Psychopharmacology (2010) 209:25–36
DOI 10.1007/s00213-009-1763-5

ORIGINAL INVESTIGATION

Depressive and anxiety symptomatology in ecstasy users: the relative contribution of genes, trauma, life stress and drug use

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Received: 13 September 2009 / Accepted: 14 December 2009 / Published online: 26 January 2010

Abstract
Rationale Previous research has identified elevated rates of depressive and anxiety symptoms amongst ecstasy users; however, few studies have examined which factors increase the likelihood of experiencing such symptoms.
Objectives The current study aimed to determine the relationship between ecstasy use and depressive/anxiety symptomatology after controlling for known environmental and genetic (polymorphism of the serotonin transporter gene) risk factors for depression and anxiety disorders.
Methods Participants consisted of a community sample of 184 18–35-year olds who had taken ecstasy at least once in the past 12 months. Participants completed an interview and questionnaires and provided a saliva sample. Mood symptoms were assessed using the Mood and Anxiety Symptom Questionnaire. Timeline methods were used to collect information on lifetime and recent ecstasy use, as well as recent other drug use and life stress. Trauma exposure was measured using the Composite International Diagnostic Interview—Trauma List. Genomic DNA was extracted from participant saliva samples.
Results Neither lifetime nor recent ecstasy use was associated with the severity of current mood symptoms, either alone or in combination with genetic risk factors. Rather, lifetime trauma, recent stressful life events, the frequency of tobacco use and recent polydrug use significantly predicted the severity of depressive and anxiety symptoms.
Conclusions These results highlight the need to consider the role of environmental factors when examining the relationship between ecstasy use and mood symptoms. Whether ecstasy exacerbates such symptoms in vulnerable individuals requires further investigation using prospective designs.

Keywords Ecstasy · MDMA · Depression · Anxiety · Serotonin transporter · Trauma · Life stress · Risk factors

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Introduction

3,4-Methylenedioxymethamphetamine (MDMA) or 'ecstasy' is a popular recreational drug, particularly amongst young people, with up to 24% of Australian 20–29-year olds reporting lifetime ecstasy use (Australian Institute of Health and Welfare 2008). Although prevalence rates have stabilised in Australia in the last 3 years, the rates are still higher than those observed in Europe and North America (United Nations Office on Drugs and Crime 2008, 2009). Ecstasy is taken for its acute effects, including feelings of euphoria, increased energy and greater sociability and connectedness with others (Cohen 1995; White et al. 2006). Increasing popularity and reports that ecstasy is neurotoxic to the serotonin system of laboratory animals (Ricaurte et al. 2000) and possibly humans (McCann et al. 2008) have raised concern about the potential psychological consequences of ecstasy use. While several studies have found that ecstasy

users have higher levels of depressive and anxiety symptoms (Lamers et al. 2006; McCardle et al. 2004; MacInnes et al. 2001) and that greater lifetime ecstasy use is related to more severe symptomatology (Sumnall and Cole 2005; Verheyden et al. 2003), other studies have found that symptom severity is related to illicit drug use in general, not ecstasy per se (Bedi et al. 2008; Sumnall et al. 2004).

While methodological differences across studies may have contributed to these mixed findings (Bedi et al. 2008; Curran 2000), limited research has explored the role of other risk factors for depression and/or anxiety on the relationship between ecstasy use and psychopathology. Causation models for depression and anxiety disorders indicate that both genetic and environmental factors contribute to their onset (Goldberg 1994; Kendler et al. 2002, 2006). Individuals with the *S* ("short") allele of the serotonin transporter gene (*5-HTTLPR*) have been found to have elevated risk for depression (Furlong et al. 1998) and anxiety-related personality traits (Lesch et al. 1996), and there is some evidence that ecstasy users with the *S* allele also exhibit abnormal emotional processing and heightened depressive symptomatology (Roiser et al. 2005).

A broad range of environmental factors have been associated with increased risk of psychopathology. In particular, adverse life events, such as trauma and life stress, have been identified as a key environmental risk factor for depression, anxiety and substance (ab)use (Kendler et al. 2002, 2006; Kessler 1997, McCauley et al. 1997). Exposure to multiple adverse life events has also been shown to further increase the risk of psychopathology (Chapman et al. 2004; Copeland et al. 2007), and childhood trauma is a particularly strong risk factor for co-occurring anxiety, mood and substance use disorders (De Graaf et al. 2002). In a study looking at the psychosocial profile of ecstasy users, Singer and colleagues found that ecstasy users reported more experiences of childhood abuse and neglect, were more likely to be depressed and exhibited more severe levels of substance use than ecstasy-naïve drug-using controls (Singer et al. 2004). Life stress has also been found to be associated with current depressive symptomatology amongst former chronic ecstasy users (MacInnes et al. 2001).

The relationship between ecstasy use and mood symptoms remains poorly understood, despite evidence that ecstasy users report greater depressive and anxiety symptomatology compared to non-drug and ecstasy-naïve drug-using controls. The current study aims to determine if ecstasy use is associated with current depressive and anxiety symptomatology, after controlling for known genetic and environmental risk factors for depression, anxiety and substance use. It was hypothesised that (1) lifetime and recent ecstasy use would be associated with the severity of current depressive and anxiety symptoms, but (2) any association between lifetime ecstasy use and severity of current depressive and anxiety symptoms would no longer be significant after controlling for other predictor variables, including *5-HTTLPR* genotype, lifetime trauma, recent life stress and other drug use.

