Psychiatric profiles of mothers who take Ecstasy/MDMA during pregnancy: Reduced depression 1 year after giving birth and quitting Ecstasy

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Abstract

Background: The recreational drug MDMA (3,4-methylenedioxymethamphetamine) or 'Ecstasy' is associated with heightened psychiatric distress and feelings of depression. The Drugs and Infancy Study (DAISY) monitored the psychiatric symptom profiles of mothers who used Ecstasy/MDMA while pregnant, and followed them over the first year post-partum.

Methods: We compared 28 young women whom took MDMA during their pregnancy with a polydrug control group of 68 women who took other psychoactive drugs while pregnant. The Brief Symptom Inventory (BSI) was completed for several periods: The first trimester of pregnancy; and 1, 4 and 12 months after childbirth. Recreational drug use was monitored at each time point.

Results: During the first trimester of pregnancy, MDMA-using mothers reported higher depression scores than the polydrug controls. At 1 year after childbirth, their BSI depression scores were significantly lower, now closer to the control group values. At the same time point, their self-reported use of MDMA became nearly zero, in contrast to their continued use of *Cannabis*/marijuana, nicotine and alcohol. We found significant symptom reductions in those with BSI obsessive-compulsive and interpersonal sensitivity, following Ecstasy/MDMA cessation.

Conclusions: The findings from this unique prospective study of young recreational drug-using mothers are consistent with previous reports of improved psychiatric health after quitting MDMA.

Keywords

Cessation, depression, drug addiction, Ecstasy, MDMA, middle class, mother, post-partum, pregnancy, quitting, recreational drugs

Introduction

'Ecstasy' or 3,4-methylenedioxymethamphetamine (MDMA) is used as an illicit drug by subgroups of adolescents and young adults. Its recreational use is mainly associated with dance clubs, all-night 'raves' and house parties (Parrott et al., 2008; Winstock et al., 2001). Population surveys in the US reveal usage levels as high as 9.5% in college students (Johnston et al., 2005; Singer et al., 2004). In the American National Survey on drug use and health, Ecstasy/MDMA is found to be used more by young women than men (Wu et al., 2010). Neuroimaging studies of abstinent MDMA users reveal significantly lower levels of the serotonin transporter (SERT) (Erritizoe et al., 2011; Kish et al., 2010), and are widely interpreted as suggesting serotonergic neurotoxicity (Benningfield and Cowan, 2013; Parrott, 2013a; Puerta et al., 2009; Ricaurte et al., 2000). Recreational use of MDMA is also associated with various neuropsychobiological problems, including memory deficits (Montgomery et al., 2010; Rogers et al., 2009; Zakzanis and Campbell, 2006), impairments in higher cognitive processing (Fox et al, 2002; Parrott, 2012, 2013b; Reay et al., 2006), sleep apnea (McCann et al., 2009), raised cortisol levels (Parrott, 2009; Parrott et al., 2012), psychosocial impairment (Topp et al., 1999) and various psychiatric problems (Briere et al., 2012; MacInnes et al., 2000; Milani et al., 2004; Morgan et al., 2002; Schifano et al., 1998; Singer et al., 2004; Verheyden et al., 2003).

Laboratory animal studies show adverse effects of MDMA upon the developing foetus (Adori et al., 2010; Skelton et al., 2008), raising concerns about potentially damaging effects when taken by female recreational users during pregnancy. To date, there has been no controlled empirical data addressing this question, although there is some evidence of adverse birth consequences (McElhatton et al., 1999; Singer et al., 2012b). To investigate the potential effects of foetal MDMA exposure on development, the US National Institute on Drug Abuse (NIDA) funded the Drugs and Infancy Study (DAISY). This prospective study monitored a group of mothers whom took recreational Ecstasy/MDMA while pregnant, and a control group of pregnant females, the other 'polydrug' users. The two groups were followed over time, in order to monitor the physical development and psychobiological well-being of their children. Over the first

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year of life, the children of MDMA-using mothers displayed significantly poorer gross psychomotor skills than control group children (Singer et al., 2012a, 2012b). The DAISY study also assessed maternal well-being, using the Brief Symptom Inventory, a self-reporting measure of psychiatric health for non-clinical populations, derived from the earlier Symptom Check List-90 (Derogatis and Nelisaratos, 1983).

This psychiatric measure was included, because previous research shows higher symptom profiles in abstinent Ecstasy/MDMA users. Soar et al. (2001) reviews the medical case study literature, which indicated an increased risk of several psychiatric disorders, including depression and psychosis, in MDMA users. Schifano et al. (1998) noted that regular Ecstasy/MDMA users are at increased risk of developing various psychiatric problems, the most frequent being depression. MacInnes et al. (2000) found significantly raised Beck Depression Inventory (BDI) scores in a non-clinical sample of abstinent regular Ecstasy/MDMA users. Singer et al. (2004) found that abstinent Ecstasy users reported significantly higher BSI scores for anxiety, depression and obsessive-compulsive disorder than non-user controls. Milani et al. (2004) reported significant gender effects, with female Ecstasy/MDMA users reporting higher levels of BSI anxiety, depression and somatization scores. Verheyden et al. (2003) investigated the reasons for quitting Ecstasy/MDMA: They found that most users in their large survey reported improved mental health after drug cessation. In the current DAISY, the BSI allowed us to prospectively monitor the psychiatric health of our pregnant mothers and to investigate how any changes in drug usage were associated with their report of psychological distress on the BSI. Based on previous findings, it might be predicted that elevated psychiatric symptoms would be evident in mothers who are continuing MDMA users, whilst those who discontinue use may show improvements; however, given its uniqueness, and the additional biopsychosocial changes associated with pregnancy and motherhood, the aims of the study were largely exploratory.

