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ORIGINAL INVESTIGATION

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Mood disorders and serotonin transporter density in ecstasy users—the influence of long-term abstention, dose, and gender

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Abstract *Rationale:* Neurotoxic effects of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") on the serotonin (5-HT) system have been described in animals and humans, but little is known about long-term effects of ecstasy use on mood. *Objectives:* To investigate short-term and long-term effects of ecstasy use on mood and its association with 5-HT neurotoxicity, dose, and gender in humans. *Methods:* Fifteen moderate ecstasy users, 23 heavy ecstasy users, 16 former heavy ecstasy users and 15 drug-using, but ecstasy-naive controls were included. Mood was assessed using the Composite International Diagnostic Interview (CIDI) and the Beck Depression Inventory (BDI). Outcomes were correlated with 5-HT transporter (SERT) density, assessed with [^{123}I]β-CIT single photon emission computed tomography (SPECT). *Results:* The prevalence of mood disorders assessed by CIDI did not differ between all groups. The overall test for differences in BDI scores between groups was near significance (P=0.056), with BDI scores higher in former heavy ecstasy users than in ecstasy-naive controls (P=0.045). BDI scores were correlated with the total number of ecstasy tablets used (r=0.310; P=0.021). No associations between CIDI or BDI outcomes and SERT density or gender were observed. *Conclusions:* These results suggest that ecstasy use is not associated with clinical depression (CIDI). However, the number of ecstasy tablets taken lifetime was associated with higher BDI scores for depressive mood, and this relationship seemed to persist after ecstasy use had stopped. We did not find that depressed mood in ecstasy users was associated with decrease in SERT density. Prospective studies are needed to establish the causal relationship between ecstasy use and depressed mood.

Keywords 3,4-Methylenedioxymethamphetamine · Ecstasy · Mood · Depression · SERT · Neuroimaging

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Introduction

Neurotoxic effects of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") on the serotonin (5-HT) system have been extensively studied in animals (e.g. Ricaurte et al. 2000). In addition, possible effects in humans were reported (e.g. Semple et al. 1999; McCann et al. 2000; Reneman et al. 2001a, 2001b). As 5-HT modulates many neuropsychological processes, including mood, we postulated that in ecstasy users 5-HT deficits are associated with increased prevalence of mood disorders.

Previous research on the functional consequences of 5-HT neurotoxicity induced by ecstasy showed converging evidence of memory impairments (Gouzoulis-Mayfrank et al. 2000; Reneman et al. 2000; Verbaten 2003). However, studies on the effect of ecstasy use on mood are less conclusive. Several case reports described individuals who developed psychiatric problems associated with the use of ecstasy, including depression (McGuire et al. 1994; Steele et al. 1994). Other studies, however, reported no difference in prevalence of depression between ecstasy users and non-users (Morgan 1998; Parrott et al. 2000).

As a short-term effect, enhanced mood was described to occur shortly after ecstasy consumption (Vollenweider

et al. 1998; Cami et al. 2000), followed by lowered mood a few days later (Curran and Travill 1997; Parrott and Lasky 1998). Women were found to be more susceptible than men to this mid-week low mood (Verheyden et al. 2002).

Studies in abstinent ecstasy users reported inconsistent results concerning the effect of ecstasy on mood. Krystal and co-workers (1992) reported no indication of clinical depression in ecstasy users after abstinence of psychoactive drugs for at least 3 weeks. However, higher depression scores were found in 1-week abstinent heavy ecstasy users than in controls (Gamma et al. 2000, 2001). Higher depression scores in moderate ecstasy users reported by Verkes and co-workers (2001) appeared not to be significant after correction for confounders.