Materials and methods

Participants

Participants consisted of a community sample of 190 individuals aged between 18 and 35 years who had taken ecstasy at least once in the last 12 months. Participants were recruited from Melbourne, Australia, via advertisements in university job websites and newsletters, a national dance music website, a free street music magazine and a local newspaper. Flyers were also distributed in locations frequented by young people such as cafes, music stores and dance music events. A 'snowballing' technique (Solowij et al. 1992) was also used to recruit the friends, family and acquaintances of individuals participating in the study. Participants were excluded if they were pregnant, were unable to converse fluently in English or had a history of a psychotic disorder.

Measures

Substance use Lifetime ecstasy use was calculated using a context-based timeline method, which asked participants to recall when they first took ecstasy and then prompted them to identify contextual information (e.g. periods of work, study, travel, living arrangements, relationships) to assist recall of their patterns of ecstasy use along a timeline. Context-based timeline methods demonstrate adequate test–retest reliability amongst people with substance use disorders (Anglin et al. 1993), and the use of timelines with life events increases recall accuracy of past drug use (Del Boca and Darkes 2003; Shillington et al. 1995). Duration of ecstasy use was calculated by subtracting age of first use from current age. A score of zero was recorded to 0.5 for 12 participants who had recently initiated ecstasy use.

Participants were also asked to report lifetime use (yes/no), age of first use and the most frequent use (never used, less than monthly, monthly, two to three times a month, weekly, daily or almost daily) of alcohol, tobacco, cannabis, amphetamines, cocaine, hallucinogens, inhalants, opiates, benzodiazepines/sedatives, ketamine and gamma-hydroxybutyric acid (GHB). The total number of substances consumed was used as a measure of lifetime polydrug use. Recent drug use was assessed using the timeline followback (TLFB) method for the preceding 28 days (Sobell and Sobell 1992). This method retrospec-

tively assesses the frequency and quantity of recent substance use anchored against life events (see "Life stress" measure below) to assist recall. The TLFB has well-established reliability and validity for assessing alcohol and illicit drug use (Fals-Stewart et al. 2000).

Mood symptoms Current depressive and anxiety symptoms were measured using the 62-item Mood and Anxiety Symptom Questionnaire—Short Form (MASQ; Watson and Clark 1991). This self-report tool provides two scales of general distress (GD) symptomatology (GD depressive and GD anxious), a depression-specific scale (anhedonic depression) and an anxiety-specific scale (anxious arousal). Participants indicated how much they had experienced each symptom over the previous week (1 = *not at all* to 5 = *extremely*). The MASQ demonstrates excellent convergent and discriminant validity between anxiety and depressive symptoms in both clinical and non-clinical samples (Watson et al. 1995) and has been found to have good sensitivity and specificity in predicting mood disorders in clinical samples (Buckby et al. 2007). All four subscales demonstrated very good internal consistency with the current sample (Cronbach's α=0.87–0.92).

Serotonin transporter Genomic DNA was extracted from participant saliva samples (Heils et al. 1996). *5-HTTLPR* was determined by polymerase chain reaction using Gotaq Hot Start polymerase (Promega), followed by identification of the 'short' (*S*) and 'long' (*L*) alleles. Genetic analyses were conducted at Monash University by one of the authors (R.B.).

Trauma The Composite International Diagnostic Interview—Trauma List (World Health Organisation 1997) was used to identify the incidence of life events meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criterion A for exposure to a traumatic event (American Psychiatric Association 2000). The first nine items relate to specific traumas experienced by the participant (e.g. physical assault). The last two items include an 'other' item for traumatic events not included in the previous nine items. The final item refers to experiencing 'a great shock' in response to someone close to them being exposed to a traumatic event. If participants respond yes to an item, they are asked if at the time they experienced feelings of 'intense fear, helplessness or horror'. Participants were given a score of 1 if they responded 'yes' to both questions relating to each item, with a total possible lifetime trauma score of 11.

Life stress Participants were asked if they had experienced any major stressful life events in the month preceding the interview while completing the TLFB. Life events were defined according to subject areas from the Psychiatric Epidemiological Research Interview—Life Events Scale (Dohrenwend et al. 1978). Subject areas included employment and study (e.g. lost job, university exams), finances (e.g. went off benefits), relationships and family (e.g. breakup of romantic relationship, family conflict), residence (e.g. moved house), health (e.g. physical illness) and crime and legal matters (e.g. victim of assault). Life events were only included if participants reported finding the event stressful. Events were tallied to provide a total recent stressful life events score. Participants also rated how stressed they felt in general over the past month (subjective stress; 1 = *not stressed at all* to 10 = *extremely stressed*).

Procedure

The study was approved by the Monash University Human Ethics Committee. Potential participants were initially screened via a brief telephone interview to ensure they met inclusion criteria. To minimise potential subacute drug effects, participants were requested to abstain from taking ecstasy for at least 7 days prior to participating, using other recreational drugs for at least 24 h, with the exception of tobacco and caffeine, and drinking alcohol within 12 h of the interview.

Individuals who provided informed consent to participate in the study were interviewed face to face for approximately 1 h by a post-graduate clinical psychology student (R.S.) and were asked to provide a saliva sample for genetic analysis. All participants were reimbursed Australian $25 for their time and travel-related expenses.