Methods

Experimental design

The data in the current report were collected as part of the maternal assessment component of DAISY, a prospective study primarily exploring the effects of recreational drug use, notably MDMA/Ecstasy, on infant social and cognitive development (Moore et al., 2010; Singer et al., 2012a, 2012b). In a mixed design, mothers who used MDMA/Ecstasy during pregnancy (MDMA/Ecstasy users) were compared with those who used other drugs, but not MDMA/Ecstasy (Polydrug user controls), across measures of drug use and symptoms of mental distress, at four distinct time periods: the first trimester of pregnancy and at 1, 4 and 12 months post-partum.

Participants

We prospectively recruited 96 pregnant women from the UK through midwife referrals, leaflets describing the study at prenatal clinics and advertisements in commercial pregnancy magazines. We sought pregnant women whom were using recreational drugs during pregnancy, listing ecstasy, tobacco, *Cannabis*, alcohol and cocaine as examples. The majority of participants were therefore recreational 'polydrug' users. Exclusionary factors included: positive HIV status, moderate or severe intellectual disability, chronic medical disorder or psychiatric diagnosis. In total, there were 28 mothers in the MDMA-exposed group, who used MDMA (and other substances) during pregnancy, and 68 non-MDMA controls (some of whom used substances during pregnancy, but not MDMA). The majority of the sample were white, married or with a partner, and educated to a UK degree level. Their mean ages at the birth of their infants were 30.3 (SD 6.4) years of age in the MDMA-exposed group and 28.4 (SD 6.2) in the controls. The groups did not differ on basic demographic profiles. Participants were informed of data confidentiality and they gave written informed consent. The study protocol was approved by ethics committees from the University of East London, UK; Case Western Reserve University, US; and the National Health Service, UK. For a fuller description of the participant sample and screening procedures, see Singer et al. (2012a).

Drug usage

All women were individually interviewed about their substance use by fully trained female research assistants. The interview was an adaptation of the Maternal Post-Partum Interview, which was developed for earlier studies of maternal cocaine exposure (Singer et al., 2002). Interview questions covered substances commonly used in the UK and were based on the University of East London Recreational Drug Usage Questionnaire (Parrott et al., 2001). The list of drugs included tobacco/cigarettes, alcohol, *Cannabis*, Ecstasy/MDMA, amphetamine, cocaine, LSD, benzodiazepines, hallucinogenic mushrooms, ketamine and opiates. It may be noted that mephedrone (m-cathinone or 'm-cat') was not on this list, since the DAISY study was undertaken before 'm-cat' was used as a recreational drug (Schifano et al., 2011). Mean usage for each drug per week was calculated by multiplying the frequency of use with the amount taken per occasion. The MDMA user group comprised women who reported taking MDMA during pregnancy or in the month prior to pregnancy. Those who reported MDMA use prior to this time were categorized as non-users, because the study was designed to assess foetal drug exposure.

Assessment battery

The study included a comprehensive battery of assessment measures, covering various aspects of child behaviour and physical health indices, maternal activities and psychological well-being (Singer et al., 2012a,2012b). This report describes the findings from the Brief Symptom Inventory (BSI) (Derogatis and Nelisaratos, 1983). This questionnaire comprises 53 self-rating questions across nine psychiatric subscales, for: depression, anxiety, phobic anxiety, hostility, somatic complaints, obsessive-compulsive behavior, interpersonal sensitivity, paranoid ideation and psychosis/schizophrenia. The summary measure, the General Severity Index (GSI), provided a general index for overall psychiatric distress. The assessments covered four occasions: first trimester of pregnancy, 1 month post-partum, 4 months post-partum and 12 months post-partum.

Table 1. Ecstasy/MDMA, alcohol, cigarettes, marijuana/*Cannabis* and cocaine usage patterns for 28 mothers whom took Ecstasy/MDMA during pregnancy and a control group of 68 polydrug users during pregnancy. Drug values represent mean weekly rates of usage, during first trimester of pregnancy and three times up to 1 year post-partum.