Only a few studies examined the long-term effect of ecstasy on mood, and their results seem to suggest that (former) heavy use of ecstasy is associated with increased symptoms of depression. MacInnes et al. (2001) examined the long-term effect of ecstasy on mood in former chronic, but currently moderate ecstasy users and found mild depressive symptoms in this group. Gerra et al. found mood changes (dysphoria) 3 weeks (1998) and 12 months (2000) after ecstasy discontinuation. Morgan and co-workers (2002) found elevated depression scores in ecstasy users and former ecstasy users who had stopped using ecstasy for at least 6 months. However, these elevated depression scores correlated only with the amount of cannabis they also used, and not with the number of ecstasy tablets.

Because all studies were conducted retrospectively, it is not certain whether the observations of increased depressive symptoms in (former) ecstasy users represents a pre-existing condition, or is caused by 5-HT deficits induced by ecstasy, or is the result of a combination of the two. Lieb and co-workers (2002) studied the (temporal) relationship between ecstasy use and mental disorders in a representative sample of adolescents and young adults in a prospective follow-up study. They reported increased prevalence of mood disorders in ecstasy users compared to non-users, but found that the mood disorder preceded the first use of ecstasy in about 45% of persons with major depression and in 70% of persons with dysthymia. However, information about the onset of ecstasy use and the onset of mood disorders prior to baseline was obtained retrospectively.

In approaching this problem of the relationship between ecstasy use and mood disorders, we thought it would be relevant to link depression scores in (former) ecstasy users with markers of 5-HT neurotoxicity. 5-HT neurotoxicity can be assessed in the living human brain by measuring 5-HT transporter (SERT) density. SERT is a structural element of the pre-synaptic membrane, and has been shown to be a reliable marker of MDMA-induced 5-HT neurotoxicity (Scheffel et al. 1992). SERT density can be assessed using the radiotracer [^{123}I]β-CIT that binds with high affinity to SERTs and dopamine transporters (DATs) (Laruelle et al. 1993) in combination with single-photon emission computed tomography (SPECT) (Reneman et al. 2002). Previous [^{123}I]β-CIT SPECT studies showed loss of SERTs in subjects with a history of ecstasy use (Semple et al. 1999) and we found the same also in the population of the current study (Reneman et al. 2001a, 2001b).

To our knowledge, only one study has investigated both mood disorders and 5-HT neurotoxicity by measuring SERT densities using positron emission tomography (PET) (Thomasius et al. 2003). In this study, significantly elevated depression scores were associated with the number of exposures to ecstasy, in recent as well as in former ecstasy users (who had stopped using ecstasy for at least 5 months) when they were compared to the scores of drug-naive controls. Evidence for 5-HT neurotoxicity was only observed in central serotonergic brain regions in current, but not in former ecstasy users. The authors did not investigate the association between 5-HT neurotoxicity (SERT availability) and depression scores.

The objective of the present study was to investigate short-term as well as long-term effects of ecstasy use on mood, and its association with SERT densities. Moreover, as there are indications that the effects of ecstasy are dose-dependent, and that female users are more susceptible than male users (Liechti et al. 2001; Reneman et al. 2001b; Verheyden et al. 2002), the influence of dose and gender were investigated as well.

Material and methods

Participants

The present study population and sub-sets of it were described in previous publications in which the effects of ecstasy on SERT (Reneman et al. 2001b), on DAT densities (Reneman et al. 2000) and on memory function (Reneman et al. 2001a) were analysed. In brief, 69 subjects, aged 18–45 years, participated in the study and were divided into four subgroups: 15 moderate ecstasy users, 23 heavy ecstasy users, 16 former heavy ecstasy users and 15 controls that used drugs, but were ecstasy-naive. Lifetime use of more than 50 tablets was defined as heavy ecstasy use, whereas lifetime use less than 50 tablets was defined as moderate ecstasy use. Individuals who had used at least 50 tablets lifetime but had stopped using ecstasy at least 12 months prior to the study were included in the subgroup of former heavy ecstasy users. Both ecstasy users and controls were recruited by means of flyers at locations in the Netherlands associated with the "rave scene" with the help of UNITY, a Dutch agency that provides harm-reduction information and advice about drugs.