Results

Participation rate and data screening

Of the original 190 consenting participants, six participants were excluded due to recent drug use (n=4) and lack of English fluency (n=2). Seven outliers on the MASQ subscales were identified with a box plot and truncated to one above the outlier scores. There were seven missing data points for the *5-HTTLPR* genotype due to failed or missing biological analyses. Following initial data screening, logarithmic transformations were used on lifetime ecstasy use, greatest number of ecstasy pills taken in a 12-h period, recent polydrug use and recent ecstasy use to reduce skewness and kurtosis and improve normality. The serotonin transporter gene was dummy-coded (gene_dummy1, gene_dummy2). Interaction terms were then created with genotype by ecstasy use to be included in the regressions. Multivariate outliers were identified using Mahalanobis distance (p<0.001). An alpha level of 0.01 was required for

statistical significance for all analyses to account for the increased likelihood of type 1 error caused by the multiple comparisons made. All data were analysed using SPSS version 17 (SPSS Inc., Chicago, IL, USA).

Sample characteristics

The final data set contained 184 participants (87 males and 97 females) with a mean age of 23.3 (SD=4.0) years. The majority of participants identified themselves as Caucasian (n=128; 72.3%), followed by Asian (n=12, 6.5%), Indian (n=11, 6.0%), mixed ethnicity (n=10, 5.4%) and a small minority identified themselves as indigenous Australian (n=2, 1.1%). One hundred and ten participants (59.8%) were born in Australia, and 169 (91.8%) reported English as the main language spoken at home. A large number of participants were currently enrolled in tertiary education (n=122, 66.3%), 51 were working full time (27.7%) and nine (4.9%) were unemployed. Ninety percent (n=166) of the sample had completed or were currently undertaking post-secondary school qualifications. Fifty-one (27.7%) participants reported that they had received one or more psychiatric diagnoses during their lifetime. The most commonly reported diagnosis was unipolar depression (n=35, 19.0%), followed by an anxiety disorder (n=17, 9.2%). Five (2.7%) participants reported a history of a substance use disorder (alcohol, methamphetamine and cocaine dependence), and one reported a diagnosis of post-traumatic stress disorder (0.5%). Fifteen (8.2%) reported that they had taken prescribed medication for a psychiatric or psychological problem in the past month.

Substance use

Self-reported lifetime and recent substance use are presented in Table 1. Participants had tried between 2 and 12 of the substances reported in Table 1 (lifetime polydrug use; M=7.4; SD=2.4). Age at first ecstasy use ranged from 12 to 31 years, and duration of ecstasy use ranged from less than 1 to 18 years (M=4.2; SD=3.6). Lifetime ecstasy use ranged from half a pill to 5,332 pills (M=172.4; SD=507.4), and typical ecstasy dose ranged from half a pill to eight pills (M=1.7; SD=0.8). With respect to recent drug use, participants had taken a mean of 2.3 other substances in the preceding 28 days, excluding ecstasy (SD=1.4; range=0–9).

Serotonin transporter

Forty-six participants were homozygous for the *S* allele of the *5-HTTLPR* (*SS*=26.0%), 89 were heterozygous (*SL*=50.3%) and 42 were homozygous for the *L* allele (*LL*=23.7%).

Trauma and life stress

Rates of self-reported traumatic events are reported in Table 2. Twenty-nine percent of the sample reported no history of traumatic events, 22.8% reported one, 15.2% reported two, 10.9% reported three and 21.7% reported four or more traumas in their lifetime (M=1.9; SD=1.8; range=0–10). Participants reported a mean of 1.3 stressful life events for the past month (SD=1.2; range=0–5), and subjective stress ratings for the past month ranged from 1 to 9 (M=4.4; SD=1.9).

Mood

Seventeen participants (9.2%) met the proposed cutoff of 76 on the depression-specific subscale of the MASQ indicative of current depression, as established in an Australian study of adolescents and young adults (Buckby et al. 2007).

Main analyses

Depressive and anxiety symptomatology: correlational analyses

Pearson's correlations between the four MASQ subscales (dependent variables, DVs) and ecstasy use are presented in Table 3. A range of other demographic, drug use, genetic and environmental variables were included in the analysis to identify other predictor variables. Examination of the correlations indicated that log lifetime ecstasy use was not associated with the severity of current depressive and anxiety symptomatology. However, as previous research has found a relationship between lifetime ecstasy and severity of depressive and anxiety symptoms, this variable was included in subsequent regressions. Log of greatest number of ecstasy pills taken in a 12-h period did not correlate with any MASQ subscale (r=0.00 to −0.12, p>0.05). Due to a high correlation between the two recent ecstasy use measures, these variables were combined to create an intensity of recent ecstasy use variable that was used in subsequent analyses (number of pills/days of ecstasy use). Lifetime frequency of tobacco use significantly correlated with anxious arousal and GD anxious and was identified as a covariate. Age at first use of cannabis significantly correlated with anxious arousal (r=−0.20, p<0.01), indicating that a younger age of cannabis onset was associated with more severe current anxiety symptoms. No other correlations between frequency of use and age of onset of individual drugs, and the DVs were found.

