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Ecstasy use and self-reported depression, impulsivity, and sensation seeking: a prospective cohort study

Maartje M. L. de Win *Department of Radiology, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands; Graduate School Neurosciences, Amsterdam, The Netherlands.*
Thelma Schilt *Department of Neurology, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands.*
Liesbeth Reneman *Department of Radiology, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands.*
Hylke Vervaeke *Bonger Institute of Criminology, University of Amsterdam, Amsterdam, The Netherlands.*
Gerry Jager *Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center, Utrecht, The Netherlands.*
Sarah Dijkink *Department of Radiology, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands.*
Jan Booij *Department of Nuclear Medicine, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands.*
Wim van den Brink *Amsterdam Institute for Addiction Research and Department of Psychiatry, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands.*

Abstract

Although there are indications that ecstasy users have higher levels of depression, impulsivity, and sensation seeking, it is unknown whether these are consequences of ecstasy use or predisposing factors for starting ecstasy use. We prospectively assessed the predictive value of depression, impulsivity, and sensation seeking on future first time ecstasy use. We also assessed whether depression, impulsivity, and sensation seeking had changed after first ecstasy use. Depression, impulsivity, and sensation seeking were assessed using self-report questionnaires in 188 ecstasy-naive volunteers with high probability for future ecstasy use. After a mean follow-up of 17 months, measurements were repeated in 59 incident ecstasy users (mean 6.0 tablets) and 61 matched persistent ecstasy-naive volunteers. Only experience seeking (subscale of the sensation seeking scale) predicted future ecstasy use (OR = 1.05, 95% CI 1.00 to 1.10), but after adjustment for potential confounders this was not significant anymore. At follow-up, significant effects of ecstasy use on the general and the disinhibition subscale of the sensation seeking scale were observed (after adjustment for potential confounders: regression coefficient B = 0.51, 95% CI 0.20 to 0.83 and B = 3.25, 95% CI 1.74 to 4.76, respectively). These data indicate that depression, impulsivity, and sensation seeking do not predict first time ecstasy use in a population of young adults with the intention to start using ecstasy and that low level ecstasy use does not seem to cause depression or impulsivity. However, low level ecstasy use may increase (certain aspects of) sensation seeking.

Keywords

depression, impulsivity, sensation seeking, psychopathology, ecstasy, MDMA, self-report questionnaires

Introduction

While the trend of using ecstasy (3,4-methylenedioxymethamphetamine, MDMA) has become increasingly widespread during the last decade, more concern has arisen about the negative consequences of the drug. The potential neurotoxicity of the party drug has been described in numerous articles over the last years. There is good evidence that MDMA causes damage to the serotonergic (5-HT) axons in animals, including rodents and non-human primates (Ricaurte *et al.*, 2000). Also in humans there are indications that ecstasy use is associated with altered serotonergic function (Gerra *et al.*, 1998; McCann *et al.*, 2000; Reneman *et al.*, 2001b; Reneman *et al.*, 2006). It is known that 5-HT modulates many physiological processes (such as vasoconstriction, thermoregulation) and neuropsychological functions (such as memory, and learning) (Cohen *et al.*, 1996; Meneses, 1999). Moreover,

Corresponding author: Maartje M.L. de Win, Department of Radiology, G1–229, University of Amsterdam, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. *Email*: m.m.dewin@amc.uva.nl

there is suggestive evidence that 5-HT function influences behavioural and psychopathological processes such as mood, anxiety, aggression, sexual behaviour, binge eating, sensation seeking, and impulsivity (Marlowe, 1993; Netter *et al.*, 1996; Lucki, 1998). In line with this, depression was found to be associated with low 5-HT transporter densities (Malison *et al.*, 1998), high sensation seeking with low serotonergic function (Netter *et al.*, 1996), and impulsive and aggressive personality traits with low levels of the main serotonin metabolite 5-HIAA in the cerebrospinal fluid (CSF) (Kruesi *et al.*, 1990; Virkkunen *et al.*, 1994).

Therefore it can be hypothesized that ecstasy-induced serotonergic depletion will be associated with increased depression, impulsivity, and sensation seeking. In accordance with this hypothesis many studies reported increased self-reported levels 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; De Win *et al.*, 2004), which was confirmed by a recent meta-analysis (Sumnall and Cole, 2005). In addition, ecstasy users were found to score higher on self-reported impulsivity (Morgan, 1998; Parrott *et al.*, 2000; Tuchtenhagen *et al.*, 2000; Daumann *et al.*, 2001, 2004; Bond *et al.*, 2004; Butler and Montgomery, 2004) and sensation/novelty seeking (Gerra *et al.*, 1998; Tuchtenhagen *et al.*, 2000; Schifano, 2000; Dughiero *et al.*, 2001). In addition, the few studies that used behavioural measurements suggest increased depression by a shift towards negative words in the Affective Go/No-Go test (Roiser *et al.*, 2005b), increased behavioural impulsivity (Morgan, 1998), and increased risk-taking (Butler and Montgomery, 2004). Others did not find differences on behavioural measurements such as decision-making (Roiser *et al.*, 2005a).

