of increased aggression in ecstasy users found in both the present study and in Curran *et al.*'s (2004) sample with an indirect, objective measure is important because it is unlikely that the group differences in this task could arise from differences in how ecstasy users and non-users subjectively rate their feelings. Furthermore, although subjective ratings may, in part at least, reflect people's subjective comparisons between the high of the weekend and the tedium of the middle of the working week, it seems improbable that differences on a subtle, objective measure would reflect this.

As the interpretative bias task was only carried out on day 4, it could be argued that pre-existing differences between the groups in aggression lead to the observed pattern of results. However, no group differences were found in trait aggression. Further, when a different information processing task was used to tap aggression, Bond *et al.* (2004) found no difference between ecstasy users abstinent for 3 weeks and controls. Mid-week lowering of mood is probably a transient phenomenon. Curran *et al.* (2004) tested participants on the night of drug use, 4 and 7 days later. They found that on day 7 of the study, group differences found on day 4 on subjective rating scales of aggression and depression were no longer present. It is possible, however, that the observed aggression effects reflect a combination of sub-acute effects and neurotoxic effects of long-term MDMA use.

As outlined in the introduction, the bias towards aggressive interpretation of ambiguous sentences and the increased self-rated aggression and depression 4 days following ecstasy use could be related to a serotonergic depletion following the massive release of 5-HT after ingestion of MDMA in ecstasy tablets. However, there are many methodological problems inherent in this type of naturalistic design that may limit the conclusions drawn (see Curran, 2000 and Cole *et al.*, 2002 for reviews). No objective measure, for example urine screening, was used on day 0 to verify use of MDMA. Unfortunately, this was not practical at many of the testing locations, and some participants expressed reluctance to take part if such tests were used. The ecstasy users did, however, show significantly higher levels than controls on day 0 of many of the known acute physical effects of stimulants, and in addition experienced empathic feelings (e.g. closeness to others, openness to others, euphoria) that are more specifically associated with MDMA use. The groups did not differ on day 4. In addition, they showed a higher pulse rate on day 0 than on day 4 of just over 20 beats per minute faster than controls, paralleling controlled studies administrating MDMA acutely (Mas *et al.*, 1999). Taken together, it seems reasonable to assume that the ecstasy tablets consumed contained MDMA. Although a few of the participants had used alcohol and cannabis several hours before testing on day 4, the amount of drug used was low. However, it may be relevant as there seemed to be some association between years of alcohol use and aggression in the control group. To clarify this issue the data was re-analysed excluding the seven participants who had used alcohol and/or cannabis of day 4, and it was found the that results were not significantly affected.

Part 1(b) – combined data set

The main finding of combining our two data sets is that both men *and* women who take ecstasy show a cognitive bias toward material with an aggressive component 4 days later. While controls were faster at completing neutral sentences than ambiguous aggressive sentences, ecstasy users showed a similar reaction time to both. The ecstasy users were faster than controls at completing possibly aggressive sentences and slower than them at completing neutral sentences. In the second part of the task ecstasy users were faster at recognizing aggressive sentences, while both groups showed similar response times to neutral sentences. Ecstasy users were also more confident in their judgements of aggressive sentences than neutral sentences while control participants showed the opposite pattern. In addition, ecstasy users were faster to respond to aggressive sentences they had not previously seen. Overall, this seems to indicate a bias toward material with aggressive content. No gender differences were found in self-rated aggression either. Thus, we have found no evidence of gender differences in aggression mid-week following weekend ecstasy use.