With respect to recent drug use, number of drug-using days in the last 28 days (excluding tobacco) and, specifically, number of alcohol using days, ecstasy using days and

Table 1 Drug use frequencies

	Ever used *n* (%)	Age at first use (years) Mean (SD)	Used in last 12 months *n* (%)	Used in last 28 days *n* (%)	Mean days of use in last 28 days[e] Mean (SD; range)	Mean amount used in last 28 days[e] Mean (SD; range)
Ecstasy	184 (100)	19.05 (2.54)	184 (100)	78 (42.4)	1.68 (1.01; 1–6)	2.90 pills (3.02; 0.25–16)
Alcohol	183[b] (100)	13.52 (2.83)	180[b] (97.8)	172 (93.5)	10.20 (6.36; 1–27)	67.70 units[f] (55.34; 1–252)
Tobacco	174 (94.6)	14.52 (2.69)	144 (78.3)	98[d] (54.4)	–	–
Cannabis	176 (95.7)	16.04 (2.42)	152 (82.6)	76 (41.3)	6.61 (8.12; 1–27)	4.12 g (11.85; 0.01–96.50)
Amphetamines	138 (75.0)	19.05 (2.56)	114 (62.0)	30 (16.3)	2.20 (1.97; 1–10)	0.51 g (0.43; 0.02–1.38)
Cocaine	102 (55.4)	20.98 (3.27)	71 (38.6)	15 (8.2)	1.2 (0.41; 1–2)	0.62 g (0.50; 0.05–1.5)
Hallucinogens	119 (64.7)	19.71 (2.82)	74 (40.2)	12 (6.5)	1.58 (1.00; 1–4)	1.69 tabs[g] (1.60; 0.25–6)
Inhalants	78 (42.4)	19.63 (3.28)	39 (21.2)	10 (5.4)	2.70 (2.71; 1–9)	23.65 inhales (38.55; 2–130)
Opiates	46 (25.0)	20.33 (3.42)	19 (10.3)	3 (1.6)	1.67 (1.15; 1–3)	0.13 g (0.15; 0.03–0.3)
Benzodiazepines/sedatives[a]	67 (36.4)	21.06 (3.47)	44 (23.9)	9 (4.9)	1.44 (0.73; 1–3)	25 mg[h] (17.32; 5–55)
Ketamine	64[c] (36.0)	21.14 (3.19)	28[c] (15.2)	4 (2.2)	1.5 (0.58; 1–2)	0.06 g (0.04; 0.03–0.11)
GHB	33[c] (18.5)	21.55 (4.12)	12[c] (6.5)	2 (1.1)	3.0 (1.41; 2–4)	29.95 ml (28.21; 10–49.90)

[a] Non-prescribed use

[b] One missing data point

[c] Six missing data points

[d] Four missing data points

[e] Includes only those participants who have used the substance in the last 28 days

[f] Each unit equivalent to 10 mg ethanol

[g] One tab equivalent to one LSD tab or four magic mushroom shakes (Thailand)

[h] Converted to diazepam equivalence

number of ecstasy pills consumed in the last 28 days negatively correlated with anhedonic depression (r=−0.19, −0.19, −0.23, −0.25, respectively, $p< 0.01$), indicating that more severe current depressive symptoms were associated with less recent drug use and specifically, less ecstasy and alcohol use. Self-reported lifetime history of unipolar depression and/or an anxiety disorder significantly correlated with all of the DVs (Spearman's rho correlations). No other correlations between the DVs and demographic or genetic variables were found. However, as gender differences have consistently been observed in the general population with regards to depression and anxiety (Australian Bureau of Statistics 2007), gender was included as a covariate in all subsequent analyses. Lifetime and log recent polydrug use were also entered as covariates in the regressions. Lifetime trauma and measures of both stressful life events and subjective life stress correlated with the DVs. Recent stressful life events were entered into the regression as this was considered to be a more objective measure of recent stress.

Depressive and anxiety symptomatology: regression analyses

A series of hierarchical regression analyses were conducted to examine the relationship between ecstasy use and the severity of depressive and anxiety symptoms, as measured by the four MASQ subscales, after controlling for demographic, genetic and environmental risk factors, including other drug use. The predictor variables were entered in four

Table 2 Lifetime prevalence of trauma experiences (n=184)

Type of trauma	*n* (%)
War	2 (1.1)
Life-threatening accident	32 (17.4)
Natural disaster	22 (12.0)
Witnessed assault/murder	67 (36.4)
Sexual assault	
Sexual abuse	23 (12.5)
Rape	12 (6.5)
Physical assault	
Physical assault	41 (22.3)
Physical abuse	20 (10.9)
Emotional abuse	73 (39.7)
Threatened with a weapon	45 (24.5)
Torture/terrorists	4 (2.2)
Other[a]	61 (33.2)
Shock[a]	60 (32.6)

[a] Relates to participants endorsing both the occurrence of the event and at the time experiencing 'intense fear, helplessness or horror'

Table 3 Correlations between MASQ subscales, demographic, psychiatric and substance use variables, serotonin transporter, recent stress and lifetime trauma (n=184)