However, it is unclear, whether these associations reflect a causal relationship, i.e. whether the use of ecstasy causes changes in mood, impulsivity, and sensation seeking. Almost all previous studies were cross-sectional and thus vulnerable for selection and interpretation bias, including reverse causation. Moreover, many confounding variables are involved such as polydrug use, lifestyle, and education, that could account for these differences and it is very difficult or even impossible to control adequately for all these factors using a retrospective design (Parrott, 2001). It is conceivable that differences between ecstasy users and non-users were already existing before the first use of ecstasy or even predispose subjects to start using ecstasy (Curran, 2000). Therefore, it has been advocated by several researchers that prospective studies should be conducted with measurements before and after a period of ecstasy use (Parrott *et al.*, 2000; Butler and Montgomery, 2004).

A causal relationship between ecstasy-induced 5-HT dysfunction and increased depression and impulsivity is suggested by findings that increased impulsivity (Morgan, 1998) and depression (De Win *et al.*, 2004; Sumnall and Cole, 2005) were positively correlated with increasing cumulative doses of ecstasy. Moreover, these studies compared ecstasy users with ecstasy-naive polydrug users and it seems implausible that individuals with high impulsivity or depression would be predisposed especially to the use of ecstasy. In rats, both MDMA (Taylor and Jentsch, 2001) and cocaine (Paine *et al.*, 2003) induced increased impulsive behaviour. On the other hand, other studies suggested that increased psychopathology is related to polydrug use rather than to the use of ecstasy alone (Daumann *et al.*, 2001, 2004; Parrott *et al.*, 2001; Thomasius *et al.*, 2003). Finally, there are studies which indicate that depression, impulsiveness, and personality traits such as sensation or novelty seeking are risk factors for substance use rather than a consequence of ecstasy use (Bardo *et al.*, 1996; Gerra *et al.*, 2004), although few longitudinal studies in humans have been performed. One longitudinal follow-up study found that sensation seeking was a predictor for substance use (Pedersen, 1991). Others observed that most (former) ecstasy users with increased depression scores reported that the onset of their mood disorder preceded their first use of ecstasy (Lieb *et al.*, 2002; De Win *et al.*, 2004). It has even been suggested that some individuals unconsciously chose to use ecstasy in an attempt to self-medicate their existing serotonergic deficiency (Gerra *et al.*, 1998).

In summary, although there are indications that ecstasy users have higher levels of depression, impulsivity, and sensation seeking, it is not known whether these symptoms appear after the onset of ecstasy use and should be considered as a consequence of ecstasy use or whether these are pre-existing and could therefore be considered as predisposing or risk factors for ecstasy use. Only a prospective follow-up study in ecstasy-naive subjects can provide evidence of the direction of these relationships. Therefore the aim of the present study was to determine whether ecstasy users differ from ecstasy-naive subjects with regard to symptoms of depression, impulsivity, and sensation seeking and if so, whether differences were present before or developed after the first use of ecstasy. We hypothesized that higher levels of depression, impulsivity, and sensation seeking are predictors of future ecstasy use in ecstasy-naive young adults (even after controlling for potential confounders). In addition, we hypothesized that depression, impulsivity, and sensation seeking increase following a period of ecstasy use (even after controlling for potential confounders).

Methods and materials

Subjects

The current study is part of the NeXT (Netherlands XTC Toxicity) study, a larger study investigating causality, course, and clinical relevance of ecstasy neurotoxicity. A detailed description of the NeXT study can be found in a special design paper (De Win *et al.*, 2005). Between April 2002 and April 2004, 188 ecstasy-naive young adults (18–35 years) with a relatively high probability to start using ecstasy in the near future were included in the study. They were actively recruited using a combination of targeted site sampling at locations such as dance events, discotheques, youth fairs, universities, colleges, and parks; advertisement through a website on the project and an Internet campaign; and snowball sampling referrals. Main criteria for inclusion were intention to probably or certainly use ecstasy for the first time in the near future (a score of 3–5 on a five-point scale; 1 = certainly not; 2 = probably not; 3 = undecided; 4 = probably yes; 5 = certainly

yes) and/or having one or more friends who already use ecstasy. Exclusion criteria were: ecstasy use in the past (at baseline session), a severe physical or mental illness, the use of psychotropic medications such as 5-HT reuptake inhibitors, pregnancy, and the use of intravenous drugs. Subjects had to abstain from use of psychoactive substances for at least 2 weeks before examinations and from alcohol for at least 1 week before examinations. This was checked in urine drug screening (enzyme-multiplied immunoassay for amphetamines, ecstasy, opiates, cocaine, benzodiazepine, cannabis, and alcohol). After recruitment we had about 550 volunteers who were willing to participate in the study, but the majority was excluded because their intention for future ecstasy use did not fulfil our criteria. A smaller part was excluded because of the other exclusion criteria or because they did not want to abstain from substance use. Subjects were paid for their participation (per session €100, or €150, depending on measurements and location for 2 days of measurements including additional brain imaging; see also De Win *et al.*, 2005).