Although it was hypothesized that this more objective measure of aggression may pick up subtle gender differences, none were observed. It is possible that gender differences in aggression vary depending on the measures used. A recent meta-analysis by Knight *et al.* (2002) found that increased aggression in men was more likely to be found in naturalistic rather than experimental studies of aggression, and furthermore, gender differences were greater for *physical* than for *verbal* aggression. This is also supported by evidence that men are more likely to use direct aggression and women indirect (Bjorkqvist, 1994). In addition, there is evidence of gender differences in responses to anger. Males tend to react with an 'anger-out' or more aggressive behavioural responses, whereas women tend to have an 'anger-in' reaction (Nunn and Thomas, 1999; Newman *et al.*, 1999). Males have been found to be more aggressive when using the Response-choice Aggression Paradigm (Zeichner *et al.*, 1999) in which participants

are led to believe they are competing with another on speed of reaction times. Electric shocks are administered to provoke them, and they have the option of giving a range of strength of shocks to their 'partners'. Zeichner *et al.* (2003) found that not only did men administer more shocks overall, but they also administered shocks earlier in the 'competition' and chose significantly higher intensity of shocks than women. However, Allen *et al.* (1996) used the Point Subtraction Aggression Paradigm, where aggression is defined by the subtraction of money from an opponent as opposed to being indexed by shock administration. They found no significant gender differences in aggressive responses. These results support the notion that while there may be gender differences in outwardly expressed behavioural aggression, there is little evidence of any gender differences in aggression assessed on other types of measures.

Tryptophan depletion reduces 5-HT function temporarily, and there is little evidence of gender differences in increased aggression following this procedure. The majority of studies investigating aggression following tryptophan depletion in healthy volunteers have been carried out on men (e.g. Bjork *et al.*, 1999; Cleare and Bond, 1995), and most have found increased aggression following the procedure using methods such as the Point Subtraction Paradigm. Two recent studies investigating aggression following tryptophan depletion in women have revealed very similar results to those found with men (Bond *et al.* 2001; Marsh *et al.* 2002). Interestingly, there appears to be some evidence that increased aggressive responding after tryptophan depletion is related to trait aggression (Cleare and Bond, 1995; Dougherty *et al.*, 1999).

From an evolutionary perspective it is advantageous for both males and females to be quick to perceive the potential for aggression in the environment. In other words, an attentional bias toward threat would benefit both genders. However, the behavioural response toward aggressive threat may have conferred evolutionary advantage if differentiated by gender. As Fessler *et al.* (2004) discuss, it could have been beneficial to males to show physically aggressive responses to other threatening males in order to secure territory and protect females, while for females more low-risk strategies may be better for ensuring survival of themselves and their offspring.

This idea that attentional bias towards aggressive material is a very different construct from outwardly aggressive behaviour or violence, is also supported by the findings of Copello and Tata (1990) who originally used a version of the interpretative bias task. They found that although non-offenders were less responsive to ambiguous aggressive material than offenders, there were no differences between violent and non-violent offenders. Both groups were therefore more aggressive than non-offenders, although one group was more violent (i.e. behaviourally aggressive) than the other. The idea that levels of aggression vary according to the method of measurement used is also supported by the lack of relationship between the subjective and objective measures of aggression employed in the present study.

The methodological problems outlined in Part 1a equally apply to the combined data set. Also, although over 100 participants were tested the low number of female ecstasy users may have affected the results. An additional problem when investigating gender differences is that phase of menstrual cycle was not controlled for in the present study, and although a recent study found no significant changes in BDI across phases of the menstrual cycle (Symonds *et al.*, 2004), it is possible that hormonal changes do make women more susceptible to changes in mood caused by 5-HT depletion following MDMA use. There are also other factors that can affect 5-HT function that have not been controlled for in any study of mid-week mood in ecstasy users, including dieting (Cowen *et al.*, 1996) and family psychiatric history (Sobczak *et al.*, 2002).