Measure	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1. Anhedonic depression	–	0.19*	0.60**	0.32**	−0.08	0.11	0.25**	−0.10	−0.01	0.21*	−0.06	−0.08	−0.05	−0.26**	−0.14	−0.19*	0.05	−0.08	0.26**	0.33**	0.08
2. Anxious arousal		–	0.43**	0.74**	−0.12	−0.06	0.29**	−0.14	−0.02	−0.01	0.05	0.03	0.18*	−0.01	0.07	−0.04	−0.07	0.08	0.18*	0.27**	0.26**
3. GD depressive			–	0.62**	−0.04	0.13	0.27**	−0.10	0.03	0.08	−0.07	−0.03	0.01	−0.09	−0.03	−0.05	0.05	−0.05	0.41**	0.46**	0.17
4. GD anxious				–	−0.02	0.05	0.35**	−0.07	0.03	−0.01	0.01	0.10	0.19*	0.00	0.13	0.05	−0.04	0.02	0.38**	0.43**	0.26**
5. Age					–	−0.15	0.20*	−0.43**	0.78**	0.03	0.37**	0.40**	0.06	0.03	0.14	0.35**	−0.02	0.15	0.03	−0.05	0.11
6. Gender[a]						–	0.05	0.05	−0.21*	0.02	−0.29**	−0.30**	−0.16	−0.07	−0.18	−0.29**	−0.01	−0.12	0.15	0.18*	−0.02
7. Depressive/anxiety diagnosis[b]							–	−0.09	0.26**	0.05	0.21*	0.22*	0.07	−0.04	0.11	−0.02	0.05	0.03	0.18*	0.29**	0.22*
8. Age at first ecstasy use								–	−0.22*	0.20*	−0.34**	−0.13	−0.27**	−0.15	−0.17	−0.04	−0.08	−0.00	0.07	−0.09	0.00
9. Ecstasy duration									–	−0.10	0.63**	0.52**	0.24**	0.13	0.27**	0.40**	0.04	0.16	−0.01	0.02	0.12
10. Days since last ecstasy										–	−0.30**	−0.27**	−0.19*	−0.84**	−0.38**	−0.14	0.00	0.03	0.17	0.13	0.00
11. Lifetime ecstasy use[c]											–	0.65**	0.41**	0.35**	0.38**	0.34**	0.04	0.09	−0.25**	−0.16	0.13
12. Lifetime polydrug use												–	0.43**	0.33**	0.56**	0.44**	0.01	0.12	0.00	−0.00	0.06
13. Lifetime tobacco (frequency)													–	0.22*	0.57**	0.29**	−0.06	0.02	−0.05	0.06	0.23*
14. Recent ecstasy (intensity)[c]														–	0.42**	0.15	−0.04	0.01	−0.19*	−0.10	−0.06
15. Recent polydrug use[c]															–	0.38**	0.04	0.01	−0.03	0.02	0.15
16. Recent drug use (days)[d]																–	0.04	0.06	−0.10	−0.07	0.09
17. Gene_dummy1																	–	−0.56**	0.02	0.03	0.04
18. Gene_dummy2																		–	−0.06	−0.06	−0.10
19. Stressful life events[e]																			–	0.45**	0.09
20. Subjective stress[e]																				–	0.15
21. Lifetime trauma																					–

*$p \leq 0.01$; **$p \leq 0.001$

[a] Males = 0, females = 1

[b] No diagnosis = 0, past or present diagnosis of unipolar depression and/or an anxiety disorder = 1 (Spearman's rho correlations)

[c] Transformed data

[d] Total drug using days, excluding tobacco

[e] Last month

steps: (1) gender, history of unipolar depression and/or an anxiety disorder and *5-HTTLPR* genotype (gene_dummy1 and gene_dummy2), (2) environmental factors: recent stressful life events and lifetime trauma, (3) other drug use: lifetime polydrug use and tobacco frequency and (4) ecstasy use and ecstasy by *5-HTTLPR* genotype interaction terms. The influence of lifetime and intensity of recent ecstasy use were examined in two separate sets of analyses.

Lifetime ecstasy use One participant was identified as a multivariate outlier and was deleted from the analysis. Table 4 shows self-reported history of unipolar depression and/or an anxiety disorder significantly predicted the MASQ subscale scores. Neither gender nor *5-HTTLPR* genotype were significant predictors. Of the drug variables, frequency of tobacco use significantly predicted GD anxious. Recent life stress was a significant predictor of the anhedonic depression, GD depressive and GD anxious subscales. Lifetime trauma was a significant predictor of anxious arousal. However, this was no longer significant after entering other drug use factors. After controlling for other variables, the extent of lifetime ecstasy use continued to have no association with the level of current depressive and/or anxiety symptomatology. The genotype × log lifetime ecstasy interaction was also non-significant. Substitution of stressful life events with recent subjective life stress produced comparable findings.[1]

Recent ecstasy use One participant was identified as a multivariate outlier and was deleted from the analysis. Consistent with the initial correlation, log recent ecstasy use was not predictive of any MASQ subscale after controlling for recent life stress, trauma, *5-HTTLPR* genotype, gender, history of depression/anxiety disorder and log recent polydrug use (see Table 5). The genotype × log recent ecstasy use interaction was also non-significant. In contrast to lifetime polydrug use, after excluding participants currently on psychotropic medication, log recent polydrug use was a significant predictor of GD anxious with participants who had taken a greater number of drugs in the preceding 28 days reporting more severe current anxiety symptoms.