The study was approved by the local medical ethics committee. To rule out any suggestion that we would approve or stimulate the use of ecstasy in ecstasy-naive subjects, subjects were informed through a brochure that stated 'From research in animals it is shown that ecstasy potentially causes damage to the "serotonergic system" in the brain. This system is important for several brain functions such as mood, impulsivity, and memory. However, we do not know whether this is also true for humans. Therefore it is important to study also in humans the potential consequences of ecstasy on the brain.' In addition each subject had to sign an informed consent form, that stated that participation was voluntary, that ecstasy is potential harmful and that the examiners do not have the intention to stimulate the use of ecstasy.

Study procedure

At baseline examination all 188 subjects completed questionnaires regarding depression, impulsivity, and sensation seeking. After inclusion and baseline examination, subjects had to complete questionnaires (four in total) sent to them by mail about their drug use every 3 months during a follow-up period of approximately 18 months.

Between 12 and 24 months after the baseline assessments all incident ecstasy users and an individually matched (gender, age, verbal intelligence, cannabis use) control group of persistent ecstasy-naive subjects (subjects from the same baseline population of ecstasy-naives who did not start to use ecstasy during the follow-up period) were invited for a follow-up session during which the self-report questionnaires (depression, impulsivity, sensation seeking) were repeated.

Assessments

Depression Current depressive symptoms were 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 (Beck and Steer, 1984; Bouman *et al.*, 1985). Total BDI scores were calculated.

Impulsivity The Dutch version of the Barratt Impulsiveness Scale (BIS-11), a consistent and reliable measure of impulsiveness, was used to assess impulsivity (Patton *et al.*, 1995). The Dutch BIS-11 contains 31 self-report items that have to be scored from one to four. Total scores and subscale scores on attentional impulsivity ('difficulty in concentrating'), motor impulsivity ('acting without thinking') and non-planning impulsivity ('thinking about the present rather than the future') were calculated.

Sensation seeking The Spannings Behoefte Lijst (SBL), a Dutch adaptation of the American Sensation Seeking Scale (Zuckerman and Link, 1968), was used to measure sensation seeking (Feij *et al.*, 1982; Feij and van Zuilen, 1984). The SBL contains 51 sensation seeking items and 16 filler items, for which respondents have to indicate on a five-point scale to what extent they (dis)agree with the statements. Both a general sensation seeking score and scores for the subscales thrill and adventure seeking (TAS), experience seeking (ES), boredom susceptibility (BS) and disinhibition (DIS) were calculated. The (sub)scale scores have proven to be reliable measures for various aspects of sensation seeking in research populations (Feij *et al.*, 1982; Feij and van Zuilen, 1984).

Potential confounders Potential confounders, such as demographic variables, education, and substance use were measured using questionnaires at baseline and at follow-up sessions. Various aspects of lifetime ecstasy use (frequency of use, cumulative number of tablets, and duration of use), and last year use of alcohol (units per week), tobacco (cigarettes per week), cannabis (number of joints last year), amphetamines (number of times used last year), and cocaine (number of times used last year) were assessed using validated substance-use questionnaires (Van de Wijngaart et al., 1997). Verbal intelligence was measured using the Dutch Adult Reading Test (DART), the Dutch version of the National Adult Reading Test (Nelson, 1991). The DART-IQ is used to estimate premorbid verbal intelligence as it is relatively insensitive to cognitive impairments caused by neurological disorders (Schmand et al., 1991).

Statistical analyses

All substance-use variables were log-transformed before the analyses because they were not normally distributed. Future ecstasy use, i.e. ecstasy use between baseline and follow-up, was categorized in a binary variable: yes = 1 and no = 0.

To test whether higher levels of depression, impulsivity, and sensation seeking predicted future incident ecstasy use, backward logistic regression analyses ($p_{in} = 0.05$; $p_{out} = 0.05$) were performed. For significance testing Likelihood Ratio tests (LR tests) were applied. First, analyses were performed with future ecstasy use as the dichotomous dependent variable and baseline measures of the total scores on depression (BDI-BL), impulsivity (BIS-BL), and sensation seeking (SBL-BL) as the dependent variables,

without (model 1, total scores) and with (model 2, total scores) adjustment for the effect of potential confounders. Second, to test whether certain aspects of impulsivity and sensation seeking predicted future ecstasy use, analyses were performed with future ecstasy use as the dichotomous dependent variable and baseline measures of the subscale scores on impulsivity (BISattentional-BL, BISmotor-BL, BISnon-planning-BL) and sensation seeking (SBL-TAS-BL, SBL-ES-BL, SBL-BS-BL, SBL-DIS-BL) as the dependent variables, also without (model 1, subscale scores) and with (model 2, subscale scores) adjustment for the effect of potential confounders. Following Hosmer and Lemeshow (2001), potential confounders (i.e. baseline measures of age, gender, verbal IQ, years of education, and substance use parameters) were defined as variables that were related to the dependent variable at the $p < 0.20$ level of significance.