In conclusion, we have found further evidence that ecstasy users show increased aggressive cognitive bias as well as increased self-rated aggression mid-week following ecstasy use. These findings add to a growing body of evidence that ecstasy users show a change of mood reflected by increased feelings of depression and aggression mid-week following ecstasy use at the weekend. In addition, our results suggest that both men *and* women have an elevated cognitive bias toward aggressive information a few days following ecstasy use. These findings could have further implications. Ecstasy is often portrayed as a benign drug increasing feelings of euphoria and empathy. The opposite effects of dysphoria and aggression, produced by its offset, are likely to have negative interpersonal consequences which may result in increased episodes of confrontation or social isolation. This may perpetuate the desire for the acute calming effects. As people who suffer from depression often also show cognitive impairments (e.g. Brand *et al.*, 1992), the lowering of mood mid-week could also be associated with impaired cognitive function in the many people that take ecstasy regularly.

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References

Allen T J, Dougherty D M, Rhoades H M, Cherek D R (1996) A study of male and female aggressive responding under conditions providing an escape response. The Psychological Record *46*: 651–664

Beck A T (1978) The Beck Depression Inventory (BDI). The Psychological Corporation. Harcourt Brace Jovanovitz Inc., USA

Bjork J M, Dougherty D M, Moeller F G, Cherek D R, Swann A C (1999) The effects of tryptophan depletion and loading on aggression in men: time course and a food-restricted control. Psychopharmacology *142*: 24–30

Bjorkqvist K (1994) Sex differences in physical, verbal and indirect aggression: A review of recent research. Sex Roles *30*: 177–188

Bond A J, Lader M H (1974) The use of analogue scales in rating subjective feelings. British Journal of Medical Psychology *47*: 211–218

Bond A J, Lader M H (1986) A method to elicit aggressive feelings and behaviour via provocation. Biological Psychiatry *22*: 69–79

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

Bond A J, Verheyden S L, Wingrove J, Curran H V (2004) Angry cognitive bias, trait aggression and impulsivity in substance users. Psychopharmacology *171*: 331–339

Brand A N, Jolles J, Gispen-de Wied C (1992) Recall and recognition

memory deficits in depression. Journal of Affective Disorders *25*: 77–86

Buchert R, Thomasius R, Wilke F, Petersen K, Nebeling B, Obrocki J, Schulze O, Schmidt U, Clausen M (2004) A Voxel-Based PET Investigation of the long-term effects of 'ecstasy' consumption on brain serotonin transporters. American Journal of Psychiatry *161*: 1181–1189

Buss A H, Perry M (1992) The aggression questionnaire. Journal of Personal and Social Psychology *63*: 452–459

Cleare A J, Bond A J (1995) The effects of tryptophan depletion and enhancement on subjective and behavioural aggression in normal subjects: evidence for role of 5-HT in control of aggression. Psychopharmacology *118*: 72–81

Cole J, Sumnall H, Grob C (2002) Sorted: ecstasy facts and fiction. The Psychologist *15*: 464–467

Copello A G, Tata P R (1990) Violent behaviour and interpretative bias: an experimental study of the resolution of ambiguity in violent offenders. British Journal of Clinical Psychology *29*: 417–428

Cowen P, Clifford E M, Walsh A E S, Williams C, Fairburn C G (1996) Moderate dieting causes 5-HT_{2C} receptor supersensitivity. Psychological Medicine *26*: 1155–1159

Curran H V (2000) Is MDMA ('Ecstasy') neurotoxic in humans? An overview of evidence and methodological problems in research. Neuropsychobiology *42*: 34–41

Curran H V, Travill R (1997) Mood and cognitive effects of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): weekend 'high' followed by mid-week low. Addiction *92*: 821–831

Curran H V, Rees H, Hoare T, Hoshi R, Bond A J (2004) Empathy and aggression: two faces of ecstasy? A study of interpretative cognitive bias and mood change in ecstasy users. Psychopharmacology *173*: 425–433

Delgado P L, Miller H L, Salomon R M, Licinio J, Krystal J (1991) Rapid serotonin depletion as a provocative challenge test for patients with major depression: Relevance to antidepressant action and the neurobiology of depression. Psychopharmacology Bulletin *29*: 321–330

Dougherty D M, Bjork J M, Marsh D M, Moeller F G (1999) Influence of trait hostility on tryptophan depletion-induced laboratory aggression. Psychiatry Research *88*: 227–232