Drug type	Maternal group	First trimester of pregnancy	1 month post-partum	4 months post-partum	12 months post-partum	ANOVA		
						Group	Time	(GxT)
Ecstasy (tablets)	Polydrug controls	0.00 +/- 0.00	0.00 +/- 0.00	0.02 +/- 0.16	0.01 +/- 0.02	No between-group analysis	< .0001	-
	Ecstasy users	0.82 +/- 1.57	0.01 +/- 0.03	0.03 +/- 0.13	0.06 +/- 0.09			
Alcohol (units)	Polydrug controls	6.94 +/- 16.90	3.11 +/- 10.66	6.48 +/-10.89	13.75 +/-24.02	n.s	.0001	.02
	Ecstasy users	12.07 +/- 16.62	1.33 +/- 1.80	5.30 +/- 5.70	6.01 +/- 5.99			
Cigarette (numbers)	Polydrug controls	28.15 +/-48.10	23.45 +/- 50.13	27.27 +/- 40.02	32.88 +/-48.14	n.s	.0001	.003
	Ecstasy users	44.78 +/- 49.50	17.88 +/-30.79	17.59 +/- 22.23	28.68 +/-34.37			
Cannabis (joints)	Polydrug controls	7.44 +/- 19.24	3.36 +/- 7.87	3.12 +/-7.51	5.26 +/-12.95	n.s	.0001	n.s.
	Ecstasy users	10.28 +/- 20.81	6.86 +/- 17.36	6.20 +/- 16.12	7.35 +/-15.46			
Cocaine (grams)	Polydrug controls	0.02 +/-0.18	0.001 +/- 0.01	0.01 +/- 0.07	0.02 +/- 0.14	.057	.013	.03
	Ecstasy users	0.23 +/- 0.85	0.01 +/- 0.04	0.02 +/- 0.06	0.02 +/- 0.05			

MDMA: 'Ecstasy' or 3,4-methylenedioxymethamphetamine.
Note: Units refer to UK units of alcohol (1 unit = 10ml or 7.9 grams of alcohol); n.s.= non-significant.

Statistical analyses

Data that were positively skewed were transformed using natural logarithm, prior to analysis; however, the means and SDs are reported for the untransformed scores. Bivariate correlations were employed to calculate the inter-relationships between variables. Multicollinearity was assessed using tolerance and variance inflation factor. We implemented repeated measures Analysis of Variance (ANOVA), using a mixed model approach, by SAS Proc Mixed with maximum estimation method, to compare the substance use for both groups, MDMA-users during pregnancy (n = 28) and non-users of MDMA during pregnancy (n = 68), at the four different assessment times (during pregnancy, 4 weeks after birth, 12 weeks and 52 weeks). As noted earlier, both groups contained polydrug users of various substances, both legal (tobacco and/or alcohol), and illegal (*Cannabis*, amphetamine and/or cocaine) (Moore et al., 2010). Because the dependent variables were repeated measures and correlated within subjects, we used an unstructured covariance matrix to account for these correlated responses. We included interaction terms between drug groups and time, to test for homogeneity of MDMA effects over time. For all BSI outcome measures, we employed repeated measures Analysis of Covariance (ANCOVA). The covariates included other substance usage that differed by MDMA status at $p < 0.10$, and were correlated with the given outcome at $p < 0.10$ on at least two time points: They were then entered into the longitudinal model. Different sets of covariates were adjusted on each psychological outcome, and included demographic variables and use of all other drugs.

Results

The socioeconomic and educational profiles of mothers enrolled in the study are described more fully elsewhere (Singer et al., 2012a). In brief, the cohort was primarily white, married or in a stable relationship, and represented a wide range of socioeconomic backgrounds that included many from middle and higher psychosocial groupings. The MDMA-using mothers and polydrug control mothers were well matched on most variables (Singer et al., 2012a). Table 1 describes the group mean weekly rates of usage for the five main types of drug used: alcohol, nicotine/cigarettes, *Cannabis*/marijuana, cocaine and Ecstasy/MDMA. Other psychoactive drugs were taken by a few individuals, and those data are described more fully elsewhere (Moore et al., 2010).

A mixed ANOVA was conducted with group as the between-conditions factor and time as the within-conditions factor. The between-groups ANOVA revealed that the two groups did not differ in overall use of alcohol, cigarettes, *Cannabis* nor cocaine; although the cocaine group effect was statistically borderline (Table 1, where the group effect for Ecstasy was not calculated, because it was used to define these two groups).

The ANOVA for the time factor was significant for all five drugs (all p = 0.01 or smaller), with lower rates of usage during the weeks after giving birth. The ANOVA grouped by time interactions were significant for alcohol and cigarettes ($F[3,88] = 4.06$; $p < 0.005$ and $F[3,88] = 3.61$; $p < 0.02$ respectively), with the MDMA mothers using slightly more than the controls during the first trimester of pregnancy, but slightly less than controls across all the other time periods (Table 1). The group x time interaction was not significant for *Cannabis*, though Ecstasy/MDMA-using mothers appeared to be taking slightly more *Cannabis* than controls, across all time points (Table 1). The group x time interaction was significant for cocaine ($F[3,88] = 3.48$; $p < 0.05$), with the most usage during the first session by Ecstasy users (Table 1).

The Ecstasy-using mothers reported taking an average of 0.84 Ecstasy tablets/week during the first trimester of pregnancy. In terms of previous lifetime usage (Singer et al., 2012a), they reported first using Ecstasy at a mean age of 20.2 years (range 14 – 29 years), had taken it on an average of 171 times/lifetime (range 6 – 936 times), and typically ingested an average of 3 tablets per occasion (range 1 – 8 tablets), with an average maximum usage per occasion of 7.4 Ecstasy tablets (range 2 – 20 tablets). Turning to their usage around the time of pregnancy, the mean total amount of MDMA used during pregnancy and in the month prior was 25 tablets (range 0.45 – 180 tablets). Within the

Table 2. Psychiatric symptoms on the Brief Symptom Inventory during and after pregnancy for 28 mothers whom took Ecstasy/MDMA during pregnancy and for a non-user control group of 68 mothers whom took other drugs during pregnancy (polydrug controls).