To test whether depression, impulsivity, and sensation seeking increased after a period of ecstasy use, separate linear regression analyses were performed with the follow-up total and subscale measures of depression (BDI-FU), impulsivity (BIS-FU), or sensation seeking (SBL-FU) as the dependent variables, ecstasy use as the independent variable and baseline measures of depression (BDI-BL), impulsivity (BIS-BL), or sensation seeking (SBL-BL) as covariates (model 1). In additional backward linear regression analyses, the observed relationships were adjusted for the effect of potential confounders, i.e. baseline measure of gender and verbal IQ and follow-up measures of age, years of education, and substance use parameters (model 2). For each analysis potential confounders were defined as variables that were related to the dependent variable at the $p < 0.20$ level of significance (Hosmer and Lemeshow, 2001). In order to test whether the amount of ecstasy use was related to changes in depression, impulsivity, or sensation seeking, separate backward linear regression analyses were performed in the group of incident ecstasy users with follow-up measures of total and subscale scores on depression (BDI-FU), impulsivity (BIS-FU), or sensation seeking (SBL-FU) as the dependent variable, the level of ecstasy use (cumulative number of tablets) as the independent variable and baseline scores on depression (BDI-BL), impulsivity (BIS-BL), or sensation seeking (SBL-BL) and potential confounders, related to the dependent variable at the level of $p < 0.20$, as covariates (model 3).

All analyses were performed using SPSS version 11.5; SPSS Inc., Chicago, IL, USA). Mean values reported in the result and discussion sections are followed by their standard deviations (mean ± SD). Odds Ratios (OR) and regression coefficients B are reported with their 95% confidence intervals (95% CI).

Results

Characteristics of the sample and substance use

Of the 188 ecstasy-naive subjects (77 M, 111 F, mean age 21.7 ± 3.0 years) at baseline, 158 (84%) completed the last follow-up questionnaires about drug use sent to them by mail. The other 30 volunteers (16%) were regarded as dropouts, either because they refused to participate in follow-up or because we could not reach them anymore. Of the 158 subjects, 64 (41%) declared they had started to use ecstasy since the inclusion in the study, while the other 94 subjects (59%) declared to be continuously ecstasy-naive. Of the 64 incident ecstasy users 59 (92%) were willing to participate in the follow-up session, together with 61 individually matched (gender, age, DART-IQ, cannabis use) persistent ecstasy-naive subjects, resulting in 120 subjects with a follow-up session. Time between baseline and follow-up measurements was on average 16.0 ± 4.6 months (range: 11.5–35.5 months) in the ecstasy group and on average 19.1 ± 7.5 months (range: 12.0–37.3 months) in the control group (mean difference 3.2 months, 95% CI 0.92 to 5.41).

Table 1 shows baseline and follow-up characteristics on demographics and substance use of subjects that participated in the follow-up session. It shows that incident ecstasy users used 6.0 tablets on average (range: 0.5–80; median 2.0 tablets) in a mean period of 20.4 ± 23.8 weeks during the average follow-up period of 16.0 months. Table 1 also shows that due to the matching between the incident ecstasy users and the persistent ecstasy-naive subjects, the two groups were very similar in terms of gender, age, and verbal IQ prior to inclusion in the study. At baseline, the two groups were also similar in terms of alcohol use, smoking, and use of amphetamine and cocaine. However, the two groups were significantly different in terms of cannabis use (48.0 versus 17.6 joints in the last year, B = 0.69, 95% CI 0.01 to 1.37). In addition, between baseline and follow-up, ecstasy users reported a significantly higher increase in the use of alcohol (B = 0.21, 95% CI 0.02 to 0.39), cannabis (B = 0.60, 95% CI 0.09 to 1.10), amphetamines (B = 0.19, 95% CI 0.01 to 0.37), and cocaine (B = 0.44, 95% CI 0.10 to 0.78) and a significantly smaller increase in age (B = −0.28, 95% CI −0.46 to −0.09) and in years of education (B = −0.49, 95% CI −0.94 to −0.05) (probably because a shorter mean follow-up period in incident ecstasy users) compared to persistent ecstasy-naive subjects.