Fessler D M T, Pillsworth E G, Flamson T J (2004) Angry men and disgusted women: An evolutionary approach to the influence of risk taking. Organizational Behavior and Human Decision Processes *95*: 107–123

Green A, Cross A, Goodwin G (1995) Review of pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy'). Pharmacology *119*: 247–266

Harris D S, Baggott M, Mendelson J, Jones R T (2002) Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. Psychopharmacology *162*: 396–405

Hoshi R, Bisla J, Curran H V (2004) The acute and sub-acute effects of 'ecstasy' (MDMA) on processing of facial expression: preliminary findings. Drug and Alcohol Dependence *76*: 297–304

Knight G P, Guthrie I K, Page M C, Fabes R A (2002) Emotional arousal and gender differences in aggression. Aggressive Behavior *28*: 366–393

Liechti M, Gamma A, Vollenweider F (2001) Gender differences in the subjective effects of MDMA. Psychopharmacology *154*: 161–168

Marsh D M, Dougherty D M, Moeller F G, Swann A C, Spiga R (2002) Laboratory-measured aggressive behaviour of women: acute tryptophan depletion and augmentation. Neuropsychopharmacology *26*: 660–671

Mas M, Farre M, de la Torre R, Roset P N, Ortuno J, Segura J, Cami J (1999) Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. Journal of Pharmacology and Experimental Therapeutics *290*: 136–145

Newman J L, Gray E A, Fuqua D R (1999) Sex differences in the relationship of anger and depression: an empirical study. Journal of Counselling and Development *77*: 198–203

Nunn J S, Thomas S L (1999) The angry male and the passive female: the role of gender and self-esteem in anger expression. Social Behaviour and Personality *27*: 145–154

Parrott A, Lasky J (1998) Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. Psychopharmacology *139*: 261–268

Reneman L, Booij J, de Bruin K, Reitsma J, de Wolff F, Gunnimg W, den Heeten G, Van de Brink W (2001) Effects of dose, sex, and long-term abstention from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. Lancet *358*: 1864–1869

Riley S C E, James C, Gregory D, Dingle H, Cadger M (2001) Patterns of recreational drug use at events in Edinburgh, Scotland. Addiction *96*: 1035–1047

Salomon R M, Kennedy J S, Johnson B W, Schmit D E, Kwentus J, Gwirsman H E, Ebert M H (2003) Association of a critical CSF tryptophan threshold level with depressive relapse. Neuropsychopharmacology *28*: 956–960

Sobczak S, Honig A, Nicolson N A, Riedel W J (2002) Effects of acute tryptophan depletion on mood and cortisol release in first-degree relatives of type I and type II bipolar patients and healthy matched controls. Neuropsychopharmacology *27*: 834–842

Solowij N, Hall W, Lee N (1992) Recreational MDMA use in Sidney: a profile of ecstasy users and their experiences with the drug. British Journal of Addiction *87*: 1161–1172

Symonds C S, Gallagher J M, Thompson J M, Young A H (2004) Effects of the menstrual cycle on mood, neurocognitive function and neuroendocrine function in healthy premenopausal women. Psychological Medicine *34*: 93–102

Verheyden S, Hadfield J, Calin T, Curran H (2002) Sub-acute effects of MDMA (3,4-methylenedioxymethamphetamine, 'ecstasy') on mood: evidence of gender differences. Psychopharmacology *161*: 23–31

Vollenweider F, 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

Zeichner A, Frey F C, Parrott D J, Butryn M F (1999) Measurement of laboratory aggression: a new response-choice paradigm. Psychological Reports *85*: 1229–1237

Zeichner A, Parrott D J, Frey F C (2003) Gender differences in laboratory aggression under response choice conditions. Aggressive Behavior *29*: 95–106

Zigmond A S, Snaith R P (1983) The Hospital Anxiety and Depression Scale. Acta Psychiatrica Scandinavica *67*: 361–370