Group	Time 1: Early-mid Pregnancy	Time 2: Postpartum 1 month	Time 3: Postpartum 4 months	Time 4: Postpartum 12 months	Paired comparison, Time 1 vs. 4
General symptoms					
Polydrug controls	0.61	0.51	0.54	0.50	-
Ecstasy users	0.79	0.71	0.81	0.56	-
Depression					
Polydrug controls	0.50	0.45	0.57	0.50	-
Ecstasy users	0.87	0.74	0.80	0.51	$p < 0.05$
Anxiety					
Polydrug controls	0.55	0.46	0.48	0.34	$p < 0.05$
Ecstasy users	0.74	0.68	0.69	0.56	-
Hostility					
Polydrug controls	0.71	0.65	0.66	0.59	-
Ecstasy users	0.74	0.80	1.24	0.55	-
Psychoticism					
Polydrug controls	0.31	0.25	0.36	0.30	-
Ecstasy users	0.52	0.51	0.62	0.42	-
Somatization					
Polydrug controls	0.58	0.36	0.27	0.32	$p < 0.001$
Ecstasy users	0.78	0.50	0.51	0.39	$p < 0.01$
Paranoid ideation					
Polydrug controls	0.61	0.48	0.64	0.66	-
Ecstasy users	0.75	0.70	066	0.73	-
Obsessive-compulsive					
Polydrug controls	1.08	1.10	0.98	0.89	-
Ecstasy users	1.20	1.23	1.31	0.82	$p < 0.05$
Interpersonal sensitivity					
Polydrug controls	0.74	0.64	0.64	0.73	-
Ecstasy users	0.92	0.85	0.96	0.57	$p < 0.05$
Phobic anxiety					
Polydrug controls	0.27	0.20	0.30	0.20	-
Ecstasy users	0.47	0.39	0.52	0.37	-

MDMA: 'Ecstasy' or 3,4-methylenedioxymethamphetamine.

polydrug control group, several women had used ecstasy/MDMA previously, but were currently non-users (Singer et al., 2012a).

The Brief Symptom Inventory findings are summarized in Table 2. The main focus of interest here is the difference in psychiatric well-being between the first and last sessions. Over that time period, the control group mothers showed a significant decline in BSI symptoms for somatization ($p < 0.001$) and anxiety ($p < 0.05$). Over the same period, the Ecstasy/MDMA subgroup mothers showed significant declines in BSI symptoms for (Table 2): somatization ($p < 0.001$), depression ($p < 0.05$), interpersonal sensitivity ($p < 0.05$) and obsessive-compulsive disorder ($p < 0.05$).

Discussion

The young mothers in the DAISY study provided a unique cohort in several respects. Although recreational polydrug users, they were predominantly middle class with middle socioeconomic status, and in stable interpersonal relationships; hence, unlike many studies of illicit drug users, they were not socially disadvantaged. The study covered an extended time period of nearly 2 years, and is to our knowledge the first study of pregnant Ecstasy/MDMA users. The cohort of almost 100 mothers was comparatively large, especially for a prospective study with repeated assessments. One of the main aims of the DAISY study was to investigate the effects of recreational Ecstasy/MDMA usage during pregnancy on subsequent child development. The main findings were that the children of Ecstasy/MDMA using mothers displayed significant psychomotor problems in comparison to control group children, as described elsewhere (Singer et al., 2012a, 2012b).

The study design allowed us to monitor changes in maternal reports of psychological well-being over time, in particular any alterations in their psychiatric status from the first to the last assessment. In this respect, both groups of mothers showed significantly higher somatization scores during the first trimester of pregnancy, when compared to 12 months post-partum (Table 2). The control group mothers also showed a significant reduction in BSI

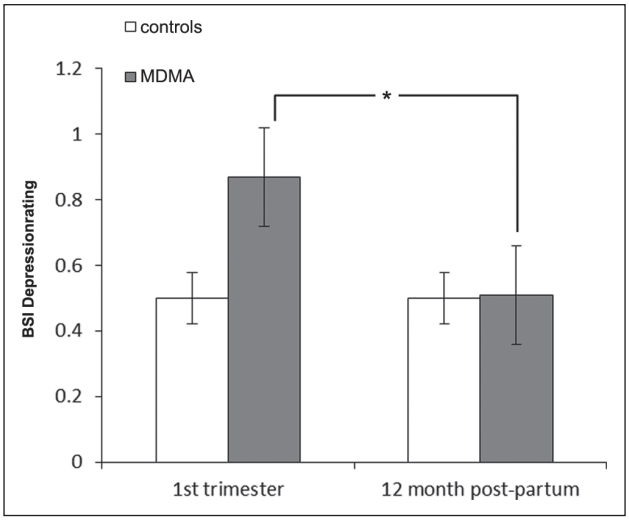

Figure 1. Brief Symptom Inventory ratings of depression during the first trimester and at 12 months post-partum, in women reporting MDMA/Ecstasy use during pregnancy, and in control women taking other recreational drugs during pregnancy.
*$p < 0.05$; Error bars indicate ±1 SE.
MDMA: 'Ecstasy' or 3,4-methylenedioxymethamphetamine.