Participants agreed to abstain from all psychoactive drugs for at least 3 weeks before the study. On the day of examination, urine drug analysis was performed with an enzyme-multiplied immunoassay for amphetamines, barbiturates, benzodiazepine metabolites, cocaine metabolite, opiates, and marijuana. Exclusion criteria were positive drug screening, pregnancy, medical or neuropsychiatric illness that impeded informed consent, and current use of antidepressive medication that could compete with [^{123}I]β-CIT for SERT binding, such as selective serotonin re-uptake inhibitors. All subjects completed the Dutch version of the National Adult Reading Test (NART), which provides an estimate of premorbid IQ (Nelson 1991). Written informed consent was obtained from all participants, and the study was approved by the local Medical Ethics Committee.

Outcome measures of mood

Lifetime and current diagnoses for mood disorders, including major depression, dysthymia and bipolar disorders, were assessed in all subjects using a computerised version of the Composite International Diagnostic Interview (CIDI, lifetime version 2.1) (WHO 1992). The CIDI is a fully structured interview that covers the criteria for diagnoses of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV) (American Psychiatric Association 1994).

Additionally, current depression was assessed using the Beck Depression Inventory (BDI) (Beck et al. 1961). The BDI is a 21-item self-report rating inventory, which measures characteristic attitudes and symptoms of depression in the week prior to assessment; higher scores indicate more depressive symptoms. The BDI showed high levels of reliability and validity across cultures (Beck and Steer 1984; Bouman et al. 1985; Kojima et al. 2002).

SPECT imaging

As described previously, ^{123}iodine-2β-carbomethoxy-3β(4-iodophenyl)tropane ([^{123}I]β-CIT) SPECT was used to measure SERT densities (Reneman 2001a, 2001b). SPECT imaging was performed with a dedicated 12-detector single-slice head scanner with a spatial resolution of 7.5 mm full-width at half-maximum (Strichman Medical Equipment 810, Inc., Medfield, Mass., USA).

Subjects were intravenously injected with approximately 3.8 mCi (140 MBq) of [^{123}I]β-CIT. Scanning was started 4 h after injection when the specific binding to SERT is regarded to be stable (Pirker et al. 2000). Subjects lay in supine position with the head parallel to the orbitomeatal line. Image analysis was performed using regions of interest (ROIs) for frontal cortex, temporal cortex, parieto-occipital cortex, occipital cortex, striatum, thalamus and cerebellum, as described earlier (Reneman et al. 2001a, 2001b). Binding ratios of [^{123}I]β-CIT were calculated by dividing binding in the ROI by binding in the cerebellum.

Statistics

We used a two-way analysis of variance with group and gender as factors to analyse differences in continuous variables (log transformed if necessary) between the four groups.

Differences in prevalence of lifetime and current mood disorders between the four groups, measured by CIDI, were analysed using the chi-square test. Overall differences in BDI scores between the four groups were analysed using the non-parametric Kruskal-Wallis test, because BDI values were not normally distributed. Post hoc, Mann-Whitney *U*-tests were performed to analyse differences in BDI scores between groups. The correlations between CIDI and BDI outcomes and lifetime ecstasy consumption (log transformed) were analysed using Spearman's correlation coefficient.

A mixed linear model was used to analyse the relationship between CIDI and BDI outcomes and SERT densities. Using this model, it was possible to analyse SPECT data from the six different brain regions studied simultaneously, taking into account both within-subject and between-subject variations. The model we designed included brain regions (6 levels), groups (4 levels), gender (2 levels), and the interaction between group and gender. Outcomes of the CIDI lifetime (2 levels) and BDI (2 levels, cut-off point=median) were added to the model to determine their effects on SERT density.

Two-sided *P*-values below 0.05 were considered to be statistically significant.

