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The sub-acute effects of recreational ecstasy (MDMA) use: a controlled study in humans

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Abstract

All previous studies of the sub-acute effects of ecstasy have failed to adequately control for group differences in psychopathology and past and concurrent substance use. The present study was designed to avoid these limitations. At an initial pre-drug baseline, a sample of 38 regular ecstasy users provided full substance histories and completed measures of personality and self-reported psychopathology. We then collected daily subjective measures of mood, cognitive impairment, restless sleep, sexual desire, craving for ecstasy and concomitant use of other substances for the next 9 days. The 20 participants who subsequently opted to take ecstasy during the 9-day assessment period reported modest sub-acute effects of ecstasy on negative mood and subjective cognitive impairment compared to those who did not after controlling for baseline group differences in psychopathology and frequency of ecstasy use. There were no significant sub-acute effects of ecstasy on interest in sexual activity or craving for ecstasy. After further controlling for co-use of alcohol with ecstasy, and the sub-acute effects of ecstasy on sleep, the sub-acute effect on mood remained marginally statistically significant but the sub-acute effect on cognitive impairment did not. The present findings suggest that the sub-acute effects of ecstasy in regular recreational users are relatively modest and transient but that such genuine effects may have been masked by, perhaps more clinically significant, chronic sequelae of regular ecstasy use in all previous studies of recreational ecstasy users.

Keywords

sub-acute, ecstasy, MDMA, 3-4-methylenedioxymethamphetamine, mood, cognition, sleep, psychopathology

Introduction

Recreational use of ecstasy (3,4-methylenedioxymethamphetamine, MDMA) has become increasingly widespread and is associated with 'clubbing' (e.g. Topp *et al.*, 1999; Winstock *et al.*, 2001). The average recreational dose of ecstasy is between one and two tablets, each containing approximately 80–150 mg of MDMA (Schifano, 1991; Henry, 1992). Most individuals use the drug at weekends once a week or less (Saunders, 1997) because tolerance to its positive effects develops rapidly (Solowij *et al.*, 1992; Davison and Parrott, 1997; Cottler *et al.*, 2001; Morgan *et al.*, 2002; Verheyden *et al.*, 2003a). Following the acute effects of ecstasy, which last from 3 to 6 h depending on dose consumed, surveys of ecstasy users suggest that they generally experience a 24–48 h period characterized by the persistence of the acute effects and the onset of additional effects including: muscle aches, fatigue, depression, irritability, difficulty in concentrating and headache (Peroutka *et al.*, 1988; Solowji *et al.*, 1992; Cohen, 1995; Davison and Parrott, 1997; Topp *et al.*, 1999; Verheyden *et al.*, 2003a, b). The latter sub-acute symptoms are similar to those reported by MDMA-naive healthy volunteers 24 h after they were administered MDMA (Vollenweider *et al.*, 1998). However, there is relatively less evidence about subsequent sub-acute effects. The available evidence suggests that only a minority of participants continue to experience: fatigue, irritability, loss of appetite, anxiety and depressed mood 3 or more days after a single dose of MDMA (Liechti *et al.*, 2000; Liechti and Vollenweider, 2000a, b; Vollenweider *et al.*, 1998). It is important to know if recreational ecstasy use also causes clinically significant sub-acute symptoms that last for several days after use because the typical regular ecstasy user, who uses the drug on a weekly or fortnightly basis, will be likely to experience such effects for a significant proportion of this time. Some studies of the sub-acute effects of ecstasy between 1 and 7 days after use have been conducted (Curran and Travill, 1997; Parrott and Lasky, 1998; Verheyden *et al.*, 2002; Curran *et al.*, 2004; Hoshi *et al.*, 2004). The first of these indicated

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that ecstasy users continued to report increased ratings for 'discontented', 'sad' and 'bored' 4 days after self-administration of the drug. Ecstasy users also exhibited lower mood than alcohol users the day after taking the drug, but were even more depressed 4 days later, at which point the scores of some users on the Beck Depression Inventory (BDI) were within the range for clinical depression (Curran and Travill, 1997). Parrott and Lasky (1998) reported that 2 days after ecstasy use participants displayed impaired memory recall and reported feeling significantly more depressed, abnormal and unsociable than they had before taking ecstasy and while on the drug. Verheyden *et al.* (2002) reported that participants reported significantly elevated BDI depression levels 4 days after taking ecstasy and the effect was more pronounced for females. Curran *et al.* (2004) reported that ecstasy users displayed a cognitive bias towards interpreting ambiguous information in an aggressive way 4 days after use. Ecstasy users also reported higher aggression and depression scores than controls 4 days after use whereas by day 7 after use, scores for both groups were similar. Hoshi *et al.* (2004) reported that ecstasy users were less accurate than controls at recognizing fearful facial expressions 4 days after use when compared with their overall ability to recognize other basic emotions. However, in contrast to Curran and Travill (1997) and Verheyden *et al.* (2002), Hoshi *et al.* (2004) failed to observe elevated BDI depression scores 4 days after ecstasy use.