Predictive value of symptoms of depression, impulsivity, and sensation seeking on future ecstasy use

Baseline total scores on the BDI, BIS, and SBL of all 64 incident ecstasy users and all 94 persistent ecstasy-naive subjects did not predict incident ecstasy use between baseline and follow-up (model 1, total scores, data not shown). Years of education and use of cannabis, alcohol, and cocaine correlated with future ecstasy use ($p < 0.20$), so they were included in model 2 as potential confounders. Also after controlling for these potential confounders, we did not observe a significant predictive effect of the baseline total scores of BDI, BIS, or SBL on future ecstasy use (model 2, total scores). However, the model showed a positive predictive effect of last year cannabis use on future ecstasy use (OR = 1.23, 95% CI 1.03 to 1.46). The analyses of subscales (model 1, subscale scores) showed a positive predictive value of the experience seeking subscale score of the SBL on future ecstasy use (OR = 1.05, 95% CI 1.00 to 1.10) and an unexpected negative predictive value of the thrill and adventure seeking subscale score of the SBL on future first ecstasy use (OR = 0.95, 95% CI 0.91 to

Table 1 Demographics, characteristics of ecstasy use and use of other substances. Values expressed as mean ± SD, outcomes as regression coefficients (95% CI)

	Baseline			Follow-up		
	Persistent ecstasy naives ($n = 61$)	Future ecstasy users ($n = 59$)	Regression coefficient B (95% CI)[a]	Persistent ecstasy naives ($n = 61$)	Future ecstasy users ($n = 61$)	Regression coefficient B (95% CI)[b]
Gender	25M, 36F	25M, 34F	−0.01 (−0.19; 0.17)			
Age	21.5 ± 2.0	21.7 ± 3.1	0.24 (−0.71; 1.19)	23.1 ± 2.1	23.0 ± 3.2	−0.28 (−0.46; 0.09)*
DART-IQ	105.1 ± 9.9	103.5 ± 9.0	−1.56 (−4.98; 1.87)			
Years of education	14.4 ± 1.8	13.9 ± 2.7	−0.45 (−1.26; 0.37)	15.9 ± 2.0	15.0 ± 2.8	−0.49 (−0.94; −0.05)*
Ecstasy						
Cumulative dose (tablets)	NA	NA		NA	6.0 ± 11.6	
Time since first tablet (weeks)	NA	NA		NA	39.2 ± 23.4	
Time since last tablet (weeks)	NA	NA		NA	18.7 ± 17.5	
Duration of ecstasy use	NA	NA		NA	20.4 ± 23.8	
Other substance (last year)						
Alcohol (units/week)	9.9 ± 9.0	8.6 ± 7.7	−0.17 (−0.51; 0.17)	8.3 ± 7.9	9.4 ± 8.7	0.21 (0.02; 0.39)*
Tobacco (cig/week)	27.6 ± 55.3	33.4 ± 47.5	0.79 (−0.06; 1.64)	25.7 ± 46.8	39.6 ± 62.6	0.26 (−0.32; 0.84)
Cannabis (joints in last year)	17.6 ± 25.1	48.0 ± 100.0	0.69 (0.01; 1.37)*	20.4 ± 49.9	48.9 ± 114.2	0.60 (0.09; 1.10)*
Amphetamine (number of times used in last year)	0.0 ± 0.0	0.1 ± 0.8	0.04 (−0.04; 0.13)	0.0 ± 0.0	0.6 ± 2.1	0.19 (0.01; 0.37)*
Cocaine (number of times used in last year)	0.4 ± 1.5	0.9 ± 2.8	0.22 (−0.07; 0.51)	0.4 ± 1.5	2.5 ± 7.3	0.44 (0.10; 0.78)*

[a] Future ecstasy users vs persistent ecstasy-naives at baseline (linear regression, regression coefficient = mean difference, substance use log-transformed).

[b] Incident ecstasy users vs persistent ecstasy-naives at follow-up (linear regression adjusted for baseline scores, substance use log-transformed).

*$p < 0.05$.

1.00). After adjustment for potential confounders (model 2, subscale scores), only the negative predictive value of the thrill and adventure seeking subscale score on future first ecstasy use remained significant (OR = 0.95, 95% CI 0.91 to 1.00). Also using the subscale model, last year cannabis use had a positive predictive value on future ecstasy use (OR = 1.30, 95% CI 1.08 to 1.56).

Influence of ecstasy use on depression, impulsivity, and sensation seeking

Table 2 shows the total and subscale scores on the BDI, BIS, and SBL of the groups of 59 incident ecstasy users and 61 persistent ecstasy-naive volunteers who completed the follow-up session. The linear regression analyses, with correction for baseline scores on depression, impulsivity, or sensation seeking (model 1), showed a significant effect of ecstasy use on the follow-up assessments of general sensation seeking (B = 0.54, 95% CI 0.20 to 0.87), SBL experience seeking (B = 1.76, 95% CI 0.09 to 3.42), and SBL disinhibition (B = 3.31, 95% CI 1.74 to 4.88). After correction for potential confounders (model 2), the effect of ecstasy use on the SBL general score (B = 0.51, 95% CI 0.20 to 0.83) and the disinhibition subscale scores (B = 3.25, 95% CI 1.74 to 4.76) remained statistically significant. Within the group of incident ecstasy users we found no significant effects of the cumulative dose of ecstasy on the follow-up scores of the questionnaires (model 3).