Results

Characteristics of the study population

Sample characteristics were described in an earlier publication (Reneman et al. 2001b). The four groups were comparable regarding age, gender, premorbid IQ (NART IQ), and use of alcohol and cannabis (Table 1). Ecstasy users had used significantly more amphetamine and cocaine than controls. Males were significantly older (on average 3.1 years) and consumed significantly more alcohol than females. Within the subgroup of heavy ecstasy users, males had used more ecstasy tablets and took higher usual doses than females (Table 1), even when corrected for body weight. Moderate and heavy ecstasy users were abstinent from ecstasy use on average for 3.6 and 2.3 months, respectively, while the former heavy ecstasy users reported to be abstinent from ecstasy for almost 2.5 years on average (Table 1).

CIDI

The prevalence of current or lifetime mood disorders according to DSM-IV criteria measured by CIDI is listed in Table 2. The groups did not differ significantly as to prevalence of lifetime (P=0.930) and current (P=0.866) mood disorders. The overall analysis showed that the prevalence of lifetime mood disorders was not significantly related to gender (P=0.203). Within the ecstasy groups, 12 out of 17 persons (71%) diagnosed with a lifetime mood disorder reported that the onset of their mood disorder had preceded the first use of ecstasy.

BDI

Results of the BDI are also listed in Table 2. Two controls did not complete the BDI questionnaire, so only the results of 13 controls are presented. The overall test for differences in BDI scores between groups was near significance (P=0.056). Post-hoc, between-group comparisons revealed significantly higher BDI scores in former heavy ecstasy users (P=0.045) than in ecstasy-naive polydrug controls. BDI scores correlated significantly (r=0.310, P=0.021) with the log-transformed total number of ecstasy tablets (Fig. 1). BDI scores did not differ between men and women (P=0.179). No significant correlations were found between BDI scores and the usual dose of ecstasy per event (r=0.144, P=0.303) or between BDI scores and the use of cannabis in the last year (r=0.213, P=0.182).

Mood and SERT

Mean SERT densities are shown in Table 3, sub-divided for subjects with and without a diagnosis of lifetime mood disorder (CIDI). In addition, mean SERT densities are given, subdivided for BDI scores above or below the

Table 1 Demographics, characteristics of ecstasy use and exposure to other substances expressed as mean±SD

	Polydrug controls (*n*=15)		Moderate ecstasy users (*n*=15)		Heavy ecstasy users (*n*=23)		Former ecstasy users (*n*=16)		*P* group[b]	*P* gender[b]
	Male (*n*=7)	Female (*n*=8)	Male (*n*=9)	Female (*n*=6)	Male (*n*=12)	Female (*n*=11)	Male (*n*=8)	Female (*n*=8)		
Demographics										
Age (years)	29.3±6.9	23.3±1.3	25.6±7.5	22.7±2.8	27.1±6.0	25.0±4.1	26.4±6.2	24.1±4.7	0.63	0.02[d]
DART-IQ[a]	104.7±6.2	106.9±7.4	111.2±11.5	112.2±8.1	106.0±9.0	104.5±8.4	105.9±11.8	102.0±7.7	0.10	0.73
Ecstasy use										
Duration of use (years)	NA	NA	4.6±3.1	3.3±1.5	6.4±3.0	4.6±2.1	4.0±2.0	5.1±3.1	0.24	0.38
Usual dose (tablets)	NA	NA	1.33±0.56	1.38±0.49	2.64±0.67	1.82±0.46	2.00±0.96	2.16±1.01	0.00[d]	0.35
Lifetime dose (tablets)[c]	NA	NA	29.5±17.5	27.3±19.7	831.8±733.0	200.9±171.2	126.9±91.4	409.3±868.7	0.00[d]	0.25
Time since last tablet (months)	NA	NA	4.3±7.5	2.7±2.1	1.97±2.67	2.6±2.1	37.1±25.4	21.0±10.1	0.00[d]	0.38
Age of onset (years)	NA	NA	21.3±6.1	19.3±3.1	20.9±4.2	20.4±3.1	22.4 ±5.6	19.0±5.0	0.99	0.16
Other substances										
Alcohol (no.of consumptions/week)	14.1±12.8	7.1±7.4	18.2±14.8	5.3±3.2	13.0±8.2	5.8±3.5	4.5±3.9	7.9±5.4	0.14	0.00[d]
Tobacco (cigarettes/day)	9.5±3.3	10.3±6.1	11.0±6.5	9.4±9.2	12.4±13.0	6.0±7.1	11.8±8.5	13.3±8.6	0.47	0.21
Last 3 months use of										
Cannabis (no. of joints)[c]	2.3±0.6	4.5±5.0	68.1±6.5	31.8±51.6	94.6±153.0	67.5±101.9	73.1±110.4	196.3±369.3	0.37	0.23
Amphetamine (no. of times used)[c]	–	–	0.4±0.8	–	3.8±7.4	3.6±5.5	–	–	0.04[d]	0.80
Usual dose amphetamine (g)	–	–	0.3±0.2	0.1±0.1	0.4±0.3	0.3±0.3	0.7±0.4	1.0±0.8	0.07	0.83
Cocaine[c]	–	–	1.2±1.1	–	4.2±2.8	4.4±3.4	–	–	0.09	0.74