symptoms of anxiety, while the MDMA subgroup showed a very similar trend (Table 2). The first trimester of pregnancy is a period of pronounced somatic body changes, and so intuitively explains the higher somatization scores in both groups of women. Thus, the reduced BSI somatization scores 1 year post-partum may reflect a return to physical normality in both groups of women. The first trimester of pregnancy is also a period of general anxiety, with natural concerns and worries over becoming pregnant. This may help to explain the comparatively higher BSI anxiety scores during the first trimester, and the reduced scores at the final session (Table 2).

The Ecstasy/MDMA-using mothers showed a different pattern of change, compared to the controls, on three BSI subscales, for: depression, obsessive compulsive disorder and interpersonal sensitivity (Table 2). The Ecstasy subgroup mothers reported feeling more depressed than control mothers at the first time point, with a statistically borderline between-group difference ($p = 0.058$, two-tail). At 1 year post-partum, the depression scores for the MDMA group had reduced significantly ($p < 0.05$), to become almost identical to the control group (Figure 1). The BSI depression scores for the control group mothers remained broadly unchanged over this period. The MDMA group also showed significant BSI reductions for interpersonal sensitivity and obsessive-compulsive disorder (Table 2). In order to examine the potential reasons for these changes, the changing patterns of drug usage over time should be noted. The Ecstasy/MDMA-group mothers had reduced their usage of Ecstasy to near-zero after giving birth (Table 1); hence, 1 year post-partum they had become former MDMA users. Their BSI improvement may reflect this cessation of Ecstasy/MDMA use.

There is extensive empirical literature demonstrating higher rates of psychiatric distress in current Ecstasy/MDMA users and psychiatric gains following drug cessation. Schifano et al. (1998) gave structured psychiatric interviews to young Ecstasy/MDMA users at an addiction centre in Italy, reporting that around one-half the sample reported symptoms of psychiatric distress, especially depression, but also psychotic disorder, impulse control disorder, bulimia and panic disorder. MacInnes et al. (2000) compared young Ecstasy/MDMA users and polydrug controls, with participants screened to exclude anyone with a prior psychiatric history. On the BDI, Ecstasy users displayed significantly higher depression scores than the non-MDMA-user controls. In a survey of over 700 young people from the UK and Italy, the SCL-90 symptom profiles of the Ecstasy polydrug users were significantly higher than the non-MDMA-user controls (Parrott et al., 2001). In a US study of abstinent MDMA users compared to non-user controls who visited raves (Singer et al., 2004), the Ecstasy/MDMA users reported significantly higher BSI depression, anxiety and obsessive-compulsive disorder than the controls. Brière et al. (2012) prospectively found that taking up recreational Ecstasy/MDMA in Canadian schoolchildren led to increased depression 1 year later. There are also indications that psychiatric health can improve after quitting. Morgan et al. (2002) report that current Ecstasy/MDMA users have elevated scores on many SCL-90 subscales, whereas former Ecstasy users have scores intermediate between the current Ecstasy users and the non-user controls. Verheyden et al. (2003) interviewed former users about their reasons for quitting Ecstasy/MDMA. Over one-half reported that 'mental health problems due to MDMA' were the *main reason* for quitting drug use: That using Ecstasy led to feelings of anxiety and depression, and that they feared for their mental health in the longer-term. Over 70% of those participants report 'improved mental health' after quitting.

An important potential confounder for Ecstasy/MDMA research is the use of other recreational drugs, because many Ecstasy users take a range of psychoactive drugs (Parrott et al., 2001; Parrott et al., 2007; Sala and Braida, 2004; Scholey et al., 2004). In the DAISY study, we collected systematic drug usage data at all four time points. As noted above, the use of Ecstasy/MDMA was largely restricted to the first trimester of pregnancy. In contrast, the use of alcohol, tobacco and *Cannabis* continued throughout the study. There is some indication of a decline in all drug use in the Ecstasy/MDMA group, with significant group/time interactions for alcohol and cigarettes, especially. As such, it could be argued that the depression effect in the Ecstasy/MDMA users was in part due to changes in alcohol and/or cigarette use, as both have been linked to higher depression scores (Munafo and Araya, 2010; Raimo and Schuckit, 1998); however, usage rates at baseline were broadly similar to 1 year post-partum, in both groups (Table 1). Hence, the changes in psychiatric status noted here (Table 2) cannot easily be attributed to alcohol, tobacco, nor *Cannabis* usage; however, the usage pattern for cocaine was very similar to Ecstasy/MDMA, with almost total cessation after the first trimester (Table 1). Thus, the selective reductions in particular psychiatric symptoms may reflect the cessation of Ecstasy/MDMA and/or cocaine usage.