Unfortunately interpretation of the findings of all of the latter studies is hampered by some serious design limitations. The majority of the latter investigators (Curran and Travill, 1997; Verheyden *et al.*, 2002; Curran *et al.*, 2004; Hoshi *et al.*, 2004) failed to collect any pre-drug baseline data. Instead, the measures of the psychological state of ecstasy users several days after taking the drug were compared to the same measures recorded while on the drug. Thus, it is not possible to determine if the purported mid-week dip in a variety of subjective measures of well-being and cognition were genuine sub-acute effects of ecstasy or more chronic impairments of mood and cognition that may have been masked by the acute effects of taking the drug. In contrast, Parrot and Lasky (1998) did employ an initial drug-free baseline assessment. They tested three groups: 15 regular ecstasy users who had taken it more than ten times; 15 novice ecstasy users who had taken it less than ten times; and 15 controls who had never taken it. After the initial drug-free baseline assessment, participants were tested three more times: on a Saturday night dance/club (on-drug), then 2 days later, and finally 7 days later. However, this study did not assess participants on a daily basis and is marred by another design limitation that is common to all of the latter studies. None employed ecstasy users who did not take ecstasy as controls for those who did. This is necessary because there is now considerable evidence that regular ecstasy use is associated with persistent psychological sequelae (e.g. Morgan, 1998, 1999, 2000), and any difference between groups after ecstasy use might be partly attributable to the chronic effects of regular ecstasy use before assessment in addition to the sub-acute effects of a particular dose of ecstasy. Indeed, the findings of Parrott and Lasky (1998) illustrate this point. Their novice users were significantly more sad at baseline than controls. Although it is unlikely that the ecstasy use of such novice users was frequent enough to be responsible for this reduced baseline mood there is some evidence that regular ecstasy use is associated with chronic depression of mood (e.g. Gerra *et al.*, 1998, 2000; Gamma *et al.*, 2000). Thus, in regular users, the transient elevation of mood after acute use of ecstasy, and the subsequent sub-acute reduction in mood, are both likely to be confounded by a chronic depression of baseline mood levels compared to lighter users and non-users. In order to fully control for any baseline differences the optimum approach is therefore to compare matched ecstasy users who do not take ecstasy to those who do. Another issue refers to the use of the BDI to measure changes in mood. Groth-Marnat (1990) reported that controversy exists over whether the revised BDI is measuring state or trait variables. Furthermore, Beck *et al.* (1961) suggested that if the BDI was re-administered within a short interval then scores could be spuriously inflated due to memory factors. A final methodological limitation is that the latter studies did not assess other substance use on the days following ecstasy use.

In the present study we aimed to avoid all of the methodological limitations outlined above. Volunteers, who all reported regular use of ecstasy, were administered a battery of psychological measures at an initial pre-drug baseline assessment on a Thursday and were subsequently assessed on a daily basis for the next 8 days. At baseline we collected full drug histories and measures of personality and self-reported psychopathology which allowed us to determine if there were any differences between those who subsequently chose to use ecstasy voluntarily during the following assessment period and those that opted to abstain for this period. We then phoned participants between 6.00 PM and 8.00 PM in the evening of the baseline day and for the next 8 days to collect daily subjective measures of mood, sleep, sexual desire, cognitive impairment, craving for ecstasy and concomitant use of other substances. In addition to collecting daily measures of mood and cognition we investigated daily subjective sleep disturbance because there is clinical (e.g. Allen *et al.*, 1993) and preclinical evidence (Biello and Dafters, 2001; Balogh *et al.*, 2004), that ecstasy/MDMA may disrupt circadian functions associated with sleep disorders, concentration difficulties and depression (Colbron *et al*, 2002). We assessed daily interest in sexual activity because there is some evidence that a minority of individuals experience a loss of sexual desire 48 h after using ecstasy (Solowij *et al.*, 1992; Parrott, 2001). We assessed craving for ecstasy on a daily basis because, although ecstasy is not normally considered to be associated with high dependence liability (e.g. von Sydow *et al.*, 2002), Topp and colleagues (1997) reported that almost half of their sample of ecstasy users would be classified as dependent on ecstasy, Cottler and colleagues reported that 43% of a sample of club drug users met DSM-IV criteria for dependence on ecstasy (Cottler *et al.*, 2001) and there are reports of cases of heavy ecstasy users who clearly meet the criteria for dependence (Jansen, 1999). Thus, it is possible that regular ecstasy users crave ecstasy in a similar fashion to the way cocaine users crave cocaine (e.g. Elman *et al.*, 2001) but, to date, craving for ecstasy in humans has not been systematically assessed. Finally, we collected daily measures of all other substance use to control for confounding by the effects of other substances on the sub-acute effects of ecstasy.

Materials and methods

Subjects

Volunteers, 20 males and 18 females, aged 18–29 years (mean ± SD = 21.6 ± 2.0) were recruited via email advertisements at the University of Sussex, by handing out flyers at local nightclubs and using the 'snowball' technique, where participants help to recruit further participants through their own contacts (Solowij *et al.*, 1992). All were regular recreational ecstasy users who reported using the drug at least once a month. Exclusion criteria included: a history of epilepsy, schizophrenia, bipolar disorder, use of heroin or any intravenous drug use, or any serious current medical condition that required medication. All participants reported that they were not under the influence of drugs or alcohol at the time of testing and gave their written consent after being informed by a written and oral description of the study. The study was approved by the University of Sussex Psychology Department Ethics Committee.