Discussion

In this sample, we found that neither lifetime nor recent ecstasy use was associated with current mood symptoms either before or after controlling for other genetic and environmental risk factors for depression, anxiety and substance (ab)use. In contrast, lifetime frequency of tobacco and a younger age of cannabis onset were associated with more severe current anxiety symptoms. Furthermore, after excluding participants currently taking prescribed psychotropic medication, recent polydrug use was associated with current general distress anxiety symptoms. While, as expected, a lifetime history of unipolar depression and/or an anxiety disorder significantly predicted current mood symptoms, no other associations between demographic or genetic variables and psychopathology were found. Instead, lifetime history of trauma and recent stressful life events were significant predictors of the severity of current depressive and anxiety symptoms, as hypothesised. In addition, when stressful life events were substituted with the subjective stress measure, stress continued to be associated with general distress symptoms and the depression-specific subscale of the MASQ. Together, these findings indicate that in this community sample of ecstasy users, current depressive and anxiety symptoms were related to environmental risk factors including other drug factors, rather than *5-HTTLPR* genotype or recent or lifetime ecstasy use.

The lack of an association between ecstasy use and current depressive/anxiety symptomatology is contrary to our hypothesis. However, these findings are consistent with other studies finding no relationship between lifetime or recent ecstasy use and depressive and anxiety symptoms (Abdallah et al. 2007; Daumann et al. 2004; Medina and Shear 2007). Indeed, mixed results have been found with regard to the relationship between the severity of mood symptoms and the use of specific substances (including ecstasy) and that a heavier pattern of drug use in general may be more strongly related to the severity of depressive and anxiety symptoms (e.g. Bedi et al. 2008; Sumnall et al. 2004). However, methodological differences between studies may be contributing to these mixed findings, including key differences in how drug use is defined (e.g. lifetime quantity, occasions of use, frequency of use, recent use) and measured (e.g. single question estimates, frequency by quantity calculations, context-based timeline methods; see Bedi and Redman 2006), as well as the statistical analyses and covariates used. Other limitations of these studies include the use of small sample sizes and the lack of appropriate control groups. Nonetheless, 17 (9.2%) ecstasy users in the current study met the diagnostic cutoff for current depression on the MASQ (Buckby et al. 2007), which is an appreciably higher rate than Australian national data on the prevalence of depression in the previous 12 months (4.1%; Australian Bureau of Statistics 2007). Similarly, the rate of self-reported lifetime depression in the current sample (19.0%) is greater than the Australian lifetime prevalence for a depressive episode (11.6%;

[1] When the regression analyses were conducted with only those participants with at least moderate lifetime ecstasy use (>20 pills; n= 114), log lifetime ecstasy use continued to have no relationship with the MASQ subscales, and the genotype × log lifetime ecstasy interaction continued to be non-significant.

Table 4 Lifetime drug use: hierarchical regression models predicting MASQ subscales from genetic, environmental and lifetime drug use factors (n=183)

	Anhedonic depression			Anxious arousal			GD depressive			GD anxious		
	β	ΔR^2	F	β	ΔR^2	F	β	ΔR^2	F	β	ΔR^2	F
Step 1		0.08*	3.94*		0.12**	5.56**		0.11**	5.18**		0.17**	9.04**
Gender[a]	0.09			−0.01			0.10			0.02		
Depressive/anxiety diagnosis[b]	0.27**			0.33**			0.29**			0.41**		
Gene_dummy1	0.01			−0.07			0.06			−0.10		
Gene_dummy2	−0.06			0.03			−0.04			−0.04		
Step 2		0.04	3.96**		0.05*	5.56**		0.12**	8.44**		0.12**	11.58**
Gender[a]	0.06			−0.01			0.05			−0.01		
Depressive/anxiety diagnosis[b]	0.23*			0.26**			0.21*			0.32**		
Gene_dummy1	0.02			−0.05			0.07			−0.08		
Gene_dummy2	−0.04			0.07			−0.01			−0.00		
Recent stress	0.20*			0.12			0.35**			0.31**		
Lifetime trauma	−0.00			0.19*			0.09			0.16		
Step 3		0.02	3.34**		0.03	5.12**		0.01	6.54**		0.03	9.69**
Gender[a]	0.02			−0.03			0.03			−0.00		
Depressive/anxiety diagnosis[b]	0.25**			0.29**			0.23*			0.33**		
Gene_dummy1	0.02			−0.03			0.08			−0.06		
Gene_dummy2	−0.03			0.09			0.01			0.01		
Recent stress	0.21*			0.13			0.35**			0.32**		
Lifetime trauma	−0.00			0.15			0.07			0.13		
Lifetime polydrug use	−0.13			−0.15			−0.11			−0.06		
Lifetime tobacco (frequency)	0.00			0.19			0.05			0.18*		
Step 4		0.01	2.59*		0.00	3.71**		0.00	4.70**		0.00	6.97**
Gender[a]	0.01			−0.02			0.02			−0.01		
Depressive/anxiety diagnosis[b]	0.25*			0.29**			0.23*			0.33**		
Gene_dummy1	−0.01			−0.07			0.07			−0.13		
Gene_dummy2	−0.27			0.16			−0.09			−0.06		
Recent stress	0.23*			0.14			0.36**			0.31**		
Lifetime trauma	−0.00			0.15			0.07			0.13		
Lifetime polydrug use	−0.19			−0.15			−0.13			−0.04		
Lifetime tobacco (frequency)	−0.01			0.19			0.05			0.19*		
Log ecstasy lifetime	0.01			0.02			−0.01			−0.09		
Interaction: gene1×ecstasy	0.04			0.05			0.02			0.09		
Interaction: gene2×ecstasy	0.28			−0.08			0.11			0.09		