Discussion

The main aim of the current study was to establish the direction of the relationship between ecstasy use and depression, impulsivity, and sensation seeking, because it is still unknown and debated whether subjects with higher levels of depression, impulsivity, and sensation seeking are predisposed to start using ecstasy or whether ecstasy use leads to higher levels of depression, impulsivity, and sensation seeking. To our knowledge, this is the first longitudinal study that prospectively examined the relationship between ecstasy use and depression, impulsivity, and sensation seeking. Incident ecstasy users and persistent ecstasy-naive volunteers were recruited by the same procedures and were very similar at baseline on potential confounders, except for the use of cannabis which was significantly higher in the incident ecstasy users.

First, we hypothesized that higher levels of depression, impulsivity, and sensation seeking would predispose for future ecstasy use in ecstasy-naive young adults. However, in our study population we found no evidence that higher total scores on the depression, impulsivity, or sensation seeking questionnaires predict incident ecstasy use. Higher scores on the experience seeking subscale of the SBL did predict future ecstasy use, which could have been expected because this subscale reflects 'a search for new sensory and psychological experiences and a unconventional lifestyle'. However, this effect disappeared after adjustment for confounding. In contrast, even after correction for potential confounders we found that subjects with a lower baseline score on

Table 2 Result from BDI, BIS and SBL self-report questionnaires. Values are uncorrected for covariates and expressed as mean ± SD, outcomes as regression coefficients (95% CI)

	Baseline		Follow-up		
	Persistent ecstasy naives ($n = 61$)	Future ecstasy users ($n = 59$)	Persistent ecstasy naives ($n = 61$)	Incident ecstasy users ($n = 59$)	Regression coefficient B (95% CI) model 1
Beck Depression Inventory					
Total	3.6 ± 4.1	4.2 ± 3.8	3.4 ± 3.5	4.6 ± 4.9	0.86 (−0.47; 2.18)
Barrat Impulsiveness Inventory					
Attentional	16.5 ± 3.5	17.1 ± 3.1	17.1 ± 3.3	18.2 ± 3.6	0.67 (−0.21; 1.56)
Motor	22.9 ± 4.2	22.8 ± 2.9	22.9 ± 4.3	23.1 ± 3.6	0.20 (−0.93; 1.33)
Non-planning	26.7 ± 4.8	26.7 ± 4.1	27.0 ± 4.9	27.7 ± 4.6	0.73 (−0.49; 1.96)
Total	68.0 ± 10.5	68.7 ± 7.1	68.9 ± 10.5	71.3 ± 9.8	1.71 (−0.69; 4.12)
Sensation Seeking Scale (SBL)					
Thrill and adventure seeking	46.3 ± 7.4	44.1 ± 7.2	45.3 ± 7.0	43.7 ± 8.0	0.22 (−1.42; 1.85)
Experience seeking	45.0 ± 8.0	47.1 ± 9.0	44.5 ± 7.9	48.0 ± 9.1	1.76 (0.09; 3.42)*
Boredom susceptibility	41.9 ± 6.6	41.3 ± 6.3	39.4 ± 7.0	40.6 ± 6.8	1.63 (−0.25; 3.51)
Disinhibition	39.8 ± 5.9	40.4 ± 5.8	38.6 ± 6.4	42.3 ± 5.6	3.31 (1.74; 4.88)*†
General sensation seeking	13.6 ± 1.4	13.6 ± 1.5	13.2 ± 1.5	13.7 ± 1.5	0.54 (0.20; 0.87)*†

*Significant differences between incident ecstasy users and persistent ecstasy-naives at follow-up (model 1, linear regression adjusted for baseline scores).

†Significant differences between incident ecstasy users and persistent ecstasy-naives at follow-up adjusted for potential confounders (model 2, backward linear regression adjusted for baseline scores and potential confounders, substance use log-transformed).