Study design

A mixed between and within factor design was used with ecstasy users who chose to use ecstasy voluntarily during a 9 day period (N = 20) and those who chose to abstain for this period (N = 18) as the two between conditions and successive days of assessment as repeated measures. After recruitment a meeting was arranged during the day on a Thursday to conduct an initial baseline assessment. The experimenter (J. Huxster) met with each participant individually in a convenient location with minimal distraction (e.g. a quiet area on campus or in the participant's home). Participants were given a number of questionnaires to complete, administered in the following order: Personal Details Questionnaire (PDQ), the 54-item Impulsiveness, Venturesomeness, and Empathy questionnaire (IVE – Eysenck and Eysenck, 1991), a General Drug Use History Questionnaire (GDUQ), the SCL-90-R (Derogatis, 1994) and finally a specific Ecstasy Use history Questionnaire (EUQ). The PDQ is a 15-item questionnaire with items on participants' age, gender, educational achievement, occupation, personal and family health history. It also includes items concerning smoking status and whether the participants had used alcohol or cannabis in the previous 24 h. The GDUQ requires participants to record whether they had ever used a number of drugs – and if so: their age at first use, duration of use, frequency of use, time since last use and usual dose consumed per session. The drugs listed were alcohol, nicotine, marijuana, ecstasy, cocaine, crack, amphetamine, pscilocybin mushrooms, LSD, PCP, mescaline, ketamine, heroin, morphine, 'poppers' (amyl nitrate), glue, solvents, barbiturates, benzodiazepines and anti-depressants. The EUQ is a 30-item questionnaire designed to explore past and present ecstasy use in detail, and to determine the participant's views on ecstasy (e.g. the potential long-term effects of taking the drug). The SCL-90-R is a 90-item psychiatric symptom checklist that employs a five-point Likert scale (0 – not at all, 1 – a little bit, 2 – moderately, 3 – quite a bit, 4 – extremely). Items correspond to one of ten dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism and additional items (including appetite, sleep, morbid thoughts and other symptoms associated with depression). A Global Severity Index (GSI) can also be derived to provide a single summary score of participants' self-reported psychopathology. The Daily Rating Scale (DRS) was left with participants on the Thursday after they had completed their baseline assessment. The experimenter then phoned each participant between 6.00 PM and 8.00 PM in the evening of that Thursday (Day 1) and then every evening on the subsequent 8 days and collected daily verbal responses to each of the ten DRS items. The DRS was adapted from the original 'six-item daily self-report measure assessing identified depressive domains' (Parker and Roy, 2003). Participants were requested to respond to each of the first seven subjective state items by rating how they felt at their worst on each day. The first nine items relating to subjective state were rated on a ten-point Likert scale from 'Not at all' to 'Extremely'. Of the 20 ecstasy users, six indicated that they had taken ecstasy later that Thursday night, six on Friday night, four on Saturday night and four on Sunday night. Thus, the data recorded for ecstasy users over the nine successive days from the Thursday to the following Friday was recoded so that the data from Day 1 indicate the baseline DRS measures a few hours before ecstasy use and the data from Day 2 indicate the responses to the DRS measures almost a full day (16–24 h) after use. One ecstasy user used it again 5 days after first use resulting in missing data for Day 6. However, data for six successive days was available from 19 users who remained ecstasy-free for at least 5 days after use.

Statistical analysis

All data were analysed with SPSS (version 11.0). Independent samples t-tests were used to test for group (ecstasy use versus no use) differences in age, gender ratio, education, personality, psychopathology and past and subsequent substance use. Prior to analysis of the DRS data, the data for the ecstasy group were recoded such that the day before voluntary use of ecstasy became the first assessed day (Day 1) and the subsequent 5 days after use became Days 2–6. The non-using controls were compared over a matched consecutive 6-day period. The data were then analysed with two way repeated measures ANOVAs with ecstasy group as a between factor and repeated measures on the day before ecstasy use and subsequent 5 days after use were used to assess group differences and changes in mood, cognitive capacity, sexual desire, sleep quality and craving for ecstasy. The Greenhouse-Geisser correction was employed if Mauchly's test for sphericity proved significant. Potential confounding variables were treated as covariates. Pearson's product moment correlation coefficient was employed to investigate correlations between dependent variables and dose-response relationships. The Bonferroni correction was employed in cases of multiple hypothesis testing.

Results

Baseline measures

Table 1 details the personal characteristics for subsequent ecstasy users (Ecstasy) and non-users (Control). There were no group differences for any of these measures.

Table 2 summarizes the substance use history means (±SD) for ecstasy users (Ecstasy) and non-users (Control). There were no statistically significant group differences for any of these measures. Of the 38 participants: all had used alcohol, ecstasy and cannabis, 33 had used cocaine, 32 pscilocybin mushrooms, 30 ketamine, 30 'poppers', 26 amphetamine, 25 LSD, ten nitrous oxide gas, ten benzodiazepines, nine opium, four mescaline, and five 'crack' experimentally.

No participants had taken ecstasy for at least 5 days prior to Day 1 of the study. Significant between-group differences were found for frequency of use per month [$t(36) = -2.34$, $p = 0.025$], days since last use [$t(36) = 2.288$, $p = 0.028$] and calculated lifetime consumption [$t(36) = -2.17$, $p = 0.036$]. There were no other group differences in ecstasy use history (see Table 3a).

There was a highly significant difference in the percentage of subsequent ecstasy users who reported that, in the past, they used cocaine in conjunction with ecstasy compared to control participants [$t(36) = -2.962$, $p = 0.005$], otherwise there were no significant group differences in the co-use of other substances (see Table 3b).

There were no significant group differences between subsequent ecstasy users (Ecstasy) and non-users (Control) for the IVE measures of personality (see Table 4a). However, there were significant group differences for the SCL-90-R GSI measure [$t(36) = -2.08$, $p = 0.046$], and the Somatization [$t(36) = -2.37$, $p = 0.023$], Anxiety [$t(36) = -2.46$, $p = 0.019$], and Additional items [$t(36) = -2.22$, $p = 0.032$], factor scores (see Table 4b). There were no group differences for the remaining SCL-90-R factor scores. However, there were significant group differences for the Ecstasy Use Questionnaire (EUQ) items: 'How much did you enjoy your last ecstasy tablet compared to the first tablet that you ever took?' [$t(36) = -3.20$, $p = 0.003$], and 'How strong was your urge to take your last ecstasy tablet?' [$t(36) = -3.34$, $p = 0.002$]. Across all participants scores for the latter two items were also positively correlated [$r = 0.434$, $p = 0.009$]. Subsequent ecstasy users indicated that they enjoyed their last tablet significantly more relative to their first, and had a stronger urge to take their last tablet, than control participants who opted to abstain from ecstasy use.