NB. When participants who had taken prescribed psychotropic medication within the last month (n=15) were excluded, depressive/anxiety diagnosis was no longer a significant predictor (p>0.01) of anhedonic depression at steps 2, 3 and 4, and recent stress was no longer significant at steps 3 and 4. For GD anxious, frequency of tobacco use was no longer significant at step 4. There were no changes to anxious arousal and GD depressive

*p≤0.01; **p≤0.001

[a] Males = 0, females = 1

[b] No = 0, yes = 1

Table 5 Recent drug use: hierarchical regression models predicting MASQ subscales from genetic, environmental and recent drug use factors (n=183)

	Anhedonic depression			Anxious arousal			GD depressive			GD anxious		
	β	ΔR^2	F	β	ΔR^2	F	β	ΔR^2	F	β	ΔR^2	F
Step 1		0.09*	4.35*		0.11**	5.36**		0.11**	5.17**		0.16**	8.26**
Gender[a]	0.08			−0.00			0.11			0.04		
Depressive/anxiety diagnosis[b]	0.28**			0.33**			0.28**			0.40**		
Gene_dummy1	−0.00			−0.06			0.08			−0.07		
Gene_dummy2	−0.08			0.03			−0.03			−0.03		
Step 2		0.04	4.28*		0.05*	5.44**		0.12**	8.40**		0.12**	10.96**
Gender[a]	0.05			−0.01			0.06			0.00		
Depressive/anxiety diagnosis[b]	0.24*			0.26**			0.20*			0.30**		
Gene_dummy1	0.00			−0.05			0.08			−0.06		
Gene_dummy2	−0.07			0.06			−0.01			0.02		
Recent stress	0.21*			0.12			0.35**			0.31**		
Lifetime trauma	0.00			0.20*			0.09			0.17*		
Step 3		0.02	4.34**		0.00	4.66**		0.00	7.22**		0.01	9.79**
Gender[a]	0.02			−0.01			0.05			0.02		
Depressive/anxiety diagnosis[b]	0.25**			0.26**			0.20*			0.29**		
Gene_dummy1	0.00			−0.05			0.08			−0.07		
Gene_dummy2	−0.07			0.06			−0.00			0.02		
Recent stress	0.20*			0.12			0.35**			0.31**		
Lifetime trauma	0.02			0.19*			0.09			0.16		
Log recent polydrug use	−0.15			0.02			−0.04			0.10		
Step 4		0.03	3.62**		0.02	3.60**		0.00	4.98**		0.01	7.07**
Gender[a]	0.04			−0.01			0.05			0.02		
Depressive/anxiety diagnosis[b]	0.24*			0.25**			0.20*			0.29**		
Gene_dummy1	0.07			−0.01			0.07			−0.01		
Gene_dummy2	−0.03			0.19			0.01			0.12		
Recent stress	0.17			0.12			0.35**			0.31**		
Lifetime trauma	0.02			0.21*			0.09			0.17		
Log recent polydrug use	−0.08			−0.00			−0.05			0.08		
Log recent ecstasy use	−0.05			0.16			0.00			0.16		
Interaction: gene1 ×ecstasy	−0.14			−0.07			0.02			−0.11		
Interaction: gene2 ×ecstasy	−0.08			−0.21			−0.02			−0.17		

NB. When participants who had taken prescribed psychotropic medication within the last month (n=15) were excluded, depressive/anxiety diagnosis was no longer a significant predictor (p>0.01) of anhedonic depression at steps 2, 3 and 4 and was no longer a significant predictor of GD depressive at steps 3 and 4. For GD anxious, trauma became non-significant at step 2, and recent polydrug use became a significant predictor at step 3. There were no changes to anxious arousal

*p≤0.01; **p≤0.001

[a] Males = 0, females = 1

[b] No = 0, yes = 1

Australian Bureau of Statistics 2007). While the results of the current study provided no evidence that the level of ecstasy use was associated with the severity of depression or anxiety symptoms, there is clearly a higher prevalence of depressive symptoms and disorder in our sample of ecstasy users. Whether these results reflect a specific vulnerability amongst ecstasy users or are reflective of a vulnerability amongst drug users in general warrants further investigation. There may also be other yet to be identified premorbid variables contributing to both mood symptoms and a heavier pattern of drug use in some individuals, which may also be contributing to differences across studies. Importantly, the current findings do not negate that ecstasy use may lead to negative psychological outcomes for some individuals. Many ecstasy users report experiencing mood symptoms and disrupted functioning in the short and long term that they attribute to their ecstasy use (Topp et al. 1999). It is possible that these negative side effects may be independent from severity of lifetime use.

The lack of significant associations between *5-HTTLPR* genotype and genotype × ecstasy interaction with current mood symptoms contrasts with past findings with ecstasy users (Roiser et al. 2005). However, it is consistent with the results of a recent meta-analysis finding that *5-HTTLPR* genotype did not predict depression, either alone or in combination with stressful life events (Risch et al. 2009). Furthermore, the same meta-analysis found a strong relationship between the number of stressful life events and risk of depression, consistent with the current findings.