There are several ways in which central nervous system (CNS) stimulant drugs like MDMA can enhance psychiatric distress. In acute terms, MDMA is a powerful mood intensifier, but it can boost positive *and* negative-feeling states; thus, increased levels of happiness and euphoria are often accompanied by emotional tension. This intensification of both positive and negative moods is reported in studies of recreational users and in placebo-controlled laboratory studies (Kirkpatrick et al., 2012; Parrott et al., 2011).

It is also noted in the psychotherapeutic situation: Two clients undergoing 'MDMA-assisted psychotherapy' experienced a resurgence of previous psychiatric problems following acute MDMA administration, with one client needing psychotherapy

for a year afterwards, to resolve the MDMA-induced problems (Greer and Tolbert, 1986; Parrott, 2007). In sub-acute terms, MDMA use is typically followed by a period of neurochemical recovery, when low moods and feelings of depression predominate; indeed, the 'mid-week blues' can often last for several days and may reach clinical levels in some individuals (Curran and Travill, 1997). Because the positive mood intensification under MDMA is brief (several hours), and the post-MDMA period of mood recovery is more prolonged (several days), the average weekly mood of Ecstasy users will often *be lower* than in non-users (Parrott and Lasky, 1998). Such effects are supported in the animal literature by the acute and subacute impact of MDMA on 5-HT, notably, delays in recovery of this transmitter in brain regions regulating emotion (Colado et al., 1999); and similar pattern reductions in other functional serotonergic factors, such as SERT and tryptophan hydroxylase (Adori et al., 2011).

In addition, in chronic terms, abstinent Ecstasy/MDMA users report higher levels of stress and lower levels of happiness than non-user controls (Scholey et al., 2011). When used repeatedly, sympathomimetic drugs such as amphetamine, cocaine and MDMA can adversely affect the hypothalamic pituitary adrenal (HPA) axis and impair homeostatic control via the stress hormone cortisol (Seyle, 1955). Indeed, acute MDMA use can increase cortisol levels by 800% in young dance club attendees (Parrott et al., 2008). While sub-chronically, recent Ecstasy/MDMA users display a 400% increase of cortisol in 3-month hair samples (Parrott et al., 2012); hence, recreational MDMA is both an acute *and* chronic stressor for the HPA axis (Parrott, 2009). There is also evidence that premorbid factors may heighten the likelihood of clinical problems in disadvantaged individuals; this interactive 'diathesis-stress' model for recreational Ecstasy/MDMA is described more fully elsewhere (Parrott, 2006). The possible causative factors (including neurotoxicity, recovery and/or HPA axis changes) for the effects observed here in the current data, and in much of the literature, still need considerable further empirical investigation.

There are several limitations to the DAISY study. We relied on self-reported drug use and cannot therefore be certain that 'Ecstasy' comprised 'MDMA'; however, data collection occurred during 2003 – 2006, which corresponded with a period of high MDMA purity in the UK. This was apparent in another study we undertook during 2006, which shows very high concordance between self-rated Ecstasy and MDMA use as detected in saliva samples (Parrott et al., 2008). The second weakness was the absence of a non-user control group, because many studies have found that polydrug users are more impaired than non-users (Morgan et al., 2002; Parrot et al., 2001). Thirdly, although the DAISY study was designed as a prospective study, this was only partially achieved (Moore et al., 2010); hence, missing data point's retrospective ratings were sometimes required (Singer et al., 2012a). Finally, the overall BSI difference scores were not large (Table 2); however, we were not expecting strong drug effects, because our participants were psychiatrically normal and their use of most drugs was similar at the first and last time points. Furthermore, although the group mean reduction of 0.2 on the BSI depression subscale may have been comparatively slight, it would still be beneficial for the individual user. It would also reduce the likelihood of individuals with prior vulnerability factors from developing more severe psychiatric problems (Parrott, 2006).

In summary, recreational stimulant drugs such as MDMA, cocaine and amphetamine, are well-known to be associated with enhanced psychiatric distress. The DAISY study found that women who took Ecstasy/MDMA during their first trimester of pregnancy reported slightly higher psychiatric symptom profiles than a control group of polydrug-using mothers. One year after giving birth, their psychiatric symptom profiles improved to values near the control group (Table 2 and Figure 1). The main explanatory factor proposed for this gain in psychiatric well-being was the cessation of Ecstasy/MDMA usage, coupled with the parallel reduction in cocaine use. Hence, this study confirmed that a reduction in stimulant drug usage can have beneficial effects on well-being. Finally, we should also note that the DAISY study investigated the effects of MDMA use during pregnancy on the child's subsequent development. It reveals that the children of MDMA-using mothers have various impairments in gross psychomotor skill (Singer et al., 2012a,2012b); hence, an important message for young females and their partners is to stop taking MDMA before pregnancy. This will protect the developing child and enhance maternal well-being.

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Conflict of interest

The authors declare no conflict of interest.

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References

Ádori C, Andó RD, Szekeres M, et al. (2011) Recovery and aging of serotonergic fibers after single and intermittent MDMA treatment in dark agouti rat. *J Comp Neurol* 519: 2353–2378.

Ádori C, Zelena D, Tímár J, et al. (2010) Intermittent prenatal MDMA exposure alters physiological but not mood related parameters in adult rat offspring. *Behav Brain Res* 206: 299–309.