Table 1 Personal details

	Ecstasy (N = 20)	Control (N = 18)
Age mean (±SD)	21.25 (±1.21)	22.1 (±2.70)
Males (N)	12	9
Females (N)	8	9
University level education (N)	17	13
Current cigarette smokers (N)	16	16
Used alcohol in last 24 h (N)	18	13
Used cannabis in last 24 h (N)	10	11

Table 2 Substance use history means (±SD)

Substance	Ecstasy (N = 20)	Control (N = 18)
Alcohol (units per week)	33.4 (14.2)	28.5 (20.0)
Nicotine (cigarettes per week)	47.8 (34.5)	35.5 (39.0)
Cannabis (joints lifetime)	1736 (2161)	1590 (2020)
Cocaine (grams lifetime)	27.7 (27.0)	27.0 (31.7)
Amphetamine (grams lifetime)	11.5 (16.6)	7.8 (13.0)
Ketamine (grams lifetime)	94.3 (179.3)	65.1 (131.0)
LSD ('trips' lifetime)	11.9 (34.2)	38.6 (146.2)
Mushrooms ('hits' lifetime)	22.1 (29.1)	38.5 (73.6)
Poppers ('hits' lifetime)	181 (321)	62 (109)

Table 3a Participants' ecstasy consumption history means (±SD)

	Ecstasy (N = 20)	Control (N = 18)
Age at first use	16.85 (1.42)	17.39 (2.35)
Duration of use in years	4.45 (1.73)	4.61 (1.97)
Frequency of use per month	3.03 (1.59)*	1.94 (1.24)
Average dose per session (tablets)	2.55 (1.38)	1.94 (1.06)
Maximum dose per session (tablets)	6.92 (3.40)	5.39 (4.01)
Days since last use	10.0 (4.08)*	13.94 (6.52)
Estimated lifetime use**	250 (272)	161 (153)
Calculated lifetime use***	411 (451)*	174 (100)

*Significant group difference at $p = 0.05$, **Refers to participants' own estimate of their lifetime use, ***Derived from usual dose *frequency *duration.

Table 3b Percentage of participants using other substances with ecstasy

	Ecstasy (N = 20)	Control (N = 18)
Alcohol	100%	78%
Cannabis	65%	67%
Cocaine	60%*	17%
Amphetamine	10%	11%
Ketamine	55%	28%
Hallucinogens	35%	28%

*Significant group difference at $p = 0.05$.

Table 4a IVE means (±SD)

IVE measures	Ecstasy (N = 20)	Control (N = 18)
Impulsiveness	9.25 (4.55)	9.73 (3.57)
Venturesomeness	11.94 (2.90)	11.50 (2.03)
Empathy	15.20 (2.78)	14.00 (3.22)

Table 4b SCL-90-R means (±SD)

SCL-90-R measures	Ecstasy (N = 20)	Control (N = 18)
GSI	0.90 (0.57)*	0.57 (0.29)
Somatization	0.91 (0.62)*	0.49 (0.47)
Obsessive-compulsive	1.22 (0.72)	1.00 (0.60)
Inter-personal sensitivity	0.87 (0.72)	0.67 (0.50)
Depression	1.10 (0.71)	0.81 (0.53)
Anxiety	1.01 (0.83)*	0.48 (0.38)
Hostility	0.51 (0.41)	0.52 (0.54)
Phobic anxiety	0.46 (0.64)	0.17 (0.34)
Paranoid ideation	0.55 (0.54)	0.62 (0.68)
Psychoticism	0.64 (0.66)	0.35 (0.39)
Additional factors	1.16 (0.61)*	0.75 (0.52)

*Significant group difference at $p = 0.05$.

As indicated above, the ecstasy users used the drug more frequently, more recently, and were calculated to have used it more in their lifetimes than controls. Frequency of ecstasy use was highly positively correlated with calculated lifetime consumption [$r = 0.671$, $p < 0.001$], and negatively correlated with time since last use [$r = -0.558$, $p < 0.001$]. Thus, to control for baseline group differences in past ecstasy use, frequency of ecstasy use per month was treated as a covariate. Ecstasy users also reported elevated SCL-90-R Global Severity Index (GSI), anxiety, somatization and restless sleep factor scores compared to controls. GSI scores were highly ($p < 0.001$) positively correlated with the specific anxiety ($r = 0.936$), somatization ($r = 0.721$) and restless sleep factor scores ($r = 0.764$). Thus, to control for this baseline difference in psychopathology between groups the GSI score was also treated as a covariate in all of the following analyses.

Daily Rating Scale (DRS) data

Negative mood The data from the four mood-related items ('How depressed did you feel?'; 'How irritable and crabby did you feel?'; 'How ruminative and brooding were you about negative things?'; 'How anxious did you feel?') were averaged to derive a summary negative mood score. Two way repeated measures ANCOVA with group as the between factor, the 6 assessment days as the within factor, and frequency of past ecstasy use and baseline GSI scores treated as covariates, yielded no main effect of group, no main effect of day, but a significant group by day interaction [$F(5, 29) = 2.603$, $p = 0.028$] (see Fig. 1).

Cognitive impairment The data from the two cognition items ('How difficult was it for you to concentrate on things?' and 'How difficult was it for you to remember things?') were averaged to derive a summary subjective cognitive impairment score. After Greenhouse-Geisser correction for significant sphericity, two way repeated measures ANCOVA with ecstasy group as the between factor, the 6 successive assessment days as the within factor and frequency of ecstasy use and GSI treated as covariates, yielded no main effect of group, or day, but a significant main group by day interaction [$F(3.063, 88.836) = 4.566$, $p = 0.005$] (see Fig. 2).