While the results of the current study are new and require replication, they indicate that the experience of depressive and anxiety symptoms in ecstasy users was associated with factors related to environmental vulnerability rather than lifetime or recent ecstasy use, consistent with our hypotheses. Recent stressful life events were associated with more severe depression-specific and general distress symptoms. Lifetime trauma significantly predicted current anxiety symptoms but not depression-related symptoms, and a greater number of lifetime trauma experiences were associated with more severe anxiety symptoms. While it is difficult to determine the direction of the relationship between these variables due to the cross-sectional nature of the study, a history of trauma has been associated with increased risk for ecstasy and other drug use, as well as depressive/anxiety symptoms, in both community and clinical samples (McCauley et al. 1997; Singer et al. 2004; Creamer et al. 2001; Fergusson and Lynskey 1997; Simpson and Miller 2002; Lubman et al. 2007). Consistent with this, frequency of tobacco use was also associated with trauma in the current sample. This vulnerability may also increase the risk of further stressful life events in an individual's immediate environment leading to increased risk of depressive and anxiety symptoms (Risch et al. 2009) and substance use (Staiger et al. 2009). This may explain why after controlling for recent stressful life events, trauma was no longer related to anxiety-related general distress symptoms. That is, life stress may mediate the relationship between trauma and current distress symptoms. Clearly, a prospective study is required to fully describe the complex relationship between these variables.

There are a number of limitations to the current study. These include the use of a cross-sectional design and the reliance upon retrospective self-report measures that may be subject to recall bias. It is also possible that the presence of current mood symptoms inflated recall of past adverse life events (Schraedley et al. 2002). The reliability of self-reported recent drug use was also not confirmed using biological analysis, although previous studies have indicated ecstasy and other drug users provide reliable data (Anglin et al. 1993; Bedi and Redman 2006). Furthermore, although detailed data were obtained on lifetime ecstasy use, the content of ecstasy tablets consumed was not determined. It is possible that participants unknowingly consumed other substances and not MDMA (Quinn et al. 2007). The measures of other drug use, including drug use frequency and the number of drugs tried (polydrug use), rather than the lifetime quantity of use, are a further limitation of the current study. These measures may not have been sensitive enough to reveal possible associations between other drug use factors and current symptoms. Although participants were required to abstain from ecstasy use for 1 week prior to the assessment, it is possible that subacute effects may have affected the data as the MASQ asks about mood symptoms in the past week. The effects of other drug use may also have impacted on our results, as only 12- and 24-h abstention periods were used for alcohol and other substances, respectively. However, consistent with other papers in this area (e.g. Bedi et al. 2008), a 24-h abstinence period was implemented for cannabis to balance potential subacute and withdrawal drug effects and participant recruitment factors. Specifically, subacute cannabis effects can last for more than 7 days (Pope et al. 2001), and abstention periods longer than 1 day may lead to withdrawal symptoms (Kouri and Pope 2000). Furthermore, given that we aimed to have a representative sample of ecstasy users with a range of other drug-using habits, an abstention period of 24 h was used in order to include regular users of other drugs. No significant correlations were found between days since last use of individual drugs and the MASQ subscales. Finally, as the interviewer was one of the authors (R.S.), this introduces a potential reporting bias as she was not blind to drug use. However, given that many of the measures were self-report scales, including those assessing depressive/anxiety symptomatology, this reduces the risk of bias.

The strengths of the current study include the recruitment of a large sample of ecstasy users with varying levels of use. Furthermore, lifetime ecstasy use was measured using a context-based timeline to aid recall as the use of timelines with life events increases recall accuracy of past drug use (Del Boca and Darkes 2003; Shillington et al. 1995). The inclusion of individuals with a psychiatric history, as well as those currently on psychotropic medications, is a further strength of the study as these individuals have often been excluded from previous research (e.g. Medina and Shear 2007; Roiser and Sahakian 2004). Furthermore, the use of the MASQ allowed for the examination of independent relationships between ecstasy use and depression-specific, anxiety-specific and general distress symptomatology. In contrast to commonly used depression scales, the depression-specific scale of the MASQ is less confounded by somatic symptoms such as sleep disturbance and loss of appetite (which are also related to substance misuse; Cole et al. 2002) and instead focuses on anhedonia and lack of positive affect. Finally, this is the first study to examine the relative contribution of genetic and environmental risk factors, including other drug use, on psychiatric symptomatology in a community sample of ecstasy users.

The current findings indicate that environmental risk factors, including a history of trauma and recent life stress, are more robust predictors of depressive and anxiety symptoms amongst ecstasy users than lifetime or recent ecstasy or *5-HTTLPR* genotype. Secondly, frequency of tobacco use, recent polydrug use and a younger age of cannabis onset were associated with depressive/anxiety symptomatology. These findings further highlight the importance of controlling for other drug use in studies of ecstasy users and emphasise the need to assess for and address environmental factors, such as a history of trauma and stressful life events, when treating ecstasy users with depression and/or anxiety. Indeed, it highlights the importance of providing coping skills training to people with depressive/anxiety symptoms and co-occurring substance use. These findings also provide one possible explanation for the mixed findings observed in the literature with respect to the relationship between depressive and anxiety symptomatology and ecstasy use. However, the relationship between trauma, depression and anxiety and drug use is complex. Whether ecstasy use exacerbates trauma or mood symptoms in people with a history of trauma or psychopathology needs further investigation. Prospective research exploring the relationship between these variables over both the short and long term is needed to fully understand the interaction between these variables.

Acknowledgements Rebecca Scott was supported by an Australian Postgraduate Award, and the project was funded by Monash University, School of Psychology and Psychiatry. Drs. Hides and Lubman are supported by the Colonial Foundation. The authors wish to thank Dr. Penelope Hasking and Dr. Simon Moss for the statistical assistance.

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