Benningfield MM and Cowan RL (2013) Brain serotonin function in MDMA (ecstasy) users: Evidence for persisting neurotoxicity. *Neuropsychopharmacol* 38: 253–255.

Brière FN, Fallu JS, Janosz M, et al. (2012) Prospective associations between meth/amphetamine (speed) and MDMA (ecstasy) use and depressive symptoms in secondary school students. *J Epidemiol Commun Health* 66: 990–994.

Colado MI, Granados R, O'Shea E, et al. (1999) The acute effect in rats of 3, 4-methylenedioxyethamphetamine (MDEA, 'Eve') on body temperature and long term degeneration of 5-HT neurones in brain: A comparison with MDMA ('Ecstasy'). *Pharmacol Toxicol* 84: 261–266.

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

Derogatis L and Nelisaratos N (1983) The Brief Symptom Inventory: An introductory report. *Psycholog Med* 13: 595–605.

Erritizoe D, Frokjaer VG, Holst KK, et al. (2011) In vivo imaging of cerebral serotonin transporter and serotonin (2A) receptor binding in 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy') and hallucinogen users. *Arch Gen Psychiatr* 68: 562–576.

Fox HC, McLean A, Turner JJD, et al. (2002) Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ('ecstasy') polydrug users. *Psychopharmacol* 162: 203–214.

Greer G and Tolbert R (1986) Subjective Reports of the Effects of MDMA in a Clinical Setting. *Journal of Psychoactive Substances* 18: 319–327.

Johnston LD, O'Malley PM, Brackman JG, et al. (2005) Monitoring the future national survey on drug abuse 1975 – 2004: Volume 2; College students and adults aged 19 – 45. Report for the US National Institute of Health, no. 05–5728. Bethesda: National Institute on Drug Abuse.

Kirkpatrick MG, Gunderson EW, Perez AY, et al. (2012) A direct comparison of the behavioral and physiological effects of methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacol* 219: 109–122.

Kish SJ, Lerch J, Furukawa Y, et al. (2010) Decreased cerebral cortical serotonin transporter binding in ecstasy users: A positron emission tomography/[(11)C]DASB and structural brain imaging study. *Brain* 133: 1779–1797.

McCann UD, Sgambati FP, Schwartz AR, et al. (2009) Sleep apnea in young abstinent recreational MDMA ('ecstasy') consumers. *Neurology* 73: 2011–2017.

McElhatton PR, Bateman DN, Evans C, et al. (1999) Congenital abnomalies after prenatal ecstasy exposure. *Lancet* 354: 1441–1442.

MacInnes N, Handley SL and Harding GFA (2001) Former chronic methylenedioxymethamphetamine (MDMA or ecstasy) users report mild depressive symptoms. *J Psychopharmacol* 15: 181–186.

Milani RM, Parrott AC, Turner JJD, et al. (2004) Gender differences in self-reported anxiety, depression and somatization among ecstasy/MDMA polydrug users, alcohol/tobacco users and nondrug users. *Addict Behav* 29: 965–971.

Montgomery C, Hatton NP, Fisk JE, et al. (2010) Assessing the functional significance of ecstasy-related memory deficits using a virtual reality paradigm. *Hum Psychopharmacol* 25: 318–325.

Moore DG, Turner JD, Parrott AC, et al. (2010) During pregnancy, recreational drug-using women stop taking ecstasy (3,4-methylenedioxy-N-methylamphetamine) and reduce alcohol consumption, but continue to smoke tobacco and Cannabis: initial findings from the Development and Infancy Study. *J Psychopharmacol* 24: 1403–1410.

Morgan MJ, McFie L, Fleetwood LH, et al. (2002) Ecstasy (MDMA): Are the psychological problems associated with its use reversed by prolonged abstinence? *Psychopharmacol* 159: 294–303.

Munafo MR and Araya R (2010) Cigarette smoking and depression: A question of causation. *Brit J Psychiatry* 196: 425–426.

Parrott AC (2006) MDMA in humans: Factors which affect the neuropsychobiological profiles of recreational Ecstasy users, the integrative role of bio-energetic stress. *J Psychopharmacol* 20: 147–163.

Parrott AC (2007) The psychotherapeutic potential of MDMA (3,4-methylenedioxymethamphetamine): an evidence-based review. *Psychopharmacology* 191: 181–193.

Parrott AC (2009) Cortisol and MDMA (3,4-methylenedioxymethamphetamine): Neurohormonal aspects of bioenergetic-stress in Ecstasy users. *Neuropsychobiol* 60: 148–158.

Parrott AC (2012) MDMA and serotonergic neurotoxicity: Empirical evidence for adverse effects in humans - no need for translation. *Brit J Pharmacol* 166: 1518–1520.

Parrott AC (2013a) MDMA neurotoxicity: the functional implications of serotonin loss in recreational ecstasy users. *Neurosci Biobehav Revs* 37: 1466–1486.

Parrott AC (2013b) Human psychobiology of MDMA or 'Ecstasy': An overview of 25 years of empirical research. *Hum Psychopharmacol* 28: 289–307.

Parrott AC, Gibbs A, Scholey AB, et al. (2011) MDMA and methamphetamine: some paradoxical negative and positive mood changes in an acute dose laboratory study. *Psychopharmacology* 215: 527–36.