Restless sleep Two way repeated measures ANCOVA of responses to the DRS item 4 'How restless was your sleep last night compared to usual?' with ecstasy group as the between factor, the 6 successive assessment days as the within factor and

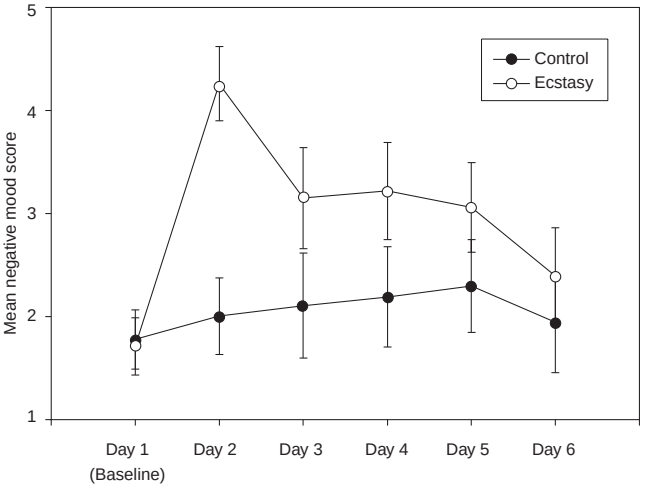

Figure 1 ANCOVA of pooled daily measures of negative mood with group as the between factor, the 6 assessment days as the within factor, and frequency of past ecstasy use and baseline GSI scores treated as covariates, yielded no main effect of group, no main effect of day, but a significant group by day interaction [$F(5, 29) = 2.603$, $p = 0.028$].

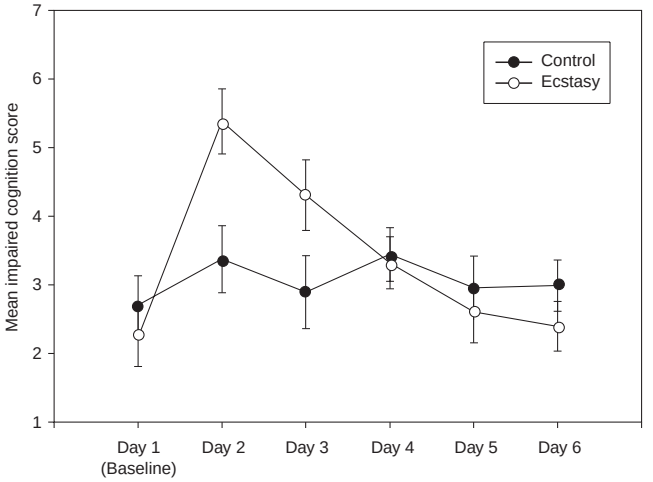

Figure 2 ANCOVA of mean daily measures of impaired cognition with group as the between factor, the 6 assessment days as the within factor, and frequency of past ecstasy use and baseline GSI scores treated as covariates, yielded no main effect of group, no main effect of day, but a significant group by day interaction [F (3.063, 88.836) = 4.566, $p = 0.005$].

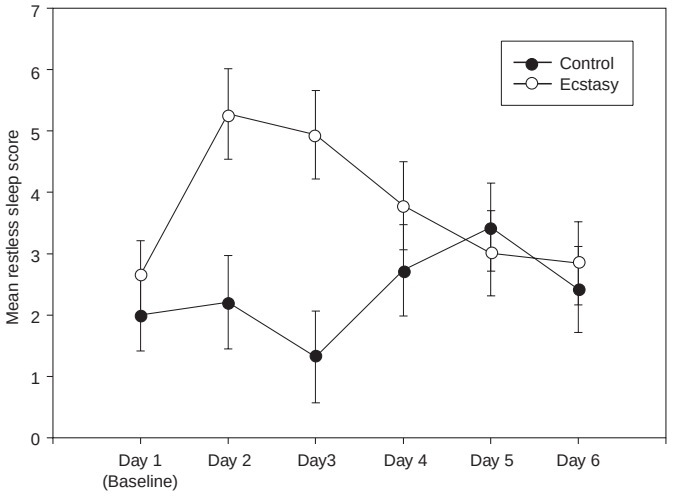

Figure 3 ANCOVA of daily measures of restless sleep with group as the between factor, the 6 assessment days as the within factor, and frequency of past ecstasy use and baseline GSI scores treated as covariates, yielded a significant main effect of group [F (1, 29) = 5.103, $p = 0.032$], no main effect of day, and a significant group by day interaction [F (5, 29) = 2.972, $p = 0.014$].

on Day 2 as covariates, yielded no effect of group, a significant effect of day [F (5, 27) = 2.591, $p = 0.028$] and a significant group by day interaction [F (5, 27) = 2.379, $p = 0.042$]. However, after Greenhouse-Geisser correction for sphericity, two way repeated measures ANCOVA of impaired cognition scores with frequency of ecstasy use, GSI and restless sleep and alcohol use on Day 2 as frequency of ecstasy use and GSI treated as covariates, yielded a significant main effect of group [F (1, 29) = 5.103, $p = 0.032$], no main effect of day and a significant group by day interaction [F (5, 29) = 2.972, $p = 0.014$] (see Fig. 3).

Sexual desire and craving for ecstasy Ecstasy proved to have little effect on interest in engaging in sexual activity (which remained moderate), or on craving for ecstasy (which ranged from none to mild), throughout the 6-day assessment period. Two way repeated measures ANCOVA of the scores for: 'How interested did you feel in engaging in sexual activity?' and 'How much did you want to take "ecstasy"?', with ecstasy group as the between factor, the 6 assessment days as the within factor and frequency of ecstasy use and GSI treated as covariates, yielded no main effects of group, day, or group by day interactions. One way ANOVA indicated a significant difference in craving between those who subsequently used ecstasy and those who did not on the day before use [F (1, 36) = 5.802, $p = 0.021$]; however, this group difference became non-significant after re-analysis with GSI treated as a covariate.