[a] DART=Dutch Adult Reading Test [b] Two-way analysis of variance [c] Variables that were log transformed [d] Statistical significant differences

Table 2 Mood disorders: frequencies of CIDI lifetime and current mood disorders (DSM-IV) and BDI scores

	Polydrug controls (*n*=15)	Moderate ecstasy users (*n*=15)	Heavy ecstasy users (*n*=23)	Former ecstasy users (*n*=16)	
CIDI lifetime mood disorders [no. (%)]	4 (27%) 2m: 29%, 2f: 25%	5 (33%) 1m: 11%, 4f: 67%	7 (30%) 5m: 42%, 2f: 18%	6 (38%) 1m: 13%, 5f: 63%	*P*group=0.930 *P*gender=0.203
CIDI current mood disorder [no. (%)]	2 (13%) 0m: 0%, 2f: 25%	3 (20%) 1m: 11%, 2f: 33%	4 (17%) 2m: 17%, 2f: 18%	4 (25%) 1m: 13%, 3f: 38%	*P*group=0.866
BDI median score (IRQ: 25–75%)	1.0 (0.0–3.0)[a] m=1.5, f=1.0	2.0 (0.0–4.0) m=0.0, f=3.5	5.0 (0.0–8.0) m=4.5, f=6.0	5.5 (1.3–10.0) m=4.0, f=7.5	*P*group=0.056 *P*gender=0.179

[a] Two subjects with missing data

Table 3 Mean overall [^{123}I]β-CIT binding ratios (±SD) for persons with/without lifetime mood disorder (*CIDI*) and BDI score above/below median score

	Polydrug controls	Moderate ecstasy users	Heavy ecstasy users	Former ecstasy users	Main effect on SERT
CIDI with lifetime mood disorder	1.31±0.12	1.18±0.14	1.14±0.12	1.23±0.06	CIDI:
CIDI without lifetime mood disorder	1.21±0.09	1.16±0.11	1.16±0.11	1.23±0.12	P=0.995
BDI above median BDI score (BDI ≥3)	1.22±0.04	1.18±0.11	1.13±0.10	1.24±0.09	BDI: P=0.410
BDI below median BDI score (BDI <3)	1.24±0.12	1.19±0.14	1.19±0.11	1.22±0.12	