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

Parrott AC, Jones L, Sands HR, et al. (2012) High cortisol levels in recent Ecstasy/MDMA users: Preliminary findings from the Swansea, Westminster and Dresden collaborative study. In: *British Psychological Society Annual Psychobiology Conference*, UK, 3–5 September 2012. Conference Abstract p.16.

Parrott AC, Lock J, Conner AC, et al. (2008) Dance clubbing on-MDMA and during abstinence from MDMA: Prospective neuroendocrine and psychobiological changes. *Neuropsychobiol* 57: 165–180.

Parrott AC, Milani RM, Gouzoulis-Mayfrank E, et al. (2007) *Cannabis* and Ecstasy/MDMA (3,4-methylenedioxymethamphetamine): An analysis of their neuropsychobiological interactions in recreational users. *J Neural Transmiss* 114: 959–968.

Parrott AC, Milani RM, Parmar R, et al. (2001) Recreational Ecstasy/MDMA and other drug users from the UK and Italy: Psychiatric symptoms and psychobiological problems. *Psychopharmacol* 159: 77–82.

Puerta E, Hervias I, Aguirre N (2009) On the mechanisms underlying 3,4-methylenedioxymethamphetamine toxicity: the dilemma of the chicken and the egg. *Neuropsychobiology* 60: 119–129.

Raimo EB and Schuckit MA (1998) Alcohol dependence and mood disorders. *Addict Behav* 23: 933–946.

Reay JL, Hamilton C, Kennedy DO, et al. (2006) MDMA polydrug users show process-specific central executive impairments coupled with impaired social and emotional judgment processes. *J Psychopharmacol* 20: 385–388.

Ricaurte GA, McCann UD, Szaboc Z, Scheffelc U (2000) Toxicodynamics and long-term toxicity of the recreational drug, 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy'). *Toxicology Letters* 112–113: 143–146.

Rogers G, Elston J, Garside R, et al. (2009) The harmful health effects of recreational ecstasy: A systematic review of observational evidence. *Health Technol Assess* 13: 1–315.

Sala M and Braida D (2005). Endocannabinoids and 3,4-methylenedioxymethamphetamine (MDMA) interaction. *Pharmacol Biochem Behav* 81: 407–416.

Schifano F, Albanese A, Fergus S, et al. (2011) Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. *Psychopharmacol* 214: 593–602.

Schifano F, Di Furia L, Forza G, et al. (1998) MDMA ('ecstasy') consumption in the context of polydrug abuse: A report on 150 patients. *Drug Alc Depend* 52: 85–90.

Scholey AB, Owen L, Gates J, et al. (2011) Hair MDMA samples are consistent with reported Ecstasy use: Findings from a study investigating effects of Ecstasy on mood and memory. *Neuropsychobiology* 63: 15–21.

Scholey AB, Parrott AC, Buchanan T, et al. (2004) Increased intensity of Ecstasy and polydrug usage in the more experienced recreational Ecstasy/MDMA users: a WWW study. *Addict Behav* 29:743–52.

Singer LT, Salvator A and Arendt RE (2002) Effects of cocaine/polydrug exposure and maternal psychological distress on infant birth outcomes. *Neurotoxicol Teratol* 24: 127–135.

Singer LT, Linares TJ, Ntiri S, et al. (2004) Psychosocial profiles of older adolescent MDMA users. *Drug Alc Depend* 74: 245–252.

Singer LT, Moore DG, Fulton S, et al. (2012a) Neurobehavioral outcomes of infants exposed to MDMA (Ecstasy) and other recreational drugs during pregnancy. *Neurotoxicol Teratol* 34: 303–310.

Singer LT, Moore DG, Min MO, et al. (2012b) One-year outcomes of prenatal exposure to MDMA and other recreational drugs. *Pediatrics* 130: 407–413.

Skelton MR, Williams MT and Vorhees CV (2008) Developmental effects of 3,4-methylenedioxymethamphetamine: A review. *Behav Pharmacol* 19: 91–111.

Soar K, Turner JJD and Parrott AC (2001) Psychiatric disorders in recreational Ecstasy (MDMA) users: A literature review focusing upon personal predisposition factors and drug histories. *Hum Psychopharmacol* 16: 641–646.

Topp L, Hando J, Dillon P, et al. (1999) Ecstasy use in Australia: Patterns of use and associated harm. *Drug Alc Depend* 55: 105–115.

Verheyden SL, Maidment R and Curran HV (2003) Quitting ecstasy: An investigation of why people stop taking the drug and their subsequent mental health. *J Psychopharmacol* 17: 371–378.

Winstock AR, Griffiths P and Stewart D (2001) Drugs and the dance music scene: A survey of current drug use patterns among a sample of dance music enthusiasts in the UK. *Drug Alc Depend* 64: 9–17.

Wu P, Liu X, Pham TH, et al. (2010) Ecstasy use among US adolescents from 1999 to 2008. *Drug Alc Depend* 112: 33–38.

Zakzanis KK and Campbell Z (2006) Memory impairment in now abstinent MDMA users and continued users: A longitudinal follow-up. *Neurology* 66: 740–741.