Restless sleep as an additional covariate Since the period of disturbed sleep coincided with the period of self-reported negative mood and cognitive impairment after ecstasy use (see Figs 1, 2, and 3), and restless sleep on Day 2 was positively correlated with negative mood on Day 2 [r = 0.339, $p = 0.037$], and impaired cognition on Day 3 [r = 0.472, $p = 0.003$], the latter analyses were conducted again with restless sleep treated as an additional covariate. Two way repeated measures ANCOVA of negative mood, with frequency of ecstasy use, GSI and restless sleep on Day 2 as covariates, yielded no effect of group, no effect of day, and a significant group by day interaction [F (5, 28) = 2.459, $p = 0.036$]. Similarly, after Greenhouse-Geisser correction for sphericity, two way repeated measures ANCOVA of impaired cognition with frequency of ecstasy use, GSI and restless sleep on Day 2 as covariates yielded no main effect of group, no main effect of day and a marginally significant group by day interaction [F (2.966, 83.060) = 2.835, $p = 0.044$].

Daily alcohol consumption After Greenhouse-Geisser correction for sphericity, two way ANCOVA of daily alcohol consumption (in units) during the 6-day assessment period with ecstasy group as the between factor, the 6 successive assessment days as the within subjects factor and frequency of ecstasy use and GSI as covariates, yielded no main effect of group, a main effect of day [F (3.741, 108.501) = 3.142, $p = 0.020$] and a significant group by day interaction [F (3.741, 108.501) = 2.835, $p = 0.031$]. Ecstasy users tended to drink more alcohol on the day that they consumed ecstasy (see Fig. 4).

Daily alcohol consumption as an additional covariate Since ecstasy users tended to drink more alcohol on the day that they consumed ecstasy the latter analyses were conducted again with alcohol consumption on Day 2 treated as an additional covariate. Two way repeated measures ANCOVA of negative mood scores, with frequency of ecstasy use, GSI, restless sleep and alcohol use

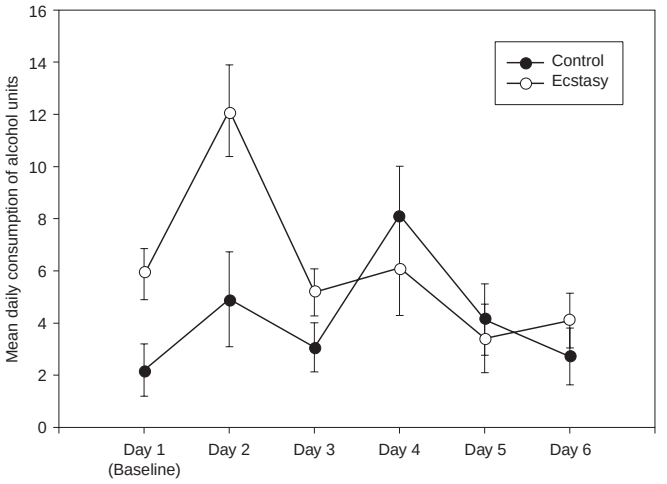

Figure 4 ANCOVA of daily measures of alcohol consumption with group as the between factor, the 6 assessment days as the within factor, and frequency of past ecstasy use and baseline GSI scores treated as covariates, yielded no main effect of group, a main effect of day [F (3.741, 108.501) = 3.142, $p = 0.020$], and a significant group by day interaction [F (3.741, 108.501) = 2.835, $p = 0.031$].

covariates yielded no main effect of group, no main effect of day and no group by day interaction.

Cigarettes After Greenhouse-Geisser correction for sphericity, two way ANCOVA of cigarettes smoked per day with ecstasy group as the between factor, 6 assessment days as the within subjects factor, and frequency of ecstasy use, GSI, restless sleep and alcohol use on Day 2 as covariates, yielded no main effect of group, or day and no group by day interaction.

Cannabis Fifteen of the 18 controls and 12 of the 20 ecstasy users reported using cannabis during the 6 successive assessment days. After Greenhouse-Geisser correction for sphericity, two way ANCOVA of cannabis joints smoked per day with ecstasy group as the between factor, the 6 assessment days as the within subjects factor, and frequency of ecstasy use, GSI, restless sleep and alcohol use on Day 2 as covariates, yielded no main effect of group, or day and no group by day interaction. Independent samples t-tests indicated there were no significant differences between mean negative mood and impaired cognition scores over the 6-day period between the 12 ecstasy users who used cannabis and the eight who did not.

Ketamine Seven controls reported using ketamine over the weekend and seven ecstasy users also reported using it – but all on the day that they consumed ecstasy. Independent samples t-tests indicated that there were no significant differences between mean negative mood and impaired cognition scores over the 6-day period between the seven ecstasy users who used ketamine and the 13 who did not.

Pscilocybin mushrooms: Five controls reported taking mushrooms on one occasion each over the weekend. Independent samples t-tests indicated that there were no significant differences between negative mood and impaired cognition scores over the 6-day period between the five controls who used mushrooms and the 13 who did not.

Use of other substances during the 6-day assessment period was not frequent enough for statistical analysis: *Cocaine*: Only four controls and four ecstasy users used cocaine; *'Poppers'*: Only one ecstasy user reported using 'poppers' (amyl nitrite) twice over the 6 days. *Amphetamine*: One ecstasy user reported using amphetamine (0.25 g) with ecstasy.