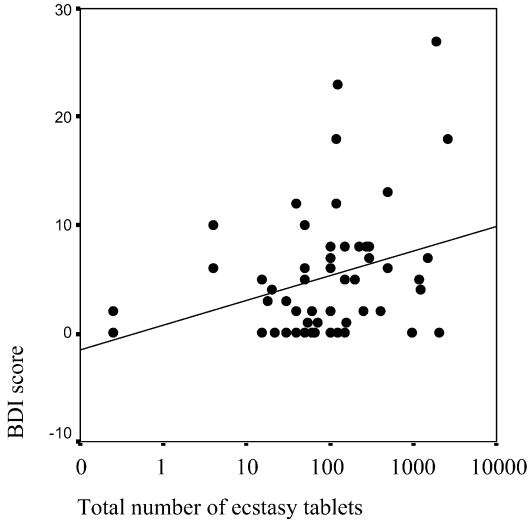

Fig. 1 Correlation between depressive symptoms (BDI scores) and lifetime ecstasy consumption (logarithmic scaling)

median value (median value=3.0). As described in an earlier publication (Reneman et al. 2001b), a significant group effect was observed (P=0.041) in overall [^{123}I]β-CIT binding ratios, in which overall SERT densities appeared to be lower in the group of heavy ecstasy users than in the other groups. Moreover, a significant interaction between group and gender was observed, in which overall SERT densities in female ecstasy users appeared to be lower than in male ecstasy users. However, we observed no main effect of CIDI (P=0.995) or BDI (P=0.410) on SERT when these variables were added to our statistical model.

Discussion

The present study investigated the short-term as well as the long-term effects of ecstasy on mood and its association with 5-HT neurotoxicity. We detected no significant effect of ecstasy use on the prevalence of CIDI-DSM-IV mood disorders. However, we found significantly more depressive symptoms (higher BDI scores) in former heavy ecstasy users than in controls that used different drugs but no ecstasy. The BDI scores also correlated with the number of ecstasy tablets used. We observed no association between mood disorders and SERT densities or gender.

The increased symptoms of depression (measured using BDI) might be caused by deficits in serotonin in (former) heavy ecstasy users, as there is evidence that ecstasy has neurotoxic effects on the serotonin system and as it is known that the serotonin system modulates many psychological functions. Because the number of participants in each group was relatively small, we cannot fully exclude the possibility of a chance finding, as indicated by the overall P-value for the difference between groups (P=0.056). However, other research groups have also reported more symptoms of depression in recent and former ecstasy users (Gerra et al. 1998, 2000; Gamma et al. 2000, 2001; MacInnes et al. 2001; Morgan et al. 2002; Thomasius et al. 2003). However, only one previous study examined the long-term effect of ecstasy use on mood in subjects that stopped using ecstasy for 1 year (Gerra et al. 2000) and found elevated depression scores in these former ecstasy users. The observation of increased depressive symptoms in former heavy ecstasy users in the present study corroborates this finding.

Using DSM-IV criteria (CIDI), we observed no difference in prevalence of current or lifetime mood disorders between ecstasy users and controls. Because CIDI gives a binary clinical diagnosis (mood disorder versus no mood disorder), the statistical power of this study might have been too low to demonstrate increased prevalence of clinical mood disorders in (former) ecstasy users. BDI, on the other hand, is more sensitive because of its gradual scale including both sub-clinical and clinical scores. BDI scores from 0 to 9 are considered to be within the normal range. Therefore, median BDI scores within all four subgroups ranging from 1.0 to 5.5 (Table 2) did not reach the clinical level of depression.

A relationship between depressive symptoms and decreased SERT availability has been reported in several diseases, such as major depression (Malison et al. 1998), seasonal affective disorders (Willeit et al. 2000), and Wilson's disease (Hesse et al. 2003). On the other hand, Dahlström et al. (2000) demonstrated elevated SERT density in depressive children and adolescents. In the present study, we found no correlation between overall SERT binding and mood disorders as measured by CIDI or BDI. Interestingly, when comparing former ecstasy users with current heavy ecstasy users, it seems that BDI scores do not improve. This is in remarkable contrast to the reversibility of decreased SERT binding, observed in former (female) heavy ecstasy users (Reneman et al. 2001a, 2001b). On the other hand, this finding is in agreement with the findings of Thomasius et al. (2003),

who observed reduced SERT binding only in current but not in former ecstasy users, while elevated depressive symptoms were reported by both current and former ecstasy users and not by ecstasy-naive polydrug controls. Although no association between depressive symptoms and SERT density was calculated, this would suggest that the observed depressive symptoms were not correlated to 5-HT neurotoxicity induced by ecstasy. We, as well as others, previously reported a similar lack of association between SERT densities and memory function (Semple et al. 1999; Reneman et al. 2001a).