the thrill and adventure seeking subscale of the SBL had a higher risk for future ecstasy use. This subscale reflects 'the need for participation in sports and activities with a strong accent on speed and danger', so it is not surprising that this subscale does not predict future ecstasy use, although the negative predictive effect is unexpected and unaccountable. Our findings are at odds with the findings of other studies that suggested that depression, impulsivity, and sensation seeking are risk factors for substance use (Pedersen, 1991; Bardo *et al.*, 1996; Gerra *et al.*, 2004). One possible explanation is that our study group, including the control group, is probably not representative of the general population of young adults, because at baseline we selected subjects with a relatively high risk for first time ecstasy use according to their intention to start using ecstasy in the near future and ecstasy use among their friends. Moreover, subjects were willing to take part in a rather challenging research project including brain scanning, neuropsychological examination, and blood sampling (see De Win *et al.*, 2005). When we compare the baseline scores of our population ($n = 158$) with 'normal' scores of volunteers of approximately the same age in other studies, our population has higher scores on sensation seeking and impulsivity: mean score on the general sensation seeking scale of 13.5 ± 1.5 in our baseline population is somewhat higher than the general scores on the SBL of 12.4 ± 1.9 and 12.8 ± 1.7 for males, and 11.7 ± 2.0 and 12.4 ± 1.7 for females reported in two Dutch university student populations (Feij *et al.*, 1982; Feij and van Zuilen, 1984). In addition, on the thrill and adventure seeking subscale our population scored higher with 45.1 ± 7.7 compared to 39.9 ± 8.8 and 41.0 ± 9.0 for males, and 37.8 ± 9.6 and 37.7 ± 9.9 for females reported in the Dutch university student populations. Also the baseline total score on the BIS of 66.3 ± 8.8 (we had to leave one item out for comparability with the English version that contains one item less than the Dutch version) of our population is slightly higher than the total scores of 63.8 ± 10.2 in university undergraduates from the United States (Patton *et al.*, 1995) and of 64.1 ± 10.1 in Italian college undergraduates (Fossati *et al.*, 2001). Compared to a sample of 192 university psychology students with a mean BDI score of 6.5 ± 7.3, the baseline depression scores of our population is lower with a mean of 3.9 ± 4.2 (Welch *et al.*, 1990). However, these differences are limited for SBL to about one standard deviation, for BDI to about half a standard deviation, and for BIS to less than one third of a standard deviation. Therefore, generally high sensation seeking and impulsivity scores, and low depression scores in our study population are probably not the single explanation for the absence of predictive values of sensation seeking, impulsivity, and depression on future ecstasy use in our study population. Probably more important are the lower variances in outcomes in our population than in the general student population, appearing from lower standard deviations on SBL, BIS, and BDI. This is probably caused by the selection procedure and could have hampered the finding of positive predictive values.

An additional finding of our study was that future ecstasy use was predicted by the amount of cannabis use during the last year prior to baseline. Although all subjects at baseline came from the same selected population with high risk to start using ecstasy in the near future it is not surprising and known from literature that subjects with more experience in other drugs are more likely to start using ecstasy as well (Pedersen and Skrondal, 1999; Zimmermann *et al.*, 2005). The predictive effect of cannabis use on future first ecstasy use is likely to be even greater in a general population, because last year prevalence of cannabis use in our persistent ecstasy-naive control group was 69% which is much higher than in the general population of the same age group (Abraham *et al.*, 2002; The Netherlands National Drug Monitor, 2003).

An important finding is the increase of general sensation seeking and of disinhibition between baseline and follow-up in incident ecstasy users relative to persistent ecstasy-naive controls. However, Table 2 suggests that these significant effects seem to result from a combination of a slight increase in sensation seeking in incident ecstasy users and a decrease in sensation seeking in the persistent ecstasy-naive volunteers during the follow-up period. This difference between ecstasy users and non-users in general sensation seeking and disinhibition, reflecting behaviour that relieves social inhibition through activities such as party going, gambling, and sex, might be caused by a difference in serotonergic activity in the brain, which is believed to play an important role in sensation seeking behaviour (Netter *et al.*, 1996). It is known that sensation-seeking scores decline with age, after having reached a peak in late adolescence (Zuckerman, 1994). Therefore we could speculate that this normal maturation occurred in the persistent ecstasy-naives, while this decrease in sensation seeking failed to occur or is delayed in incident ecstasy users. A possible explanation is that consumption of psychoactive agents might affect neurobiological and psychophysiological strengths and weaknesses that predispose or protect an individual from psychoactive abuse, especially during adolescence (Witt, 1994; Laviola *et al.*, 2000) and possibly also during young adulthood. In line with this, the incident ecstasy users showed a relative increase in use of alcohol, cannabis, amphetamines, and cocaine and a relative 'decrease' in years of education between baseline and follow-up compared to the persistent ecstasy-naives. An alternative explanation is that shared factors, such as lifestyle or personality have 'caused' both increased sensation seeking, increased substance use and incident ecstasy use.

We did not find any effect of ecstasy use on depression and impulsivity. This is in contrast with results of previous studies that reported ecstasy users to have higher levels of depression and/or impulsivity (Morgan, 1998; Gamma *et al.*, 2000; MacInnes *et al.*, 2001; Thomasius *et al.*, 2003; Bond *et al.*, 2004; Butler and Montgomery, 2004; Sumnall and Cole, 2005), although these studies did not have baseline measurements prior to first ecstasy use. The absence of a clear effect of ecstasy on mood and impulsivity might be related to the fact that in the present study most incident ecstasy users only experimented with ecstasy use on a single or a few occasions and almost no heavy users were involved. Therefore, it is likely that ecstasy-induced depression and impulsivity only becomes apparent after higher cumulative dosages. This would be in concordance with findings that depression (Parrott *et al.*, 2002), impulsivity (Halpern *et al.*, 2004), and especially memory problems in ecstasy users are dose related (Bolla *et al.*, 1998; Morgan, 2000; Gouzoulis-Mayfrank *et al.*, 2000; Reneman *et al.*, 2001a), although it was shown that even novice ecstasy users who used

ecstasy less than ten times reported a diversity of problems which they attributed to their ecstasy use (Parrott *et al.*, 2002). Especially because there is growing interest in the possible medical benefits of low dose ecstasy as an adjuvant to psychotherapy (Check, 2004; Bender, 2005), it is an important finding that low doses of ecstasy use do not seem to cause increased depression or impulsivity.