Dose-response relationships Across all participants the number of ecstasy tablets consumed during the 6-day assessment period was positively correlated with negative mood [$r = 0.668$, $p < 0.001$] (see Fig. 5), impaired cognition [$r = 0.543$, $p < 0.001$] and restless sleep [$r = 0.408$, $p = 0.011$] the day after use. Negative mood on Day 2 was also positively correlated with negative mood on Day 3 [$r = 0.604$, $p < 0.001$], and impaired cognition on Day 2 [$r = 0.611$, $p < 0.001$] and Day 3 [$r = 0.487$, $p = 0.002$]. The number of ecstasy tablets consumed during the 6-day assessment period was positively correlated with the past frequency of ecstasy use per month [$r = 0.387$, $p = 0.017$] and negatively correlated with the time since last use [$r = -0.402$, $p = 0.012$]. Negative mood scores on Day 2 were also positively correlated with the frequency of ecstasy use per month [$r = 0.426$, $p = 0.008$], calculated lifetime consumption [$r = 0.498$, $p = 0.001$] and negatively correlated with the time since last use [$r = -0.481$, $p = 0.002$]. Finally, alcohol consumed in the 6-day period correlated

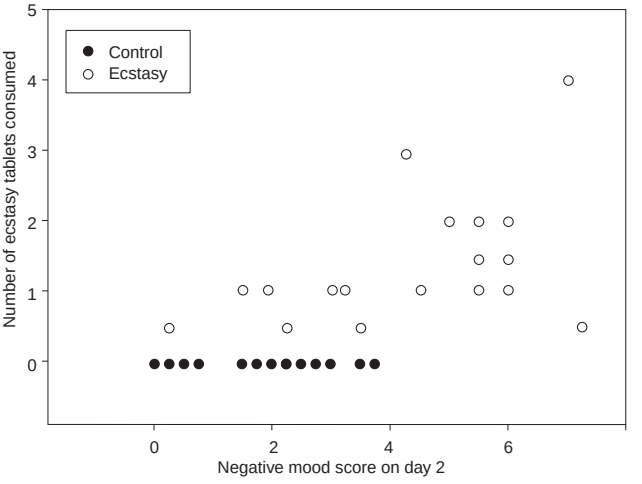

Figure 5 Across all participants the number of ecstasy tablets consumed during the 6-day assessment period was positively correlated with negative mood [$r = 0.668$, $p < 0.001$] the day after use. Among ecstasy users alone the number of tablets consumed during the 6-day assessment period was also marginally positively correlated with negative mood [$r = 0.446$, $p = 0.049$] the day after use – but after correction for multiple hypothesis testing the latter correlation was not significant.

positively with ecstasy tablets taken in the same period [r = 0.386, $p = 0.017$].

Among ecstasy users alone the number of tablets consumed during the 6-day assessment period was marginally positively correlated with the negative mood score [r = 0.446, $p = 0.049$] but not with the impaired cognition or restless sleep scores on Day 2. However, after correction for multiple hypothesis testing the latter correlation was not significant. The day after use, negative mood was positively correlated with the extent of self-reported impaired cognition [r = 0.531, $p = 0.016$].

Finally, there was a positive correlation between participants' urge to take their last ecstasy tablet and self-reported SCL-90-R anxiety scores at baseline (r = 0.348, $p = 0.041$), but DRS measures of craving were not correlated with either SCL-90-R measures of anxiety or DRS daily ratings of anxiety.

Discussion

The results of the present study emphasize the importance of controlling for differences in baseline psychopathology and past use of ecstasy and other substances, as well as subsequent co-use of other substances, when attempting to determine the specific sub-acute effects of ecstasy. In the present study a group of 20 ecstasy users who opted to consume ecstasy after baseline assessment during a 9-day follow-up period did not differ from a group of 18 ecstasy users who opted not to take ecstasy in terms of age, personality and most measures of past substance use other than ecstasy. A greater percentage of subsequent ecstasy users reported using cocaine in conjunction with ecstasy – although the actual number of individuals reporting cocaine use during the subsequent assessment period did not differ. Subsequent ecstasy users also indicated that they enjoyed their last tablet more, and had a stronger urge to take their last tablet, compared to control participants who opted to abstain from ecstasy use. Furthermore, they also reported elevated SCL-90-R global psychopathology, anxiety, somatization and restless sleep factor scores compared to controls. Finally, as might be expected, the subsequent ecstasy users reported using it more frequently, more recently, and (on the basis of their frequency of use) were calculated to have used more in their lifetimes than those who did not take it.

After controlling for past group differences in psychopathology and frequency of ecstasy use the volunteers who opted to take ecstasy reported modest sub-acute effects of ecstasy on negative mood (depression, irritability, rumination and anxiety) and subjective cognition (memory and concentration) compared to controls. The elevation of self-reported impaired cognition returned to baseline within 48 h after use. However, in contrast, after a relatively marked rise in negative mood 24 h after ecstasy use, negative mood then tended to plateau before gradually returning to baseline 3–4 days after use. Sleep was also disrupted in ecstasy users for 48 h after ecstasy use. When disrupted sleep was treated as an additional covariate the sub-acute effect of ecstasy on negative mood remained unchanged whereas the sub-acute effect on subjective cognition was attenuated but remained marginally significant. However, ecstasy users also tended to drink more alcohol on the day that they consumed ecstasy and when alcohol use over the 6-day assessment period was also included as a covariate the sub-acute effect of ecstasy on mood remained marginally significant but the effect on cognition became non-significant.

There were no group differences in the daily use of other substances during the extracted 6-day comparison period. Furthermore, there were no significant differences between negative mood and impaired cognition scores over this period between the 12 ecstasy users who used cannabis and the eight who did not. Similarly, there were no significant differences between the seven ecstasy users who used ketamine and the 13 who did not. Across all participants there was evidence of dose-response relationships between the number of ecstasy tablets consumed during the study and the magnitude of the sub-acute effects on mood, cognition and sleep suggesting a pharmacological effect. However, within the group that used ecstasy during the study this relationship was only marginally significant for negative mood and was not significant for cognition and sleep impairment. Furthermore, after correction for multiple hypothesis testing the latter dose-response relationship failed to achieve statistical significance.