There are several possible explanations why we did not observe a correlation between mood and SERT densities. The first explanation is that depressive symptoms in (former) ecstasy users are not attributable to 5-HT deficits induced by ecstasy. This is in concordance with our observation and with the observation of Lieb et al. (2002) that the majority of (former) ecstasy users with mood disorders reported the onset of their mood disorder preceding the first use of ecstasy. On the other hand, we observed a modest but significant correlation between the extent of previous ecstasy consumption and symptoms of depression, similar to the one described by Thomasius et al. (2003), which suggests that increased depressive symptoms might be at least partially attributable to ecstasy use. A second explanation therefore might be that, although loss of SERT is indicative of axonal loss or damage, recovery of SERT densities does not imply normal (behavioural) function. Possibly in line with this, Hatzidimitriou et al. (1999) showed that after administration of neurotoxic doses of MDMA in non-human primates partial recovery of brain serotonin axons was accompanied by development of altered reinnervation patterns. A final explanation might be that the radiotracer [^{123}I]β-CIT used in this study has a limited sensitivity in detecting 5-HT neurotoxicity because it is not selective for binding to SERTs. The use of a selective radiotracer for SERTs might be more sensitive and therefore more capable of detecting a possible correlation between mood and SERT densities.

We found no correlation between gender and prevalence of lifetime mood disorders (CIDI) or BDI scores, whereas earlier findings in the same study population suggested that females are more vulnerable to the effects of ecstasy on SERT densities than males (Reneman et al. 2001b). It was also reported elsewhere that females had a more pronounced subjective response to ecstasy and were more susceptible to mid-week low mood (Liechti et al. 2001; Verheyden et al. 2002). Moreover, mood disorders in the Netherlands were reported to be almost twice as common among females as among males (Bijl et al. 1998). Probably because of the low prevalence of clinical mood disorders within all subgroups, we did not observe overall significant differences in mood between males and females.

The relatively small groups and the low prevalence of clinical mood disorders within the groups resulted in limited statistical power of this study, especially with regard to the control of and adjustment for potential confounders. However, except for the lifetime number of tablets, we found no significant correlations between BDI scores and other characteristics of ecstasy use, such as duration of use, usual dose, time since last tablet, and age of onset of ecstasy use. In addition, we did not find any significant correlation between BDI scores and other potential confounders, such as use of alcohol, tobacco, cannabis, amphetamine or cocaine. We therefore believe that it is unlikely that these factors confounded our results, but because of the limited statistical power of this study a potential influence cannot be entirely excluded.

In conclusion, our findings suggest that symptoms of depression in ecstasy users are related to the number of ecstasy tablets used. Moreover, our findings suggest that symptoms of depression may still be present more than 1 year after ecstasy use is stopped. When a clinical depression is ecstasy-related, involving the serotonergic neurotransmitter system, this should have implications for treatment. As suggested by Haddad et al. (2002), in that case treatment with norepinephrine reuptake inhibitors such as reboxetine, would be preferable over selective serotonine re-uptake inhibitors (SSRIs) such as fluoxetine, since the norepinephrine system is thought to remain intact in ecstasy users. Because this study has limited statistical power, our results need confirmation from larger studies. Moreover as this study was performed retrospectively, and as we found no evidence that mood disorders in ecstasy users are correlated to decreased SERT binding, no final conclusion can be drawn about the causal nature of the observed relationship between ecstasy use and depressed mood. It remains possible that there are pre-existing differences in mood between ecstasy users and controls. In order to establish a causal relationship prospective studies are in progress.

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