In spite of the prospective nature this study has some limitations. First, although it is possible with the current prospective study design to establish the temporal direction of relationships between variables, it is still impossible to establish with certainty whether relationships are really causal in origin, especially because it is not possible to perform a perfect randomized study on ecstasy neurotoxicity in humans. Therefore, causal interpretation of the observed effects is hampered because there might be residual confounding (due to imperfect measurement of some confounders and the absence of measures of other potential confounders). Second, it is very difficult to include a representative sample of 'potential' novice ecstasy users. We noticed for example that higher educated subjects were more likely to participate in our study than subjects with lower levels of education. Moreover, we already discussed that subjects took part in a rather challenging research project including brain scanning, neuropsychological examination, and blood sampling. This probably induced selection of subjects with a high motivation, which may restrict the generalization of our findings. Third, although the follow-up period was relatively short and we cannot know whether subjects will become heavy users after the follow-up period, it seems that most of the incident ecstasy users only took one or a few tablets and can be classified as experimenters rather than as abusers. It is likely that these experimenters or novice users have a different personality profile (e.g. lower levels of impulsivity and sensation seeking) than subjects who become abusers or heavy (polydrug) users (McCown, 1988; Parrott *et al.*, 2000, 2002). Therefore the results of our ecstasy users can probably not be extrapolated to heavy ecstasy users. On the other hand, the results are probably more representative for ecstasy users in general, because only 20–30% of the ecstasy users consume ecstasy on a regular basis (Drugs Informatie en Monitoring Systeem, 2003a). Fourth, inherent to the non-experimental design, there was no control over dosage and purity of the ecstasy tablets taken. Recent surveys in the Netherlands, however, confirm that in 2003 and 2004 95% of the tablets sold as ecstasy contain MDMA as the major component (Drugs Informatie en Monitoring Systeem, 2003b, 2004). Fifth, the environmental circumstances under which ecstasy was taken and the simultaneous use of other substances in our study was heterogeneous. As the study mainly involved low-dose and moderate ecstasy users, it was impossible to control for patterns of use, although there are indications that this may play a significant role in potential damage (Topp *et al.*, 2004). Frequency and amount of drug use were mainly assessed through self-report questionnaires, although abstinence of drug use before measurements were verified by urine analyses. As in other studies, most of the incident ecstasy users also used cannabis and some of them also used cocaine and amphetamine, although we were able to adequately control for these confounders. It is virtually impossible to include only 'pure' ecstasy users, because most of them are polydrug users. Schuster even found that in a group of merely novice ecstasy users, 97% of them had used cannabis and 59% had used cocaine (Schuster *et al.*, 1998). Sixth, because of medical ethics we had to inform subjects about the potential negative consequences of ecstasy use at baseline and this could have had consequences for future ecstasy use and self-reported outcomes such as depression, impulsivity, and sensation seeking. Although this information might have led to limited use of ecstasy this is not very likely because 41% of the baseline population still started to use ecstasy. Regarding the self-report questionnaires, the information might have prompted subjects to report the effects about which they were warned. On the other hand, the period between informed consent at baseline and follow-up measurements was 16.0 months on average for incident ecstasy users so it is not very likely that many subjects will have remembered the exact contents of the original warning at follow-up. Moreover, ecstasy users did not differ from persistent ecstasy-naives at follow-up on depression and impulsivity (mentioned in the information brochure), but they did differ on sensation seeking, while this was not mentioned in the information brochure. Seventh, we only measured depression, impulsivity, and sensation seeking with self-report questionnaires and we did not perform behavioural measurements. Self-reported psychopathological abnormalities might not only reflect real abnormalities but might be biased by lack of insight, neurotic personality, or suggestibility of the subject, and behavioural measurements are probably less sensitive to these forms of bias.

In conclusion, we could not confirm that depression, impulsivity, or sensation seeking are predictors for first ecstasy use in a selected population of young adults with a relative high risk of future ecstasy use, although future ecstasy use was predicted by cannabis use. In addition, our data suggest that relatively low doses of ecstasy use do not cause increased levels of depression or impulsivity, although we found an effect of ecstasy use on certain aspects of sensation seeking. This latter finding may indicate that ecstasy use (or some related factor) prevents a normal decrease in sensation seeking observed in persistent non-users.

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