The present findings suggest that if all baseline differences between ecstasy users and non-users are systematically controlled for, there is little evidence that ecstasy produces much more than modest and relatively transient sub-acute effects on mood and cognition. Furthermore if elevated co-use of alcohol and the sub-acute effects of ecstasy on sleep are controlled for, the residual sub-acute effect of ecstasy on mood is even more modest and the sub-acute effects on self-reported cognitive impairment become statistically non-significant. This profile is very different from the widely accepted view that ecstasy produces such potent sub-acute effects on mood that some users become so depressed 4 days after use that their Beck Depression Inventory (BDI) scores fall within the range for clinical depression (Curran and Travill, 1997; Verheyden *et al.*, 2002). However, the latter findings have not been replicated by the same laboratory (Hoshi *et al.*, 2004), and they derive from studies without baseline data or adequate control for other substance use. If the present data had been presented without controlling for baseline differences in mood and substance use the apparent sub-acute effects of ecstasy would have looked far more impressive (data not shown) but this would have conflated chronic differences between more and less frequent users of ecstasy and the actual sub-acute effects of a specific dose of ecstasy. The present findings are more in line with those of Parrott and Lasky (1998) who reported that 2 days after ecstasy use participants reported feeling more depressed, abnormal and unsociable than they had before taking ecstasy and while on the drug. However, these investigators did not statistically control for baseline differences in ecstasy use or other substance use either before or during their study. Perhaps, not surprisingly, the present results are most consistent with those of Liechti and Vollenweider and colleagues (Liechti *et al.*, 2000; Liechti and Vollenweider, 2000a, b; Vollenweider *et al.*, 1998) who administered a single dose of 1.5 mg/kg of MDMA to volunteers under double-blind placebo-controlled conditions. For example, Liechti and Vollenweider (2000a) reported that signs of depressed mood, including irritability,

brooding, and gloomy thoughts, together with difficulty concentrating, were only observed in approximately one third of their mainly ecstasy-naive participants within 3 days after MDMA administration.

The fact that the ecstasy users in the present study exhibited elevated global psychopathology, anxiety, somatization and restless sleep factor scores compared to control ecstasy users who opted not to take ecstasy is interesting and is in agreement with previous reports of associations between the extent of ecstasy use and self-reported psychopathology (e.g. Allen *et al.*, 1993; Schifano *et al.*, 1998; Parrott *et al.*, 2000; Morgan *et al.*, 2002; Lieb *et al.*, 2002; Thomasius *et al.*, 2003). For example, we (Morgan *et al.*, 2002) reported that current ecstasy users exhibited particularly elevated ($p < 0.01$) GSI and anxiety scores compared to polydrug users who did not use ecstasy. Interestingly, the GSI and anxiety scores in question were in a similar range to those reported by the ecstasy users in the present study. Although it is likely that such elevated psychopathology is associated with the greater frequency of use of ecstasy by those who used it in the present study it is also possible that it is associated with their reported elevated past use of cocaine with ecstasy. However, in contrast to our findings (Morgan *et al.*, 2002), and those of others (e.g. Thomasius *et al.*, 2003; Daumann *et al.*, 2004) the present results provide no support for an association between the extent of self-reported psychopathology and cannabis consumption. Nor do they provide any evidence that co-use of cannabis with ecstasy is neuroprotective (e.g. Gonzalez *et al.*, 2004).

Although the present study employed a design that catered for many of the shortcomings of past studies of the sub-acute effects of recreational ecstasy use there were some methodological limitations with our approach that characterize research in this area. These included problems with sampling and the reliability of self-reported drug histories (e.g. Morgan, 2000). However, Thomasius and colleagues (2003) reported 95% concordance between self-reported ecstasy use and the results of confirmatory hair analyses suggesting that the present self-reported drug histories are likely to be reasonably reliable. Optimally, it would also have been helpful to collect more detailed information about the activities of participants on the night that they either did or did not take ecstasy and exactly when they went to sleep. Another shortcoming was the lack of any objective behavioural measures of cognitive performance. In future we plan to address these issues by replicating and augmenting the present methodology with larger sample sizes, using assays to confirm drug histories, and administering more detailed daily assessment items and a battery of repeated neuropsychological and physiological measures. It is possible that the relatively modest sub-acute effects of ecstasy observed in the present study reflect a high degree of tolerance for such effects in particularly frequent users. On the other hand the frequent users who consumed ecstasy during the present study reported that they experienced significantly less tolerance to the acute effects of their last ecstasy dose compared to their first than the control participants. Ecstasy proved to have few sub-acute effects on interest in engaging in sexual activity (which remained moderate), or on craving for ecstasy (which ranged from none to mild), throughout the 6-day assessment period. However, the participants who went on to consume ecstasy did indicate an increased urge to take the drug the day before they consumed it suggesting that mild craving for ecstasy is associated with an intent to use it.

There was also a positive correlation between participants' urge to take their last ecstasy tablet and self-reported SCL-90-R anxiety scores at baseline. This could suggest that elevated trait-like anxiety at baseline might predispose ecstasy users to take ecstasy. However, the DRS measures of daily craving and anxiety state were not correlated, and nor were measures of daily craving and SCL-90-R anxiety, suggesting that this effect is not particularly robust. The lack of effect of ecstasy on sexual desire appears to contrast with survey evidence (Solowij *et al.*, 1992; Parrott, 2001). However, Solowij *et al.* (1992) reported that only 12% of their respondents reported a loss of sexual urges 48 h after using ecstasy. The present data suggest that the sub-acute effects of ecstasy in regular recreational users are relatively modest but that such genuine effects may have been masked by, perhaps more clinically significant, chronic sequelae of regular ecstasy use in all previous studies of recreational ecstasy users.

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